Chapter 13

Aseptic Production Facilities

Section 13.1

General Aseptic Production Facility Requirements

Contents:

13.1.0 Introduction

Successful Aseptic Production Facilities (APF) projects require continuous and collaborative effort from project initiation to the end of the project facility life cycle. NIH's APFs produce therapeutic and diagnostic products for human use, inclusive of those required to follow Current Good Manufacturing Practice (cGMP) regulations, and aseptic processing (for those manufacturing biological products), for the production of Phase-I and II clinical trial products (See Figure 13.1.0). These facilities are subject to requirements, which do not directly fit within the scope of other DRM sections. This chapter references sections of the DRM where the criteria are the same as other NIH facilities.

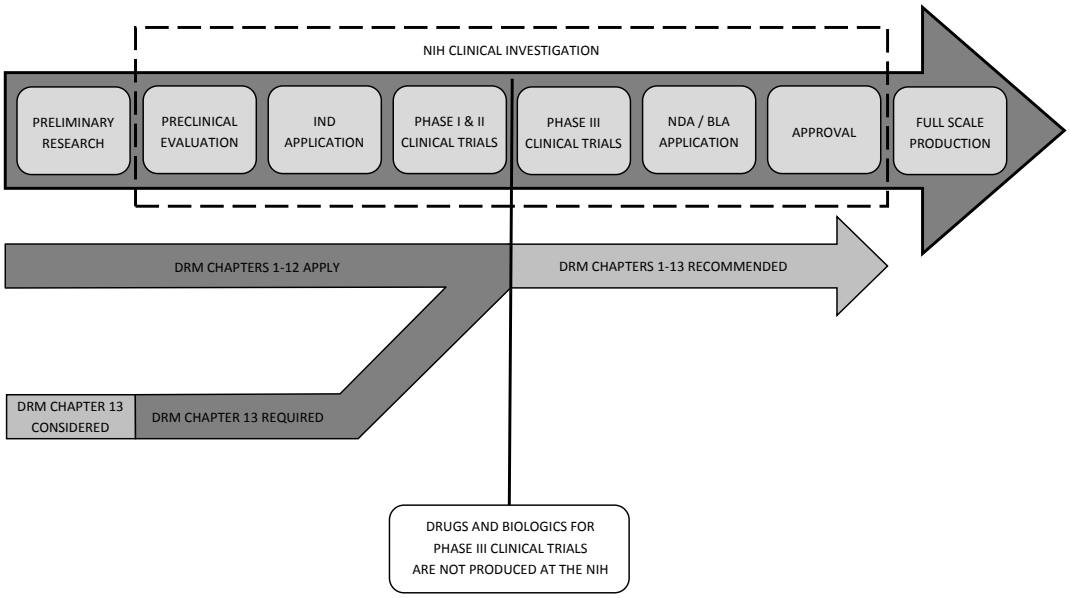
The purpose of this chapter is to establish minimum criteria for NIH APFs which helps ensure that patients receive products of appropriate strength, identity, quality, purity, and other factors related to patient safety; this chapter focuses on those factors that can be directly or indirectly impacted by the facility. This chapter is intended to provide requirements and reinforce strategies to mitigate risks where the facility can have a direct or indirect impact. See Figure 13.1.0 for additional information on how this chapter relates to supporting the overall clinical investigation process.

This risk reduction is accomplished by:

1. Designing and constructing APFs:
    a. To facilitate product safety, cleaning, maintenance, and operations to mitigate potential risks to product, patients, and staff.
    b. To minimize potential contamination and to limit mix-ups, cross-contamination, and exposure to objectionable chemical and microbiological contaminants.
    c. To be robust and resilient in order to operate under control, even with partial/complete failure of primary systems.
2. Manufacturing, storing and dispensing human-use drugs, biologics, and related materials, in highly controlled environments.
3. Following strict documentation, change control, and validation processes throughout the APF life cycle.

Failure to adequately design, build, and operate APFs under-control, can result in the potential contamination of products, threaten patient and worker safety, cause injury, illness, complications, or even death. Failure to maintain control of the facility can result in worker injury, illness, or death. Due to the level of risk inherent in APFs, there are significantly higher requirements for these facilities, compared with typical laboratories (e.g., BSL-2, 2/3, etc.).

Figure 13.1.0 DRM Chapter 13 Application



Due to the nature of APFs and their regulation, accommodation for an existing facility cannot be 'grandfathered' into a plan to update or replace the facility.

Within cGMP, the good practice guidance and (GxP) regulations are ever evolving. When new practices are promulgated, compliance shall be initiated within a reasonable time, or by a stipulated date (i.e., a "comply by" date is given by the authoring body). APF facilities must be maintained in a current state of compliance, requiring vigilant surveillance of the good practice guidance and GxPs throughout the life cycle of the facility.

Figure 13.1.0 is a diagram indicating that DRM Chapter 13 is intended to be a requirement for facilities producing Phase-I and II clinical trials at NIH; taken into consideration before, and as recommended practice, after.

13.1.1 Statutes, Regulations, Standards, and Guidelines

Aseptic Production Facilities are highly regulated environments; applicable statutes, codes, standards, regulations, and guidelines are based upon the product being produced, and the locations the drugs and biologics are administered (e.g., extra-jurisdictional enforcement may be applicable). See Table 13.1.1.

Above and beyond these requirements are Good Engineering Practice (GEP) and cGMP which are, at their core, driven by risk analysis.

At NIH, the primary focus is Phase-I and II clinical trials. The codes, standards, regulations, and guidelines provide the minimum requirements for design,

Table 13.1.1 Diagram indicating high-level organization of regulations into Pharmaceuticals, Biologics and Medical Device Facilities

<table>
<tr><th colspan="5">Drugs</th></tr>
<tr><th>Pharmaceuticals</th><th colspan="3">Biologics</th><th>Medical Devices</th></tr>
<tr><td>USP <795> Pharmaceutical Compounding - Nonsterile Preparations</td><td rowspan="6">Products not subject to Human Cells, Tissues, and cellular and tissue-based Products (HCT/P) regulations</td><td rowspan="6">21 CFR Part 1271, Section 361 - Minimal Manipulation of Human Cells, Tissues, and Cellular Tissue-Based Products</td><td rowspan="6">21 CFR Part 1271 Section 351 - More Than Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products</td><td rowspan="6">21 CFR Parts 800-1299</td></tr>
<tr><td>USP <797> Pharmaceutical Compounding - Sterile Preparations</td></tr>
<tr><td>USP <800> Hazardous Drugs - Handling in Healthcare Settings</td></tr>
<tr><td>USP <823> Positron Emission Tomography - Compounding</td></tr>
<tr><td>21 CFR 353a - Pharmacy Compounding</td></tr>
<tr><td>21 CFR 353b - Outsourcing Facilities</td></tr>
<tr><td colspan="5">QC Analytic Laboratories Performing Release and Stability Testing</td></tr>
</table>

construction, O&M for facilities associated with Phase-I and II clinical trials, with increasing requirements at each level.

NIH intends to design, build, and operate all APFs to meet the more stringent Phase-II, or better requirements, in lieu of the less restrictive Phase-I requirements to the extent practicable, and in a manner which prioritizes patient and worker safety.

Standing up and operating facilities in this manner are true to our mission and goals, particularly to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

The following list of statutes, regulations, standards, and guidelines are in addition to those found in Section 1.2. The user shall define the Current Good Manufacturing Practice (cGMP) and harmonized regulatory environment (GxP), applicable to the APF during the predesign phase, and adhered to throughout the design (where expanded into the URS and BOD), and later used as a reference point for commissioning, qualification, validation, operation and maintenance of these facilities.

Statutes (Laws passed by Congress):

A. Federal Food, Drug, and Cosmetic Act (FD&C Act):

1. Section 503 A & Amendments (Amended by the Compounding Quality Act, as described in Section 106(a) of the Act) - Pharmacy Compounding of Human Drug Products <Traditional Pharmacy>
2. Section 503 B - < Outsourcing Facility>

B. Public Health Service Act (PHSA):

1. Section 351 - Regulation of Biologics
2. Section 361 - Regulation of HCT/Ps

Regulations (have the full force of the statute):

A. Title 21 Code of Federal Regulations (CFR), Chapter I - Food and Drug Administration (FDA), Department of Health and Human Services (DHHS):

1. Subchapter C – Drugs: General
    a. Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding Drugs, General
    b. Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
2. Subchapter D – Drugs for Human Use
    a. Part 312: Investigational new drug application
3. Subchapter F – Biologics
    a. Part 600: Biological Products: General
    b. Part 606: Current Good Manufacturing Practice for Blood and Blood Components
4. Subchapter L – Regulations under Certain Other Acts Administered by the FDA
    a. Part 1270: Regulations of Human Tissue Intended For Transplantation
    b. Part 1271: Regulations of Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/P's)

B. The United States Pharmacopeia and The National Formulary (USP-NF), latest edition

C. American Society of Mechanical Engineers (ASME) Bioprocessing Equipment Standard

D. International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (BSS)

Standards:

A. U.S. Pharmacopeia (USP) General Chapters:

1. <795> Pharmaceutical Compounding — Nonsterile Preparations
2. <797> Pharmaceutical Compounding—Sterile Preparations
3. <800> Hazardous Drugs—Handling in Healthcare Settings
4. <823> Positron Emission Tomography — Compounding
5. <1046> Cellular and Tissue-Based Products <1116> Microbiological Controls and

Monitoring of Aseptic Processing Environments

6. <1163> Quality Assurance in Pharmaceutical Compounding
7. <1168> Compounding for Phase-I Investigational Studies
8. <1231> Water for Pharmaceutical Purposes

B. Institute of Environmental Sciences and Technology (IEST)

1. IEST-RP-CC001: HEPA and ULPA Filters
2. IEST-RP-CC002.3: Unidirectional-Flow, Clean-Air Devices
3. IEST-RP-CC006.3: Testing Cleanrooms
4. IEST-CC012: Considerations in Cleanroom Design
5. IEST-RP-CC013.2: Calibration Procedures and Guidelines or Select Equipment Used in Testing Cleanrooms and Other Controlled Environments
6. IEST-CC018: Cleanroom Housekeeping: Operating and Monitoring Procedures
7. IEST-CC026: Cleanroom Operations
8. IEST-RP-CC034: HEPA and ULPA Filter Leak Tests
9. IEST-CC045: Design Considerations for Critical Exhaust Systems
10. IEST-CC047: Cleanroom Lighting
11. IEST-CC048: Guidance for Design, Performance, and Operations of Controlled Environments per USP 797 International Society of Pharmaceutical Engineers (ISPE)

C. Baseline Pharmaceutical Engineering Guide for New and Renovated Facilities:

1. Volume - 3: Sterile Product Manufacturing Facilities
2. Volume - 5: Commissioning and Qualification
3. Volume - 6: Biopharmaceutical Manufacturing Facilities
4. Volume - 7: Risk-Based Manufacture of Pharmaceutical Products

D. International Standards Organization (ISO) - Cleanroom Standards:

1. ISO 14644-1: Cleanrooms and Associated Controlled Environments – Part 1: Classification of air cleanliness by particle concentration
2. ISO 14644-2: Cleanrooms and associated controlled environments – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
3. ISO 14644-3: Cleanrooms and associated controlled environments – Part 3: Test Methods
4. ISO 14644-4: Cleanrooms and Associated Controlled Environments–Part 4: Design, Construction and Startup.
5. ISO 14644-5: Cleanrooms and Associated Controlled Environments–Part 5: Operations
6. ISO 14644-6: Cleanrooms and Associated Controlled Environments–Part 6: Vocabulary
7. ISO 3746: Acoustics — Determination of sound power levels and sound energy levels of noise sources using sound pressure — Survey method using an enveloping measurement surface over a reflecting plane

Guidelines:

A. Controlled Environment Testing Association:

1. CAG-003-2006: Sterile Compounding Facilities
2. CAG-005-2007: Servicing Hazardous Drug Compounding Primary Engineering Controls
3. CAG-008-2010: CETA Certification Matrix for Sterile Compounding Facilities
4. CAG-009-2011v3: CETA Certification Application Guide USP <797> Viable Environmental Sampling & Gowning Evaluation

B. Facility Guidelines Institute (FGI)'s Guidelines for

Design and Construction of Hospitals and Outpatient Facilities

C. FDA Guidance for Industry (GFI):

1. cGMP for Phase I Investigational Drugs
2. INDs for Phase II and Phase III Studies; Chemistry, Manufacturing, and Controls Information
3. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
4. PET Drugs — Current Good Manufacturing Practice (cGMP)
5. HCT/P Guide
6. Quality Systems Approach to
7. Pharmaceutical cGMP Regulations
8. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production
9. cGMP for Phase I Investigational Drugs
10. INDs for Phase II and Phase III Studies

D. FDA – Other documents:

1. CDER Manual of Policies and Procedures (MaPPs), 4723.1 Standing Operating Procedures for NDA/ANDA Field Alert Reports
2. Office of Regulatory Affairs, Chapter 4, Compliance Policy Guide

E. Federal Register Notices for Proposed Changes and Final Changes to cGMP

F. International Society for Pharmaceutical Engineering (ISPE) - ISPE Good Practice Guides:

1. Heating, Ventilation and Air Conditioning (HVAC)
2. Process Gases
3. Project Management for the Pharmaceutical Industry

G. International Standards Organization (ISO) - ISO/IEC Guide 51, Safety aspects — Guidelines for their inclusion in standards

H. International Conference on Harmonization (ICH):

1. ICH-Q7 Good Manufacturing Practice
2. ICH-Q9 Quality Risk Management National Environmental Balancing Bureau, Procedural Standards for Certified Testing of Cleanrooms

13.1.2 Coordination Between Statutes, Regulations, Standards, and Guidelines

The products produced in APFs are regulated by the local jurisdictional requirements, of both where the APF is located, and any extra-jurisdictional requirements of where the products are to be dispensed. A harmonization analysis shall be performed, giving full consideration to all applicable requirements, including extra-jurisdictional requirements, as applicable. These analyses shall be incorporated into the user's statement of requirements (SOR) and the derivative user requirement specification (URS), giving deference to the most stringent requirement when comparing multiple statutes, regulations, standards, and guidelines (i.e., cGMP and GxP). The harmonization report should also provide a rationale for each such determination. In instances where the most restrictive requirement is not obvious, a risk analysis shall be performed to determine the minimum requirement.

Caution should be taken in conducting harmonization analyses. Typically cGMP SMEs are engaged in the development of these analyses either to produce the report, as a consultant, or reviewer. The A/E shall compare the GMP and GxP requirements detailed in the draft harmonization report with the various "normal" building codes (IBC, Life safety code, etc.) and conduct their due diligence analyses. The final harmonization report shall describe the comprehensive regulatory environment for the APF at the initiation of the design phase, and serve as a basis for ongoing confirmation of conformance to all current requirements.

13.1.3 Definitions

Certain definitions listed below are the same as defined by the International Society for Pharmaceutical Engineering (ISPE) and Commission Electrotechnique Internationale (IEC). These are denoted with the organization's acronym in italics and brackets following the definition.

Advanced Aseptic Processing: The use of barrier technology that separates aseptic processes from operators and other background risks. This includes the application of both isolation and Restricted Access Barrier System (RABS) technologies as well as closed processing. See Aseptic Processing.

Air Change Rate / Ventilation Rate (similar to Air Changes per Hour, or ACH): The calculated number of times the total air volume of a defined space is replaced in a given unit of time, calculated by dividing the total volumetric flow of the room supply (or exhaust, in some cases) by the gross volume of the room. Calculation of air changes should be calculated only on supply, and exclude transfer air or calculation based on room exhaust air.

Airflow Visualization Study (AVS): Verification of airflow patterns through the observation of the airflow-induced behavior of visible neutrally buoyant, non-charged particles in an airstream. This method allows for, determination of the potential impact of unintended airflow patterns with the intent of optimizing control of contamination in clean environments.

Airlock: A space with interlocked doors, constructed to maintain air pressure control when items or people move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area. Airlocks are commonly used for donning/doffing PPE and gowning as well as cleaning/sanitizing or otherwise preparing materials for entry to /exit of clean space. See Bubble Airlock, Cascade Airlock, Sink Airlock, and Figure 13.1.3.

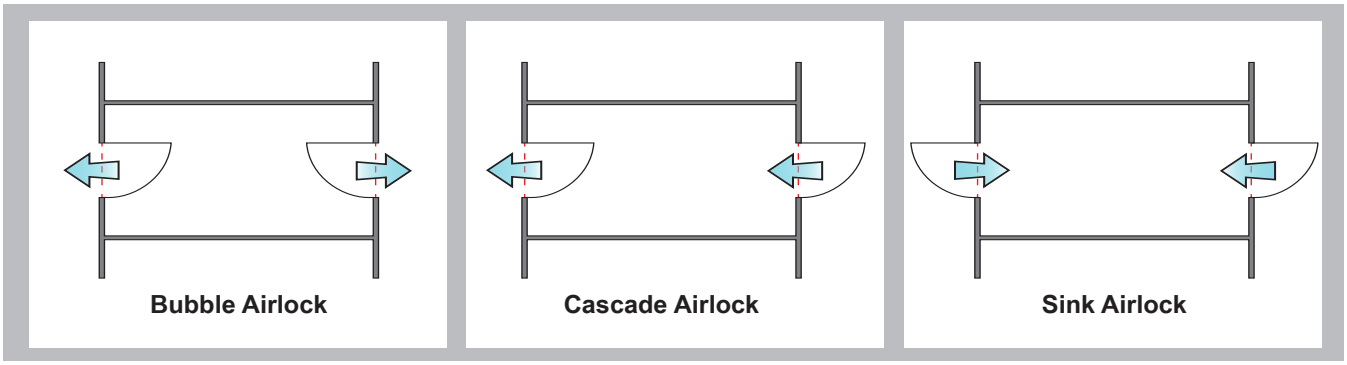
Ambient Environment: The general environmental conditions in non-classified space where no HVAC systems are present.

Anteroom (This definition applies to APF Anterooms only, and supersedes descriptions within other DRM chapters.)**:** A room that is used for donning/doffing personal protective equipment (PPE), and is often combined with an airlock function, and/or accommodates pass throughs and/or observation windows due to its proximal relationship to higher and lower ISO classified spaces. A room proximate to a manufacturing or compounding space, which is entered prior to the clean space; often an airlock.

APF Spaces: For the purposes of DRM Chapter 13, the sequence of spaces shall be considered:

1. **Building:** NIH owned or leased biomedical research and research support structure, as described per the NIH Facility Information Management System (FIMS).
2. **Facility:** A division of a building; the area within the boundary of the APF, its support and the mechanical and electrical rooms supporting the APF. Facility access shall be controlled per NIH Policy Manual Chapter 1406

Figure 13.1.3 Airlock Configurations



- Access to Manufacturing and Compounding for Human Administration Areas in NIH Facilities. The boundary of a facility is often not congruent.

3. **Suite:** A division of a facility. Each APF is comprised of one or more zones which may operate independently of one another to accommodate cleaning, maintenance, or production needs. Each of those rooms, or clusters of rooms is referred to collectively as a suite.

4. **Room:** A division of a suite enclosed by walls, floor, and ceiling.

Aseptic: Aseptic, is free from gross (i.e., visible to the unaided-eye) contamination, is regularly cleaned with appropriate materials, and techniques to inert and remove pathogenic microorganisms, leaving films of product which retard future biological activity. Aseptic areas shall be part of the environmental monitoring plan. Compare with "Clean."

Aseptic Processing: A process by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave). Literally, processing without addition of microbial contamination.

Aseptic Production Facility (APF): Facilities which produce drug and/or biologic products for human injection, implantation, ingestion, inhalation, or absorption. This includes facilities where non-aseptic products are produced using aseptic practices.

At-Rest (Static): A cleanroom which is complete with all services functioning and with production equipment installed and capable of being operated or operating, as specified, but without operating personnel within the facility.

Basis of Design (BOD): See Section 1.3. Additionally, this document begins to be authored during predesign and is progressively updated through design up to project closeout.

Beyond-use date (BUD): The date or time after which a Compound Sterile Preparation (CSP) cannot be stored, transported or used and must be discarded. The date or time is determined from the date or time when the preparation was compounded.

Biological Safety Cabinet (BSC): A ventilated cabinet with unidirectional HEPA-filtered supply airflow and HEPA-filtered exhaust to protect workers from hazardous materials and maintain the cleanliness (asepsis) of product and process. A BSC is used to prepare a Compounded Sterile Preparation (CSP) and must be capable of providing and maintaining an ISO Class 5 environment or better.

Biologics: A biologic drug (biologics), produced from living organisms, or contain living organisms. Biologics include a wide range of products such as vaccines, blood and blood components used for transfusion and as a raw material for drug products, diagnostic and therapeutic allergenic extracts, cellular and tissue-based products (HCT/Ps), gene therapy, tissues (except vascularized organs for transplantation), recombinant therapeutic proteins, and vaccines for use in humans. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are produced in APFs.

Bubble Airlock: An airlock configuration having a higher pressure inside the airlock to lower pressure on the outsides. This retards the flow of air between the adjacent rooms through the airlock by creating a high-pressure barrier. See Cascade Airlock, Sink Airlock, and Figure 13.1.3.

Buffer Area: An ISO Class 7 (or ISO Class 8 if using an isolator) or cleaner area where the Primary engineering control (PEC) that generates and maintains an ISO Class 5 environment is physically located.

Calibration: The act of comparing an instrument of unknown accuracy with a standard of known accuracy to detect, correlate, report, or eliminate by adjustment any variation in the accuracy of the tested instrument. The periodicity of re-calibration of each facility instrument must be delineated in the URS unless a calibration program standard operating procedure (SOP) exists for that facility.

Calibration Management: The facility program within NIH APFs, whose purpose is to ensure that any measuring or detection instrument or system that monitors conditions that have a direct or indirect impact on

product quality, safety, purity and efficacy is operating within its specified accuracy and tolerance. Typically, this includes temperature, humidity, and differential pressure, but may include others on a site-by-site basis.

Cascade Airlock: An airlock configuration having a higher pressure on one side of the airlock to lower pressure on the other side of the airlock. This retards the flow of air between the adjacent rooms through the airlock where the dusts and other contaminants are of a primary concern in a single direction. See Bubble Airlock, Sink Airlock, and Figure 13.1.3.

Classified Space: Areas where HVAC systems are specifically designed to reduce airborne contaminants below a specified level (as defined in ISO classes) and both temperature and relative humidity (RH) are controlled more tightly than in the ambient environment. These areas must be performance verified/qualified. ISO Classification:

1. **Temperature Controlled:** Areas where HVAC systems are specifically designed to control both temperature and (where applicable) Relative Humidity (RH) more tightly than in the ambient environment. Temperature and RH are typically qualified in these areas and temperature mapping is expected. This designation is typically found in warehouse spaces, cold rooms, and logistics support spaces.

2. **Uncontrolled (UC):** Areas where the HVAC systems may be present, but no claim is made or qualified for the specific control of particulate, temperature or humidity. These areas are sometimes referred to as "General" or "Comfort Controlled" areas within pharmaceutical facilities such as offices and technical spaces. May also be designated "Not Controlled (NC)".

3. **Controlled Not Classified (CNC):** Areas where HVAC systems are specifically designed to reduce airborne contaminants below the level of the ambient environment and both temperature and Relative Humidity (RH) are controlled more tightly than in the ambient environment. Qualification is common. No claim is made or qualified for the specific control of particulate. Typical systems will have heating, cooling and filtration meeting MERV 13 or better.

4. **Controlled Not Classified with Local Monitoring (CNC+):** These areas are typically qualified to meet ISO 8 requirements at rest only, to control temperature and humidity within a specified band. These areas are generally aligned with PIC/S designation "Grade D."

5. **Class-8:** A classified space that satisfies the Food and Drug Administration, United States Department of Health and Human Services (FDA) requirements for ISO 8 measured via airborne 0.5µm particulate in the "in-operation" state, as well as EMA and PIC/S requirements to meet ISO 8 measured via airborne 0.5µm and 5.0µm particulate in the "in-operation" state and meet ISO 7 measured via airborne 0.5µm and 5.0µm particulate in the "at-rest" state.

6. **Class-7:** A classified space that satisfies FDA requirements for ISO 7 measured via airborne 0.5µm particulate in the "in-operation" state, as well as European Medicine Agency (EMA) and Pharmaceutical Inspection Cooperation/ Scheme (PIC/S) requirements to meet ISO 7 measured via airborne 0.5µm and 5.0µm particulate in the "in-operation" state and meet ISO 5 measured via airborne 0.5µm and 5.0µm particulate in the "at-rest" state.

7. **Class-5:** A classified space that satisfies FDA requirements for ISO 5 measured via airborne 0.5µm particulate in the "in-operation" state, as well as EMA and PIC/S requirements to meet ISO 5 measured via airborne 0.5µ particulate and ISO 4.8 measured via airborne 5.0µ particulate in the "in-operation" and "at-rest" states.

Clean: Clean indicates a condition which is free from gross contamination upon visual inspection and regularly cleaned with appropriate materials, and techniques to retard biological activity. Clean areas may be part of the environmental monitoring plan. Compare with "Aseptic."

Clean Corridor: A design element in APFs, within the facility, where properly gowned persons can traverse between various areas, typically starting at the main entry of the suite. The clean corridor is principally used to provide a unidirectional flow within the facility.

Within the clean corridor, air quality is specified and monitored, and it is included in the EM plan. Contrast with "Return Corridor."

Cleanroom: A specially constructed room in which the air supply, air distribution, filtration of air supply, materials of construction, and operating procedures are regulated to control airborne particle concentrations to meet appropriate cleanliness levels and other relevant parameters (i.e., temperature, humidity, pressure, etc.) as defined in ISO classifications or any other regulatory entity.

Cleanroom Performance Testing (CPT): The act of evaluating the performance of a cleanroom by performing a series of defined tests with prescribed procedures and reporting requirements. The most common and critical of these are airborne particulate classification (certification) and monitoring.

Closed Process: A process condition when the product, materials, critical components or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment. A process step (or system) in which the product and product contact surfaces are not exposed to the immediate room environment. [*ISPE*]

Colony-Forming Unit (CFU): A unit used to estimate the number of viable (defined as the ability to multiply under controlled conditions) bacteria or fungal cells in a sample. Counting with colony-forming units requires culturing the microbes then counting only viable colonies. There is a certain, understood degree of uncertainty associated with this type of counting, as opposed to microscopic examination, which furnishes a total cell count (viable and non-viable cell count).

Commissioning: APF commissioning is a quality oriented process for verifying and documenting that the performance of facilities, systems and assemblies meets the objectives and criteria as defined in the Commissioning Master Plan.

Compound Sterile Preparation (CSP): A preparation intended to be sterile that is created by combining, diluting, pooling, or otherwise altering a drug product or bulk drug substance.

Compounding Aseptic Isolator (CAI): A type of physical barrier system (enclosure) that uses HEPA Filtration to provide an ISO Class-5 clean air environment, designed to give high sterility assurance for the aseptic compounding of sterile drugs. A CAI must provide a high-integrity material transfer component; provide an automated sporicidal decontamination system, and maintain a significant overpressure to the surrounding environment. Operator access into a CAI is usually via fixed gloves integrated into the wall of the unit.

Compounding Aseptic Containment Isolator (CACI): A type of Compounding Aseptic Isolator, designed for the compounding of sterile hazardous drugs. A CACI is similar to a CAI, but may not be positively pressurized to the surrounding room and may possess other features (e.g., transfer airlocks) to minimize the release of drug or drug products into the surrounding environment.

Contaminant: Any particulate, molecular, non-particulate and biological entity that can adversely affect the product or process.

Contamination: Adulteration of a product by the introduction of impurities of a chemical or microbiological nature or, foreign matter, into or onto, a starting material or intermediate, during production, sampling, packaging, repacking, storage and transport. Contamination poses a significant risk to patient and worker safety. The design, construction, operation and maintenance of APFs are intended to lower the likelihood of the occurrence of contamination.

Critical Component: A component within a system where the operation, contact, data, control, alarm, or failure may have a direct impact on product quality or the ability to know product quality. [*ISPE*]

Critical Location: The location where the product is exposed and/or the location where a cleaned product contact surface is exposed.

Critical Process Parameter (CPP): A process parameter whose variability impacts a quality attribute and therefore needs to be controlled to ensure the process produces the desired quality. [*ISPE*]

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality. [*ISPE*]

Cross-Contamination: Contamination of a starting material, intermediate product, or finished product by another material or product.

Dead Band: A setpoint range established to prevent unintended system reaction, such as simultaneous heating and cooling.

Design Qualification: Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose. See Section 13.16.4. [*ISPE*]

Design Target: A value for a critical parameter that is more conservative than its acceptance criterion, used by designers to assure that the system is capable of meeting the acceptance criterion. Design Targets should not be used for system qualification; they are aspirational values that may not be achieved in reality. [*ISPE*]

Differential Pressure (ΔP): The difference between two pressures measured between a sample point and reference point.

Dilution Ventilation: Reduction in airborne contamination via mixing of clean incoming air with contaminated air within the room and removal of an equivalent amount to exhaust or recirculation via treatment (e.g., filtration).

Direct Impact System: A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with Good Engineering Practice and also are subject to Qualification Practices that incorporate the enhanced review, control and testing against specifications or other requirements necessary for GMP compliance. [*ISPE*]

Disinfecting Agent: A chemical agent that destroys vegetative forms of harmful microorganisms (such as bacteria and fungi) but that may be less effective in destroying spores. Disinfecting agents kill/inert 100% of the bio-active particles on the surface (may require pre-cleaning), including 100% of vegetative bacteria, target viruses and target fungi. The efficacy of the agent is dependent on concentration, time, temperature, surface characteristics, and the bioburden present on the surface.

Displacement Ventilation: Reduction in airborne contamination via "plug flow" of clean incoming air forcing contaminated air within the room to exhaust or recirculation via treatment (e.g., filtration).

Drug: A drug is a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and intended to affect the structure or any function of the body of human or animal, but not a device or component, or accessory of a device. Drugs are manufactured in APFs.

Dynamic Conditions: Testing performed simultaneously with real or simulated operational activities, including garbing, people, and processes.

Excipient: A pharmacologically inactive substance formulated alongside the active pharmaceutical ingredient of a medication, included for the purpose of long-term stabilization; for bulking up solid formulations that contain potent active ingredients in small amounts; or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity, or enhancing solubility.

Exit/Return Corridor: A design element in unidirectional APFs where properly gowned persons can traverse between various areas within the facility, typically starting at the exit of the processing rooms/anterooms, continuing to the exit. The exit/return corridor is principally used to provide a unidirectional flow within the facility and provides a route to equipment rooms, freezer rooms, waste collection areas, etc., then back to the entrance to the suite for reentry, with appropriate donning/doffing of PPE as required by SOP. Within the exit/return corridor, air quality may be specified, monitored, and included in the EM plan.

Facility Critical Parameter: A room variable, such as temperature, humidity, air changes, room pressure, viable/non-viable particle counts, etc. that can negatively impact product production or storage.

Failure Mode and Effects Analysis (FMEA): A procedure for reliability analysis intended to identify failures, at the basic component level, which has significant consequences affecting the system performance in the application considered. [*IEC & ISPE*]

First Air: Undisrupted airflow coming directly from a HEPA filtered source into a room, whether by the supply air system, or a HEPA-filtered recirculation system. It specifically excludes transfer air and exhaust air.

Filter Integrity Test: A test to identify very fine leaks within HEPA filters, performed by injecting a challenge aerosol of fine particles (usually Poly Alpha Olefin – PAO) upstream of the filter media, measuring the downstream concentration of the particulate across

each square inch of the filter face and calculating the penetration to determine if that square area meets or exceeds a target penetration. Consistent with FDA recommendations, the target penetration shall be less than 0.01%.

Good Clinical Practice (GCP): An international quality standard that is provided by ICH, an international body that defines a set of standards, which governments can then transpose into regulations for clinical trials involving human subjects.

Good Documentation Practice (GDP): A term used to describe standards by which documents are created and maintained. While some GDP standards are codified by various regulations, others are not, but still considered part of a cGMP Quality Management System. GDP, enable communications of intent and consistency of actions (ISO 9000: 2000).

Good Engineering Practice (GEP): Established engineering methods and standards that are applied throughout a project's life-cycle to deliver appropriate, cost-effective solutions. [*ISPE*]

Good Laboratory Practice (GLP): A set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies.

Good Manufacturing Practice (GMP): A system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Good Practice (GxP): GxP is a generally, summary term which serves as an abbreviation for "Good Practice." In APFs, the term GxP is related to Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), Good Tissue Practice (GTP), Good Documentation Practice (GDP), and Good Engineering Practice GEP). In many cases, the full detail of the individual GxPs is detailed in statures, regulation, and/or guidelines.

GxP Harmonization Analysis: The process by which the totality of GxP affecting a given facility (statutes, regulations, standards, and guidelines) are reviewed; conflicts identified; and, with appropriate risk analyses, a resolution to those conflicts are determined, and documented. The analysis must include a narrative describing how each determination was made. The most restrictive condition shall prevail.

GxP Environment: A term that describes the totality of the regulatory environment for a facility, including, but is not limited to adherence to applicable:

- Statutes, Regulations, Standards and Guidelines
- Regulatory Agency Guidance
- Regulatory Citations (e.g., FDA 483s)
- Good Engineering Practice (GEP)
- Good Manufacturing Practice (GMP)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Good Documentation Practice (GDP)

Grandfathering: A concept that is typical in design and construction codes, wherein new codes, when promulgated, are enforceable on new construction, and are not retroactively enforceable on existing building stocks. Grandfathering does not exist in cGMP environments, where, compliance with the "current" best practices and GxP regulatory environments are mandatory.

Hazardous Drug: Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing hazardous drugs in structure or toxicity.

ISO Class: An air quality classification from the International Organization for Standardization, per ISO 14644-1 standards, which specify the cleanliness of spaces by airborne particulate via decimal logarithm of the number of particles 0.1 µm or larger permitted per cubic meter of air.

Laminar Airflow Workbench (LAFW): A cabinet that provides an ISO Class 5 or better environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow across the work area.

Media Fill Test: A simulation used to qualify processes and personnel engaged in sterile compounding to ensure

that the processes and personnel are able to produce sterile CSPs without contamination.

Microbial Contamination: The presence of microorganisms in, or on, an item.

Minimum Efficiency Reporting Value (MERV): the ASHRAE 52.2 method of testing filter efficiency by challenging filters with particles of multiple sizes and integrating the efficiency into a single number rating. The higher the MERV number the more efficient the filter. MERV 14/15 is approximately equivalent to a 95% (ASHRAE 52.1) efficient filter.

Non-Unidirectional Airflow Cleanroom: Air distribution where the supply air entering the clean zone mixes with the internal air by means of induction.

Occupancy State(s): Three conditions of various stages of testing of a cleanroom: As-Built, At-Rest, and Operational.

Operating Range: The validated acceptance criteria within which a control parameter must remain, wherein acceptable product is being manufactured. [*ISPE*]

Operational Facility: A cleanroom which is complete with all services functioning, and with production equipment installed and operating under normal conditions with all operating personnel present.

Pass Through: An enclosure with seals on interlocking doors that are positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.

Particle: A solid or liquid object which, for purposes of classification of air cleanliness, has a threshold (lower limit) size of 0.5 microns (µm).

Particle Count: Concentration expressed in terms of the number of particles per unit volume of air. Normally associated with the particles in the cleanroom or clean zone.

Particle Generation Rate: The number of particles of a specified size range released into a room (per hour) by processes, people, or in the supply air.

Phase I Clinical Trial: A clinical trial that uses a small group of patients and looks at the highest dose of the new treatment that can be given safely without serious side effects. It is the safety aspect of the trial.

Phase II Clinical Trial: A clinical trial that uses a larger group of patients to provide more information about the treatment's safety and how well it works. This is the efficacy phase of the drug trial.

Pharmaceutical Inspection Co-operation Scheme (PIC/S): PIC/S is the abbreviation and logo used to describe both the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) operating together in parallel.

Primary Engineering Control (PEC): A device or zone that provides an ISO Class 5 environment for sterile compounding. This terminology may also be used for process closure or other technology which excludes contaminants from the product.

Piping and Instrumentation Diagram (P&ID): Detailed diagrams which describe systems, and schematically indicates the configuration of the system and its components. The diagram indicates physical characteristics, such as pipe size, valves, equipment, etc. It also indicates the sensors, instrumentation, and control functions or interlocks.

Process Diagrams:

1. **Block Flow Diagram (BFD):** These diagrams are developed early in the project planning process to schematically depict the intended flows of the intended processes for the facility. The blocks describe different equipment or operations which are connected by directional input and output streams that describe the intended function of a facility. Critical information about unique processes should be noted. This document is subject to review and sign-off.

2. **Process Flow Diagrams (PFD):** Subsequent to the BFD, and represents a significant advance in detail and specification over the prior document. All major pieces of equipment shall be represented on the diagram, each with a unique identifier and descriptive name. All process streams shall be shown and identified by number. Basic control loops, illustrating the control strategy shall be shown. Integral to the PFD package is a narrative process description and equipment descriptions. This is a complex document that will be integral to the design process, updated and resubmitted along with

all design submissions after 50%. This document is subject to review and sign-off, under document control. For additional information, see Section 13.3.9.

3. **Piping and Instrumentation Diagram (P&ID):** Each PFD may require multiple P&IDs, depending on complexity. These diagrams shall comply with ISA Standard ISA-S5-1. This is a comprehensive diagram which describes systems, and schematically indicates the configuration of the system and its components. The diagram indicates physical characteristics, such as pipe size, valves, equipment, etc. It also indicates the sensors, instrumentation, and control functions or interlocks. Only one operation is depicted on each diagram. This diagram will be updated to an as-built document and maintained throughout the life cycle of the project. This document is subject to review and sign-off, under document control.

4. **Material, Equipment and Personnel Flow Diagrams (MEPF):** These diagrams are a component of the URS, and must be regularly updated to reflect changes to the facility. These diagrams are to be single-process flow only. The number and subject of these diagrams will vary by facility. Diagrams may include, but not be limited to PPE Zones; and flows, such as Raw Material, Waste Material, Personnel, Equipment, Finished Product, etc. See Section 13.2.3.

Project Closeout/Handover: The demarcation between the construction phase and when the user initiates their Performance Qualification (PQ). This milestone is characterized by the facility acceptance of the documents and facility as described in Section 13.18, Project Closeout and Handover Phase.

Qualification: The process of determining that a specific system, facility and/or equipment is able to achieve the acceptance criteria as defined in the Validation Master Plan (VMP), documenting that it is fit/ready for intended use, and it conforms to design specifications. Commissioning + Enhanced Documentation = Qualification.

Quality Assurance (QA): A part of the Quality Control Unit (QCU) responsible for developing a system of procedures, activities, and oversight that ensures that operational and quality standards are consistently met. GMP QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, and (3) auditing and performing/evaluating trend analyses. APF QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, (3) auditing and performing/ evaluating trend analyses, and (4) review and approval of all proposed construction and maintenance work within APFs or on systems which support APFs to ensure ongoing under control operation of the facilities and conformance with GxPs.

Quality Control (QC): A part of the Quality Control Unit (QCU) responsible for implementing a system of procedures, activities, and oversight that defined by Quality Assurance, to ensure that operational and quality standards are consistently met. GMP QC usually involves (1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products; (2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release. APF QC primarily involves the review and inspection of construction and maintenance activities for conformance with the design requirements and work plans, approved in advance by the APF QA (FCIS).

Quality Control Unit (QCU): A synonym for the Quality Unit, sometimes used by the FDA.

Quality Unit: A group within an organization who is tasked by cGMP regulation with the responsibility and authority to create, monitor, and implement a quality system. Such activities do not substitute for, or preclude, the daily responsibility of manufacturing personnel to build quality into the product. Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the cGMP regulations, between quality control (QC) and quality assurance (QA) functions.

RACI Matrix: A matrix that defines who will do the work and be responsible for its completion (R) , who will remain accountable for the completion of the work (A), who will be consulted as the work is being progressed (C), and who should be informed of the work upon completion (I).

Range: The upper and lower limits of an instrument's ability to measure the value of a quantity for which the instrument is calibrated.

Record Documents: For APF projects, the DRM recognizes the AIA definitions of the following (See Section 13.18, Project Closeout and Handover Phase for additional description of non-drawing project record documents):

1. **As-Designed Record Drawings:** Record of everything the Architect and Engineer(s) designed for the Project, and includes the original Construction Documents plus all addenda, Architect's Supplemental Instructions, Change Orders, Construction Change Directives and minor changes in the work – typically a full set of editable CAD files and PDF files of each sheet.

2. **As-Constructed Record Drawings:** Record of the Project as constructed based on information the contractor provides to the Owner/ Government under the contract for construction - typically color scan of the contractor's field set with all markups.

3. **Record of the Work As Constructed Drawings:** Record of the Project as constructed based on information the Contractor provides to the Owner Government under the contract for construction coupled with re-survey by the Architect and Engineer(s) – typically a full set of editable CAD files and PDF files of each sheet, BIMs; editable MS Word and indexed PDF files of the BOD and specifications.

Recovery: A test defined in ISO 14644-3 that challenges room environmental performance by measuring the time required for contamination to reduce by a stipulated amount, generally one or two log, after the particle generation in the space ceases.

Restricted Access Barrier System (RABS): A type of physical barrier enclosure for aseptic processing or compounding of sterile drugs. A RABS is similar to a CAI, but may return air to the room without internal recirculation and lacks a gaseous decontamination system. The term "open RABS" refers to a RABS where air is returned to the room, while a "closed RABS" employs primarily internal recirculation as is more similar to a CACI. Operator access into a RABS is usually via fixed gloves integrated into the wall of the unit. The background for a RABS should meet ISO 7 "in-operation".

Risk Assessment (RA): Risk assessment is a process conducted to identify and mitigate risks to the product. Risk assessments shall be performed in accordance with ICH Q9, "Quality Risk Management," using appropriate procedures, facilitators, and structured tools. The assessment shall be limited to cGMP compliance risks associated with the facility design/construction, including personnel, equipment, and material movement, etc. Every step in the processes shall be reviewed for susceptibility, to contamination and cross-contamination. See Section 13.2.3.

Risk assessment is initially provided by the user under Statement of Requirements (SOR) during the predesign phase which are later developed into a facility design/ construction risk assessment during the design phase. Risk assessments are then performed throughout the life cycle of the project/facility, as needed. Risk assessments become separate, signed, change controlled documents upon acceptance. These Risk Assessments will be reviewed and revised, as required by SOP.

Risk Management: Per ICH Q9, systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk, or similar methodology.

Sanitizing Agent: An agent that reduces the viability of bacteria, viruses, and fungi by killing/inerting >99.9% of bio-active particles remaining on the surface after pre-cleaning. The efficacy of the agent is dependent on concentration, time, temperature, surface characteristics, and the bioburden present on the surface.

Sink Airlock: An airlock configuration having lower-pressure inside the airlock to higher pressure on the outsides. This retards the flow of air between the adjacent rooms through the airlock by creating a low-pressure barrier. See Bubble Airlock, Cascade Airlock, and Figure 13.1.3.

State of Control: Describes the condition where the direct and indirect impact processes, equipment and facility are operating with stability, and within the ranges specified in the URS, and in a manner which maximizes the probability that the product being produced will meet all quality requirements.

Static Conditions: Testing performed without real or simulated operational activities (see "at-rest").

Sterilizing Agent: An agent that kills/inerts 100% of the bio-active particles, including all microorganisms and spores, on the surface after pre-cleaning. The efficacy of the agent is dependent on concentration, time, temperature, surface characteristics, and the bioburden present on the surface.

Subject Matter Expert (SME): A person who is an authority in a particular subject, possessing in-depth knowledge and understanding of the subject based upon their education, training, and experience, and an awareness of the history and current technology trends, issues and research in that subject.

Testing, Adjusting, and Balancing (TAB): TAB is a systematic process or service applied to heating, ventilating and air conditioning (HVAC) systems and other environmental systems to achieve and document air and hydronic flow rates. The periodicity of re-TAB shall be described in the URS.

Transfer Air: Air movement, through door opening cycles, leakage of door seals or around penetrations, via transfer grills, or other means. Transfer air is not to be used in the calculation of air change rates in APF, even if the source room is of equal or greater classification to the room the air enters.

Training Records: Documentation of who was trained, when they were trained, the mastery of the training that they have demonstrated, who trained them, the duration of the training currency, and a copy of all training materials used in that training.

Unidirectional Airflow: Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines.

User Requirement Specification (URS): A document that describes the project requirements and acceptance criteria for a facility. The URS describes process and system flows, as well as warning and alert values for environmental constraints. This document is authored during predesign and progressively updated through the life cycle of a facility to be current. This document is subject to change control.

Validation: Establishing documented evidence that a process or system, when operated within established parameters can perform effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes. Validation is establishing documented evidence to provide a high degree of assurance that a specific system, process or facility will consistently produce a product meeting its predetermined specifications and quality attributes. [*ISPE*]

Validation Master Plan (VMP): A user-initiated, multidisciplinary document which creates the structure for the quality management process, including all validations required to open and operate an APF. It shall identify processes and equipment to be validated, the schedule of their performance/time constraints, and the periodicity or conditions for required revalidation. The VMP should establish the philosophy, intentions, and approaches for establishing validation adequacy, as well as requirements for execution and reporting. The VMP shall be reviewed not less than annually, and the plan for that review shall be incorporated into the VMP. The VMP shall take into account all applicable regulations, codes, guides, SOPs, GDP, and GMP. This document is subject to review and sign-off, under document control. See Section 13.16.2.

Vector: In molecular cloning, a vector is a DNA molecule used as a vehicle to artificially carry foreign genetic material into another cell, where it can be replicated and/or expressed.

Work Zone: An area within the cleanroom which is designated for clean work and for which CPT is required. The work zone shall be identified by an entrance and exit plane normal to the airflow (where there is unidirectional airflow).

13.1.4 Abbreviations

The following list of abbreviations is provided for the benefit of the reader.

A

ACH – Air Changes per Hour

AFT – Airflow Test

AHRI – Air Conditioning, Heating & Refrigeration Institute

APD – Airflow Pressure Differential Test

APF – Aseptic Production Facility

APT – Airborne Particle Test

AQM – Air Quality Monitoring

ASME – American Society of Mechanical Engineers

AVS – Airflow Visualization Study

AZM – Auto Zero Modules

B

BAS – Building Automation System

BEA – Business Essential Attributes

BFD – Block Flow Diagram

BOD – Basis of Design

BSC – Biological Safety Cabinet

BSS – Basic Safety Standards

BUD – Beyond-use Date

C

CA – Compressed Air

CACI – Compound Aseptic Containment Isolator

CAI – Compounding Aseptic Isolator

CAPA – Corrective and Preventative Action

CAS – Coating Application Specialist

CCTV – Closed Circuit Television

CBER – Center for Biologics Evaluation and Research

CD – Construction Document Phase

CDER – Center for Drug Evaluation and Research

CETA – Controlled Environment Testing Association

CFR – Code of Federal Regulations

CFU – Colony-Forming Unit

cGMP – Current Good Manufacturing Practice

CIP – Coating Inspector Program

CIP – Clean-in-Place

CIT – Cleaning Integrity Test

CMMS – Computerized Maintenance Management System

CMP – Commissioning Master Plan

CNC – Controlled Not Classified

CNC + – Controlled Not Classified with Local Monitoring

CO – Contracting Officer

CO_2 – Carbon Dioxide

COR – Contracting Officer Representatives

C-PEC – Containment Primary Engineering Control

CPP –Critical Process Parameter

CPT – Cleanroom Performance Testing

CPVC –Chlorinated Polyvinyl Chloride

CQ – Construction Qualification

CQA – Critical Quality Attribute

CQM – Certified Quality Manager

CQP – Construction Quality Plan

CQV-PM – Commissioning, Qualification, and Validation Project Manager

CSA – Critical Safety Attributes

C-SCA – Containment Segregated Compounding Area

CSP – Compounded Sterile Preparation

CSV – Computer System Validation

CUP – Central Utility Plant

CV – Cleaning Validation

Cx – Commissioning

D

DCS – Distributed Control System

DD – Design Development Phase

DEP – Division of Environmental Protection

DFM – Division of Fire Marshall

DFOM – Division of Facilities Operations and Maintenance

DHHS – Department of Health and Human Services

DOP – Dioctyl Phalate

dP – Differential Pressure

DQ –Design Qualification

DTR – Division of Technical Resources

DVR – Digital Video Recorder

E

E-ACR – Effective Air Change Rate

EF – Exhaust Fan

EM – Environmental Monitoring

EMA – European Medicine Agency

EMS – Environmental Monitoring System

EMT –Electric Metallic Tubing

EU – European Union

F

FAT – Factory Acceptance Test

FCIS – Facility Compliance and Inspection Services

FD&C Act – Federal Food, Drug, and Cosmetic Act

FDA – United States Food and Drug Administration

FDCA – The Federal Food, Drug and Cosmetic Act

FFU – Fan-filter Unit

FGI – Facility Guidelines Institute

FIMS – Facility Information Management System

FIT – Filter Integrity Test

FM –Factory Mutual Global

FMEA – Failure Mode and Effects Analysis

FPE – Fire Protection Engineer

FRP – Fiber-Reinforced Plastic

G

GCP – Good Clinical Practice

GDP – Good Documentation Practice

GEP – Good Engineering Practice

GFI – Guidance for Industry

GLP – Good Laboratory Practice

GMP – Good Manufacturing Practice

GxP – Good Practice

H

HD – Hazardous Drugs

HDPE – High Density Polyethylene

HMI – Human Machine Interface

HVAC – Heating, Ventilation and Air Conditioning

I

IEST – Institute of Environmental Sciences and Technology

IPM – Integrated Pest Management

IPT – Integrated Project Team

IQ – Installation Qualification

ISO – International Standards Organization

ISPE – International Society of Pharmaceutical Engineers

IV – Intravenous

K

KPI – Key Performance Indicator

L

LAFW – Laminar Airflow Workbench

LAN – Local Area Network

LEED – Leadership in Energy and Environmental Design

LN2 – Liquid Nitrogen

LOD – Line of Demarcation

LUT – Lighting Uniformity Test

M

MEPF – Material, Equipment and Personnel Flow Diagrams

MERV – Minimum Efficiency Reporting Value

MPPs – Manual of Policies and Procedures

MUS – Modular Unit System

N

N2 – Nitrogen

NEC – National Electrical Code

NEEB – National Environmental Balancing Bureau

NRC – Nuclear Regulatory Commission

O

O&M – Operation and Maintenance

O2 – Oxygen

OA – Optional Attributes

OA – Outside Air

OOS – Out-of-Specification

OQ – Operational Qualification

ORF – Office of Research Facilities

ORSC – Office of Research Support and Compliance

P

P&ID – Piping and Instrumentation Diagram

PAO – Poly Alpha Olefin

PdM – Predictive Maintenance

PEC – Primary Engineering Control

PEM – Project Execution Manager

PEP – Project Execution Plan

PET – Positron Emission Tomography

PFD – Process Flow Diagrams

PgMP – Program Managements Professional

PHSA – Public Health Service Act

PI – Product Information

PIC/S – Pharmaceutical Inspection Cooperation / Scheme

PLC – Programmable Logic Controller

PM – Project Manager

PM – Preventive Maintenance

PMI – Project Management Institute

PMI-RMP – PMI Risk Management Professional

PMP – Project Management Professional

PO – Project Officer

POR – Program of Requirements

PQ – Performance Qualification

PVMP – Project Validation Master Plan

Q

QA – Quality Assurance

QC – Quality Control

QCU – Quality Control Unit

QP – Qualification Plan/Protocol

QRM – Quality Risk Management

QVxA – Qualification/Validation Authority

R

RA – Risk Assessment

RABS – Restricted Access Barrier System

RCA – Root Cause Analysis

RDS – Room Data Sheets

RH – Relative Humidity

S

SAT – Site Acceptance Test

SD – Schematic Design Phase

SEC – Secondary Engineering Controls

SLIA – System Level Impact Assessment

SME – Subject Matter Expert

SOP – Standard Operating Procedures

SOW – Statement of Work

SPD-2 – Surge Protection Device

SPT – Sound Pressure Test

SSPC – Society for Protective Coatings

T

TAB – Testing, Adjusting, and Balancing

TT&MT – Temperature and Moisture/Humidity Transmitters

TUT – Temperature Uniformity Test

U

UBC – Uniform Building Code

UC – Uncontrolled

UL – Underwriter's Laboratory

UMC – Uniform Mechanical Code

UPS – Uninterruptable Power Supply

URS – User Requirement Specification

USP-NF – The United States Pharmacopeia and The National Formulary

V

VE – Value Engineering

VFDs – Variable Frequency Drives

VGE – Variable Geometry Nozzle

VMP – Validation Master Plan

Vx – Validation

Section 13.2

Predesign Phase

Contents:

13.2.0 Introduction

This section outlines the processes and requirements that must be initiated from the pre-planning level of APF projects. The design must be obtained from concepts, parameters, and data outlined in the following sections of Chapter 13, in addition to those found in Section 2.1, Research Laboratory Predesign. Refer to DRM discipline-specific chapters for additional information.

13.2.1 Project Initiation

NIH requires a collaborative, integrated planning and design process that initiates and maintains an Integrated Project Team (IPT), per Section 1.8.2.1.1, in all stages of a project planning and delivery. The assembly of this IPT is initiated during predesign and continued through the design phase.

In addition to the stakeholders listed within Section 2.1.0, APF IPTs shall include the following additional internal and external stakeholders, as needed:

Internal Stakeholders:

- NIH Program Chief/Principal/Responsible Individual
- NIH Program Quality Assurance (QA) Office
- Office of Research Facilities (ORF) /Division of Technical Resources (DTR)/ Facility Compliance and Inspection Services (FCIS)
- Clinical Center/ Office of Research Support and Compliance (ORSC)

External Stakeholders:

- Subject Matter Experts (SMEs)
- Food and Drug Administration (FDA)/ Center for Biologics Evaluation and Research (CBER)
- Food and Drug Administration (FDA)/ Center for Drug Evaluation and Research (CDER)
- Other consultants added during this phase, as needed.

The APF project is initiated by NIH (including the user group and internal stakeholders) who define the Project Program (See Section 2.1.2, and the following APF product related specific requirements):

A. Objectives:

1. What is the product to be produced?
    a. Define the product(s) to be produced and the APF General Parameters (See APF Questionnaire, Exhibit 13.1).
    b. Define the initial state of control requirements, including facility Critical Process Parameters (CPP) and Critical Quality Attributes (CQA), such as required ISO levels, temperature and humidity to the extent known.
    c. What are the GxP regulatory parameters which must be satisfied? There may be more than one regulation that applies, which will need to be harmonized.
    d. What harmonization analyses are required?
    e. What feasibility studies are required?
    f. What risk analyses are required?
2. Objectives and acceptance criteria of the proposed facility/work to be performed.

B. Deliverables:

1. Narrative description of the project and objectives
2. Overview of the program, including major processes, equipment, personnel and material requirements
3. Feasibility and risk analysis studies, as required
4. Project Execution Plan (PEP), to be developed by the project officer (PO)/contracting officer's representative (COR), or PO/COR.

This initiative is led by the user group until the assignment of an NIH PO/COR to the project, and the delegation of certain authorities by the contracting officer (CO) to this individual. The PO/COR is thereafter responsible for leading the project through project initiation,

Predesign, Design, Construction, and through the Facility Validation phases, to the turnover of the facility to the Users and Facility Management.

C. End User Roles and Responsibilities: The End User (hereafter referred to as "user"), including their Institute and Center leadership initiate the APF project. Users shall be involved during the early stages of project definition, design, construction, commissioning, qualification, and validation. The main tasks for the End User include but are not limited to the following:

1. Develop the Statement Of Requirements (SOR), per Section 13.2.3.
    a. Generate a detailed equipment list.
    b. Support the Integrated Project Team (IPT) in the development of the User Requirement Specifications (URS), based on the SOR, per Section 13.2.3. See Section 1.8.2.1.1, Employ Integrated Design Principles.
2. Develop the Validation Master Plan (VMP) to support Qualification and Validation Activities.
    a. Support the IPT in the development of the Project Validation Master Plan (PVMP), based on the VMP, per Section 13.16.2.
3. Develop any risk assessments as required to support the SOR, URS, or VMP.
4. Act as the official Point Of Contact (POC) with the FDA for all correspondence and Type-C meetings, as required.
5. Provide review, comments, and sign-off on:
    a. Statement Of Work (SOW) packages for engaging SME, A/E, construction, and other services, as related to the APF project
    b. URS
    c. PVMP
    d. Basis Of Design (BOD)
    e. Design Drawings and Specifications
    f. Qualification protocols and testing
6. Approve and respect the "design freeze".
7. Take ownership of the facility once the project has been completed.

13.2.2 Data Collection (Predesign)

Data Collection is the process of assessing product, user, equipment, facility and project needs. The APF have requirements that exceed those outlined in Section 2.1.2.2, Exhibit 2.1 Research Facilities Program Questionnaire, and Appendix F, Room Data Sheets. These additional needs and requirements shall be captured and documented in the following ways:

A. Program Questionnaire: An APF-specific Questionnaire, See Exhibit 13.1, which includes the following sections:

1. General Parameters
2. Program Parameters
3. Regulatory Parameters
4. Standard Operating Procedures
5. Design Parameters
6. Material Flow Parameters
7. Personnel Flow Parameters
8. Safety & Security System Parameters
9. Mechanical System Parameters
10. Electrical System Parameters
11. Facility O&M Parameters

B. Room Data Sheets (RDS): APF-specific Room Data Sheet(s) (Exhibit 13.2) are developed during predesign; then updated at each design submission; and at the end of the design-phase becomes a signed, change controlled document. The RDS are updated and included with the project closeout documents.

C. Process Diagrams: Block Flow Diagrams (BFDs) are developed during predesign of new facilities, and are a precursor to Process Flow Diagrams (PFD). BFD are

developed by the user group and/or consultants during predesign to describe the relationship and processes of personnel, materials, waste, equipment, and other critical flows. At this stage, the diagrams shall not be architectonic but rather, simple diagrams where the principal functions and equipment are represented by blocks, connected by lines that show the relationships between the blocks. The diagrams are to be accompanied with notes that capture the step by step process flow of the items. These will be refined in later phases; however broad organizational philosophies should be established at this schematic design phase.

1. **Material, Equipment and Personnel Flow (MEPF) Diagrams:** In renovation projects of existing facilities, where the facility or portions of it remain operational during a renovation, the existing MEPFs (which are a part of the URS), shall be maintained as current, including updates of temporary conditions during construction. This may require multiple iterations, as the construction progresses (i.e., showing the flow impacts of temporary barriers, etc.).

D. GxP Harmonization: Typically, the GxP environment for a given APF is an amalgam of multiple Statutes, Regulations, Standards, Guidelines, and Codes, some of which may be extra jurisdictional. During predesign, a comprehensive list of all applicable requirements shall be developed, based on product and location of administration. ***This report becomes a signed, change controlled document upon acceptance.***

E. Equipment Schedule: The compilation of data on all equipment associated with the program, along with its associated requirements, shall be collected and documented via a schedule. Associated equipment requirements shall include measurement, clearances (for operation and service), utility needs, heat output, environmental requirements, etc. as well as, any unique requirements. Specific detailed equipment data (i.e., equipment cut sheet) will be required later, during the design phase, for use in the design of the suite/facility.

13.2.3 Documentation (Predesign)

This section describes specific documents which are initiated at the predesign phase of APF projects.

A. Project Execution Plan (PEP): The document that establishes the means for executing, controlling, and monitoring the progress of the project. The PEP is developed by the PO/COR, during Predesign, in consultation with the user group and other project stakeholders. The PEP includes the following:

1. Brief narrative description of the scope of the project(s) including design criteria
2. Project approach & execution
    a. Assigns critical responsibilities, supported by contracts and MOUs, as appropriate (a RACI matrix is typically employed for this task).
    b. Lists the members of the Integrated Project Team
    c. Review management: Lists of reviewers and schedule of reviews/documents to be reviewed
    d. Schedule of approvers per document
    e. Status reporting plan
    f. Progress document and data management plan
    g. Record management plan
    h. Change management plan
3. Project schedule
4. Project funding
5. Procurement and contracts strategy
6. Scope of services

The PEP shall be reviewed and approved by the User Group, ORSC and DTR/FCIS at the conclusion of predesign and prior to initiating design-phase activities. The PEP is a living document, and shall be maintained and updated as necessary throughout the life cycle of the project. See Exhibit 13.4, Aseptic PEP Checklist.

B. Statement of Requirements (SOR): Initiated by the user, clearly, concisely, individually, defines the facility requirements and acceptance criteria. Requirements

should be specific, measurable/testable, achievable, and realistic. Requirements that shall be addressed include, but are not limited to:

1. Regulatory requirements, including any GxP harmonization analysis.
2. Operational requirements:
    a. By whom and how the facility will be used
    b. PPE requirements
    c. Type of process
    d. Process description
    e. Cleaning procedures and validation
3. Functional requirements:
    a. What the facility will do
    b. Functions that the facility must perform
    c. Level and type of activity
4. Technical requirements for specific systems:
    a. HVAC
    b. Electrical
    c. Computer systems
    d. Gas systems
    e. Water
    f. Cx & Vx
    g. Environmental and equipment monitoring programs
    h. Interface requirements (i.e., what systems need to be interfaced to, such as sensors to BAS)
    i. Security requirements
    j. Maintenance/service accessibility requirements for mechanical equipment in classified space
5. Contamination and cross-contamination issues
6. Lab equipment
7. User's risk assessment

Requirements should include specific acceptable ranges, alert and warning levels.

Any changes to the Statement of Requirements shall be addressed under change control.

C. User Requirement Specifications (URS): This is a facility oriented document, based on the user's statement of requirements. Developed during predesign, the URS establishes and documents the user/project requirements as well as the acceptance criteria for an APF. During design and/or preliminary design development, the URS is used by the design engineers, to establish the required functions for each user specified item/requirement.

During predesign, the SOR is created by the end-user. At the beginning of the design phase, the SOR is expanded upon by the A/E design team to create the URS. At the end of design, the URS becomes a signed, change controlled document. The URS shall be updated and maintained current throughout the life cycle of the facility.

The end user shall be responsible for defining the quality critical requirements for the URS. This may include:

1. Temp for the product, process and worker comfort
2. Humidity for product, process, worker comfort, or microbial control
3. Air flow direction and differential pressure (dP) for contamination control, properties of expected airborne contaminants
4. Area classification: airborne particles, including viable and non-viable (i.e. ISO-14644)
5. Clean up (recovery) times from in-use to at-rest (classified spaces)
6. Process containment and exposure sites (high contamination risk areas)
7. Compressed gases
8. High purity water

The URS is the foundational document used in the development of the Basis Of Design (BOD), the Design itself, Design Qualification (DQ), and the Validation Master

Plan (VMP), inclusive of Installation Qualification (IQ) for installation, Operational Qualification (OQ) for functionality, and Performance Qualification (PQ) for operability.

NIH requires that a reviewed and approved URS describe the following information prior to the start of construction:

1. **Narrative:** Clear and concise narrative, describing the product, process and project
    a. Spatial requirements
    b. Environmental requirements (i.e., EM procedures)
    c. Security requirements
    d. Maintenance requirements
    e. Availability requirements (i.e., 24/7/365)
    f. Data requirements
    g. Constraints to be observed
2. **Critical Quality Attributes (CQA):** Attributes that could have a direct impact on the quality of the product being produced or processed, in the space or equipment. Quality attributes may affect the safety and/or efficacy of the product or processes. A quality attribute is a regulatory or compliance related attribute that can be measured/tested and will form the basis for qualification testing. Examples may include, but are not limited to:
    a. ISO Classification
    b. Differential Pressure
    c. Airflow Direction
    d. Temperature
    e. Relative Humidity
    f. Type of PEC
3. **Critical Safety Attributes (CSA):** Factors which could have a direct impact on the safety of the patients, employees, or the community at large. These attributes may also relate to cross-contamination protection of the product. A safety attribute is a regulatory or compliance related attribute that can be measured/tested and will form the basis for qualification testing. Examples may include, but are not limited to:
    a. Differential Pressure
    b. Airflow Direction
    c. Radiation Shielding
    d. Fire Protection
4. **Business Essential Attributes (BEA):** Attributes that have been identified by site operations, the business unit or the company as being essential, strictly from a business perspective. They define capacity parameters necessary to meet the production plan and will include facility engineering and environmental and personnel safety requirements that are necessary to support the facility. BEA requirements are typically tested during commissioning, but not tested during qualification.
    a. Output Requirements
    b. Schedule Requirements
    c. Budget Requirements
5. **Optional Attributes (OA):** Attributes that have been identified by the team as being desirable, but not essential. Optional attributes may increase the capability or life expectancy of capital equipment, or reduce the manpower required to operate a system. Those optional attributes that remain in the project will be qualified as if they could potentially become CQAs in the future or will be simply commissioned only if they will not.
6. **Process Diagrams:** The URS shall include the BFDs and MERFs at the predesign phase. As the design progresses, the PFDs, P&IDs, and updated MERFs shall be included. Updated PFDs, P&IDs, and MERFs shall be included. During the Operations and Management phase, the PFDs, P&IDs, and MERFs shall be updated as required, and kept current.

At Qualification/Validation of the facility, the URS document shall be reviewed for compliance and a

traceability document shall be developed to support the requirements stated in the URS.

13.2.4 APF Contractor Qualifications

The qualification of an APF is a regulatory requirement. A systematic qualification process for the individuals involved in the design, construction, commissioning, qualification, and validation of the facility is, therefore, a requirement.

Project-specific qualification requirements shall be included in the SOW for each contract. Not every contractor type, described below, will be required on every project; however, in general, it is recommended that the COR and CO develop appropriate language that stipulates a minimum level of experience in successful projects of similar scale, complexity and regulatory requirements within the prior 5 years, commensurate with the level of risk and complexity of the project being developed.

A. APF Team: For all APF projects, the Architects, System Integrators, Engineers, Construction Contractors, Commissioning Agents, Validation Agents, their consultants and subcontractors shall have the required education, training, experience, or any combination thereof, to perform their assigned functions in such a manner as to provide assurance that APF will be built, activated, operated, and maintained in a manner that meets the regulatory requirements for that facility.

B. A/E Design Team Qualification: To be deemed qualified, design firms must demonstrate a full working knowledge of process flow integration, cleanroom construction details, materials, and methods. Specifically, the design team must demonstrate a full understanding of the specialized, integrated HVAC design, BAS/EMS surveillance, system and facility qualification, validation, O&M of systems that create and sustain a regulated environment.

Senior design staff of every discipline shall be led by persons having not less than 5 years of experience (within the prior 10 years), in APF design and/or operation. The design lead shall be a member of ISPE, PDA or BPE and have a demonstrated understanding of aseptic/sterile processing, including workflows, prevention of mix-up and cross-contamination, cleanroom design, cleaning and gowning, qualification and validation.

At least one (1) member of the project design team engaged in the day-to-day project activities shall have demonstrated fluency with (as appropriate to the project):

1. 21 CFR 210, 211, 216, 600, 1271
2. Sections 501-503 of the Federal Food, Drug and Cosmetic Act
3. FDA Guidance for industry:
    a. "Sterile Products Produced by Aseptic Processing…"
    b. "Regulation of Human Cells, Tissues…"
    c. "Homologous Use of Human Cells…"
    d. USP 795, 797, 800, 823, 1046, 1047

C. Commissioning Agent/Authority (CxA): The CxA shall be an independent entity and should be engaged by the end of the schematic design phase. The CxA generally performs design review, development, and execution of the Cx Plan.

D. CxA Qualification: To be deemed qualified, the CxA shall:

1. Be independent of the project design and/or construction team.
2. At least one (1) member of the CxA team engaged in the day-to-day project activities shall have a minimum of 3-5+ years of experience in commissioning of APF HVAC systems, utility distribution systems, building automation systems, and troubleshooting of systems.
3. Demonstrate significant relevant commissioning experience, including technical and management expertise on APF projects of similar scope, size, and type.
4. Bring a total building commissioning perspective to the project.
5. Have field startup experience, controls and

understanding of multiple sequences of operations scenarios within an APF.

6. Demonstrate strengths in HVAC, Utility Distribution Systems, Building Automation Systems, and troubleshooting of interconnected systems within an APF.

7. Have documented commissioning process experience on projects of similar scope as the APF project that's being commissioned. The experience must extend from early in the design phase through post-occupancy.

8. Mechanical Engineer or other technical engineering degree is preferred.

9. CxA and/or LEED certification is beneficial.

E. Commissioning, Qualification, Validation (CQV) Authority: The CQV shall be an independent entity and shall meet the minimum requirements for Cx and Vx.

F. GMP Project Execution Manager (PEM): A contractor, generally engaged during the predesign phase, unaffiliated with the design or construction entities engaged in the project. A PEM is similar to an Owner's Representative and supports the PO/COR. The PEM shall assist the COR in overseeing the project, from inception to turnover. The PEM is differentiated from a Certified Quality Manager (CQM) in their enhanced role in strategic planning, and coordination between the various stakeholders within the project, as well as advising the PO/COR on APF-specific requirements. The PEM shall be responsible for:

1. Creating, maintaining schedule, including coordination between contractors.

2. Ensuring project documents are created and maintained per Good Documentation Practices (GDP) and in a timely manner.

3. Maintain the project Change Management process.

4. Review and comment on all project documents for completeness, correctness, fitness for intended purpose, and coordination.

5. Perform on-site inspections for the quality of workmanship and materials, conformity with plans and specifications, on-site safety, project schedule vs. progress.

6. Manage and document all project meetings.

7. Witness and document critical work being performed, including coordinating testing by the user group, CxA, QVxA, etc.

8. Other functions as identified by the COR in the PEM's SOW.

G. PEM Qualification: To be deemed qualified, the PEM shall:

1. Be able to demonstrate their familiarity with APF projects and the project's GxP requirements.

2. Shall have a combination of experience in the construction, activation and operation of APFs, and education training as deemed at least minimal for the tasks related to the specific project.

3. Should have a relevant master's or professional degree; Project Management Institute (PMI) certified as a Project Management Professional (PMP), minimum; Program Management Professional (PgMP) and/or PMI Risk Management Professional (PMI-RMP) preferred. A Senior Level FAC-P/PM shall be considered equivalent.

H. IDIQ Design/Build Contractors: The CO/COR shall stipulate in the SOW language that the teaming relationships conform to the A/E and Construction Contractor requirements of this section. It is not the intent to bar an inadequate IDIQ pool but shall require that the work is performed by qualified subcontractors. There is no waiver of the minimum self-performance requirement of the IDIQ-holder unless stipulated, in writing, by the CO.

I. O&M Contractor(s): Contractor shall be adequately trained in all relevant practices for proper cleanroom operation, maintenance, and in-process control. Training shall be documented and maintained as current. The responsibility for providing training shall be clearly defined in the SOW.

J. Qualification/Validation Authority (QVxA): The Qualification/Validation Authority should be engaged by the end of the schematic design phase.

K. QVxA Qualification: To be deemed qualified, the QVxA must demonstrate:

1. Significant relevant qualification/validation experience, including technical and management expertise on APF projects of similar scope, size, and type.
2. The QVxA performing the day to day work on the project must have documented commissioning experience on projects with a similar scope of work, specifically cleanroom certification tests in accordance with ISO 14644.
3. The QVxA shall have documented experience with performing IOPQ on facility systems including HVAC, compressed gases, and water systems. In addition, where applicable, QVxA shall have experience in PQ of environmental monitoring, and IOPQ's of various user equipment.

13.2.5 Deliverables / Document Review and Approval (Predesign)

There are many documents and processes that are specific to APF projects. Some of these documents are subject to validation (approved by signature from appropriate parties), and some are subject to review by parties above and beyond those specified in Section 1.5.3.3, NIH Technical Review Staff. Table 13.2.5, below, provides a typical framework for the documents associated with this phase, although there will be some facility and project specific variations, this table should be considered as general and informative, but not exhaustive or inclusive of the document requirements of a specific project. Those specific requirements should be developed during this phase and documented in the PEP.

13.2.6 Supplier Qualification

Supplier Qualification is a risk assessment tool within the quality system that establishes the minimum requirements to identify, select, approve and qualify suppliers of all materials and services utilized in the design, construction, validation, operations and maintenance of the APFs. The supplier of the goods or services must adequately document that the goods and services meet or exceed the minimum criteria that have been established and are fit for use for the described purpose. Audits may be a helpful tool to establish the legality, suitability and competence of the contractor to provide what has been contracted for. Third-party laboratory testing may be necessary to establish conformance to the requirements of the contract and applicable regulations.

Supplier qualification should include, but is generally a subset of the following for non-critical production materials, construction and operations materials, and services:

1. Review of the contract specification language
2. The supplier selection process
3. Review of product produced, its components, and documentation
4. Review of services to be provided, particularly the qualifications and training documentation of the personnel performing the work.
5. Sample evaluation
6. Due diligence process
7. Quality Assurance of all suppliers
8. Change control and production assessment as necessary
9. Supply chain of custody/security
10. Ongoing monitoring and evaluation

Table 13.2.5 APF Document Review and Approval (Predesign)

Document	Signed	Controlled	PO/COR	Per DRM Section 1.5.3.3	FCIS	ORSC	DFOM	NIH Program (User)	User QA	External Regulatory Agencies
Project Execution Plan			IRS		R	R		R	R	
Statement of Requirements (SOR)	•		R		R	RS		IRS	RS	
GxP Harmonization Report	•	•	R	R	RS	RS		IRS	RS	R
Feasibility Study Report(s)	•		IRS	R	RS	RS		RS	RS	R
Program Questionnaire			IRS	R	R	R		R	R	
User Requirement Specifications (URS)	•	•	R	R	RS	RS		IRS	RS	R
Room Data Sheets (RDS)			IRS	R	R	R		R	R	R
Process Diagrams: Block Flow Diagrams (BFD)			R	R	RS	R		IR	R	R
Equipment Schedule			R	R	R	R		IR	R	

I *Initiated By*
R *Reviewer*
S *Signatory*

Note: Unless indicated otherwise, PO/COR is responsible for the management of the above document(s).

Section 13.3

Design Phase

Contents:

13.3.0 Introduction

This section describes the additional design requirements associated with the transition from predesign, through the execution of design phase activities, inclusive of schematic design, design development, and construction document sub-phases. The design shall conform to Good Engineering Practice.

13.3.1 Schematic Design (SD)

A. Feasibility Study: A feasibility study is conducted to explore the viability of an idea and developed during the design. This study is an evaluation and analysis of a proposed project to determine:

1. Is the project technically feasible?
2. What are the facility risks for executing the project?
3. Does the proposed project fulfil the GxP requirements?
4. What would be the risks for operating the facility, if designed, constructed and operated as proposed?
5. Is the project feasible to be designed, constructed, commissioned, validated, operated and maintained as proposed, within the limitations of current schedule and budget?

The objective of the feasibility study is to provide a filtering of needs in a structured way without spending too much time or money on the project's viability/feasibility.

Options to explore include:

1. Site selection
2. Constructability assessment
3. Operations and maintainability review
4. Cost and schedule assessments
5. Objectives and acceptance criteria of the work (if not developed during predesign)

The list of conceptual design options should be specified to give the project team boundaries and to help define the time and effort required for the project.

13.3.2 Design Development (DD)

A. Data Collection (Design): The APF Data Collection requirement includes supplementary requirements to those found in Exhibit 2.1, Research Facilities Program Questionnaire. During the Design phase, initial data collection will be expanded, confirmed, modified, or redeveloped.

1. **Program Questionnaire:** Originally developed during Predesign, updated as required.
2. **Room Data Sheets (RDS):** Originally developed during predesign and, updated at each design submission. At the end of the design phase, the RDS becomes a signed, change controlled document. The RDS are updated and included in the project closeout documents.
3. **Process Diagrams:** Originally developed during Predesign, as simple Block Flow Diagrams (BFD), these shall be updated and expanded. An analysis of components, drug product containers, material, personnel, product and waste flows, are critical for detecting and minimizing crossed-paths to prevent contamination or mix-ups during operation. An approach for the smooth, efficient and safe flow of materials, waste, personnel, and product shall be developed at minimum, at the individual APF site; however, it may also be necessary to study these flows in a room, suite, facility, building level, wing, and/or whole building level.
4. **Process Flow Diagrams (PFDs):** These have additional detail, and narrative, and are overlaid upon the facility floorplan (showing walls, doors, windows, equipment, and furniture in sufficient detail to provide full context to the process being illustrated). The diagrams shall be accompanied by a narrative explaining the scientific work/process being illustrated. The following minimum PFDs are generally

required, but may vary depending on the facility:

a. Scientific Workflow

b. (Raw) Material Flows

c. Waste Material Flows

d. Finished Product Flow

e. Contamination Sources and Mitigation: Cross-Contamination Prevention Diagram

f. Personnel Flows

g. PPE Donning/Doffing Diagram

h. Equipment Flows

i. Basic Airflow Diagram including Critical Control Elements

j. Room Classification Map (ISO/CNC/NC)

k. Pressure and Airflow Direction Map

l. Airlock Arrangements

m. Access Control Diagram

The PFDs are updated and expanded throughout the design phase. At the end of the design phase, PFDs become signed, change controlled documents, maintained throughout the life cycle of the facility.

5. **Piping and Instrumentation Diagrams (P&ID):** These are a comprehensive diagram which builds upon and coordinates with PFDs to describe systems and components in detail. Each PFD may require multiple P&IDs, as only one operation is depicted on each diagram. At the end of the design phase, P&IDs become signed, change controlled documents, maintained throughout the life cycle of the facility.

6. **GxP Harmonization:** Originally developed during Predesign, updated as required.

7. **Quality Risk Management (QRM) Report:** QRM is a robust, structured process for:

   a. Risk Assessment

   b. Risk Control

   c. Communication

   d. Management of risks to the product being produced, spanning the life cycle of the facility.

   A formalized risk assessment shall be conducted to identify and mitigate risks to the product in accordance with ICH Q9, "Quality Risk Management," using appropriate procedures, facilitators, and structured tools. The assessment shall be limited to cGMP compliance risks associated with the facility design/construction, including flow of personnel and material, prevention of mix up, contamination mitigation, risks of aerosolization, handling of hazardous material, determination of ISO classification, engineering vs. administrative controls, environmental monitoring, flood damage, pest control, loss of utilities, loss of differential pressure, redundancy requirements, and appropriate preventative maintenance measures. Every step in the processes shall be reviewed for susceptibility to contamination and cross-contamination.

   Various methodologies are available, but the one selected for the project must support a scientific and practical approach to decision-making. The selected methodology shall provide documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk. Figure 13.3.2 describes a typical structure but is not reflective of all projects or APFs.

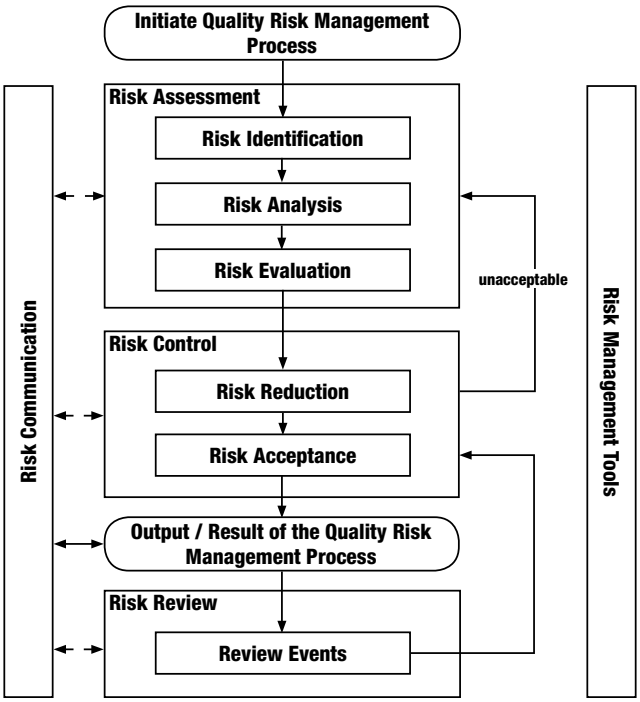
   One of the most frequently deployed methodologies for NIH APFs is Failure Mode Effects Analysis (FMEA). Under this methodology, potential failure modes for processes and likely effect on outcomes and/or product performance is evaluated; then risk reduction can be used to mitigate the potential failures. FMEA can be used to prioritize risks, monitor the effectiveness of the mitigation strategy, and be used as a basis for further analysis, changes to SOP, or additional facility modifications.

   The QRM shall organize the various Risk

Assessments into a single, cohesive report.

8. **Equipment Schedule:** Originally developed during Predesign, will be updated as required.

Figure 13.3.2 Risk Analysis Diagram (From FDA ICH Q9, Figure 1: Overview of a typical quality risk management process)



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative, or regulatory requirements but also to indicate that the risk assessment process should be revisited.

B. Basis Of Design (BOD): The BOD serves to document the parameters of the project, the design intent, and includes narratives, which explain and document all important requirements and decisions made during the design process. APF projects shall have a BOD, developed during the Design phase and progressively updated during design submissions. The BOD becomes a signed, change controlled document upon acceptance of the final design submission. The BOD shall be maintained throughout the life cycle of the project and any subsequent changes shall be under change control. This is in contrast with the URS, which shall be updated throughout the life of the facility.

The BOD establishes the basis for a detailed design and shall be well coordinated with the URS. In addition to the BOD report requirements found in Appendix E, A/E Submission Requirements, APF BODs should include the following additional information, but may vary depending on project-specific requirements, as determined by the COR:

1. System Design Narratives: Concepts on which systems are based, rationale and methodologies, and how BOD satisfies the URS.
2. System Equipment BOD Products (i.e. critical plumbing utilities, etc.)
3. System Level Risk Assessment:
    a. AHU Zone Map
    b. HVAC Control Philosophy
    c. Plumbing Diagram
    d. Electrical Diagram
    e. Fire Protection Diagram
    f. Low-Voltage Diagram
    g. Preliminary Sections of Critical Areas

C. Validation, Commissioning, and Qualification Documents: As described in Section 13.16, Facility Commissioning & Validation (Vx).

13.3.3 APF Design Considerations

In addition to organizational, operational, infrastructure issues encountered in the typical design process, additional factors, not limited to the following, shall be taken into consideration during APF design.

A. Multiple Product Production: A critical design decision in the planning of an APF is whether multiple products or a single product will be produced in the facility. If multiple products are to be produced, will this

production be campaigned or be concurrent?

1. **Campaigned Production:** Campaigned production is a production strategy which is characterized by a facility, suite, or room making a single product at a time, followed by a robust cleaning and, if required, equipment reconfiguration, prior to commencing production of the next sequential product. A strong Environmental Monitoring (EM) and Quality program are required to ensure adequate line clearance and cleaning efficacy have been met. Generally, this is the most restrictive multi-product strategy, by SOP, but carries the least risk. A risk analysis is required to substantiate the decisions associated with campaigned production.

2. **Concurrent Production:** Concurrent production is a production strategy which is characterized by suite(s), or room(s), each making different products at a time. SOPs are established for cross-contamination and mix-up risk mitigation and enhanced Environmental Monitoring (EM). This strategy carries a high demand on the HVAC and other facility systems to protect the products. A risk analysis is required to substantiate the decisions associated with concurrent production. The risk analysis should be iterative, in order to assure that identified mitigations are implemented and to verify that new risks have not been created by the design or construction.

B. Personal Protective Equipment (PPE) Requirements: Not later than during Schematic Design, a clear understanding of the gowning requirements and associated space needs for shelving, bench, full-length mirrors, waste containers, etc.

C. Cleaning Protocols: Not later than during Schematic Design, a clear understanding of the cleaning protocols and chemicals used to ensure selection of appropriate finish materials.

D. Environmental Monitoring System (EMS) and Building Management System (BMS): Not later than during Design Development, a clear understanding of the Environmental Monitoring System (EMS) and Building Management System (BMS) systems, including sensor compatibility, sensor co-location, and calibration strategy.

E. Mechanical, Electrical, Plumbing, and Fire Protection) MEP-FP Design Strategy: Equipment requiring servicing, piping, cabling, etc. should be minimized within classified spaces to avoid problems with adequate cleaning and mitigate risks associated with leakage and the disruptions caused by the entrance of DFOM for scheduled and unscheduled maintenance activities.

F. Modular Unit Systems (MUS): APF modular unit systems include both road-trailer-mounted pre-engineered and off-trailer variants. In both cases, the system manufacturer will assume the roles and responsibility of designer and builder. The review process for modular systems is the same as for conventional construction means and methods. APF that are developed via these methodologies are subject to Factory Acceptance Testing (FAT) and Site Acceptance Testing (SAT) following installation.

MUS facilities shall be modular, to facilitate future expansion or reconfiguration. To the extent practicable, they should be deployment ready when they leave the factory. Additionally, an APF MUS should have the following minimum characteristics:

1. **Minimum Structural Capacities & Requirements:** See Section 13.7.

2. **Minimum HVAC Capacities & Requirements:** Refer to Chapter 6 for general MEP requirements and Section 13.8 for APF-specific HVAC requirements.

3. **Supplemental MUS APF MEP Requirements:**

    a. MUS shall be capable of sustaining the URS indoor design conditions on a 24/7 basis.

    b. Where practicable, the MUS shall be connected to the campus chilled water loop.

    c. Where campus chilled water is not practical, n+1 redundant and dedicated air-cooled chillers and pumps shall be provided. AHU and exhaust fans shall be redundant.

    d. Where campus steam is not practical, n+1 redundant and dedicated boilers and pumps shall be provided. Gas boilers are preferred over electric.

e. MUS mechanical systems shall be capable of tying into the campus BAS system for monitoring, alarms, trend analysis and assist during maintenance and trouble-shooting. This includes both source (i.e., chillers, pumps, etc.) and distribution equipment, devices and sensors.

f. All sinks shall be tied-into the campus domestic water and sanitary waste loop (i.e., no tanks). If this tie-in requires disinfection or neutralization prior to discharge, that capacity will be integral to the MUS.

g. Eyewashes shall be mobile units with sealed water reservoirs in lieu of standard tank-type (which require chemical maintenance), or plumbed units, which require regular testing.

h. Compressed gases such as Nitrogen (N_2), Carbon Dioxide (CO_2), Oxygen (O_2) and compressed air, if required, will be provided via cylinder gases supplied from automatic cylinder change over manifolds. The cylinders shall be located in a ventilated and heated enclosure with proper access for replacing the cylinders.

i. AHUs, valves, dampers, terminal units, heaters, controls, etc. shall be located within the MUS, in areas that allow for serviceability from outside the cleanroom spaces. Provide adequate access to mechanical equipment to minimize downtime during repair. Proper service clearances shall be provided to and around equipment.

j. Main equipment (i.e., exhaust fan, pumps).

k. The MUS shall be configured to supply its emergency/standby power if required, to conform to the URS.

l. The inside and outside of the MUS shall be configured for digital video cameras and equipped with digital video recorder(s) (DVR).

4. **Other Supplemental Minimum Requirements:**

a. Minimum clear height should be not less than 2.4 m (8 ft.).

b. MUS design shall include all floor level change and weather enclosure requirements.

c. MUS shall not be installed in direct soil contact. The MUS should be installed on a prepared concrete slab, extending a minimum 1.5 m (5 ft.) beyond the face of the MUS in all directions, and/or elevated not less than 914 mm (3 ft.) above adjacent grade – which much be de-sodded, covered with washed 51 mm (2 in.) or larger gravel, over weed stopping geotextile fabric.

d. Road trailer-type MUS shall be based on gooseneck/King-Pin chassis (i.e., semi-trailer structure).

e. Non-Road trailer-type MUS shall be based on standard-size sea crates or similar structures.

f. MUS shall be designed to facilitate gaseous decontamination.

g. MUS shall be designed and tested to meet CETA CAG-003-2006 Certification Guide for Sterile Compounding Facilities.

h. All work surfaces shall be stainless steel. All shelving shall be open wire-type to promote observation and airflow.

i. The manufacturer shall provide full documentation support for third-party IQ/OQ/PQ validation activities.

j. The manufacturer shall provide video recorded operator and maintenance training, along with full supporting documents and manuals.

k. A dedicated EMS monitoring system shall be provided for monitoring critical parameters such as temperature, humidity and differential pressure as described in Section 13.16.

G. Additional APF Design Considerations:

1. Exterior windows should be minimized, but

where provided shall be detailed to limit the possibility of moisture migration.

2. Provide the location and detailing of emergency showers, eyewashes, and other safety devices to minimize their contribution to the bioburden of the facility especially in the ISO classified spaces.
3. Define the level of required physical security/ access control.
4. Door interlocks and red/green light indicator lamps (physical, procedural, or both).
5. Modular wall and ceiling panel systems vs. traditional epoxy-coated gypsum wallboard construction.

13.3.4 Common APF Design Elements

ISO levels of classification are based on air purity, and the number of airborne particulate sized (≥ 0.5 µm, ≥ 5 µm) which are measured "in operation" as well as, "at-rest" state. Engineering controls monitor parameters such as temperature and humidity level due to their potential impact on particle generation and microorganism proliferation.

A. Space Classifications: The progression of space classifications generally includes, in order from least to most clean:

1. **Not Classified (NC):** Areas where the HVAC systems are present, but no claim is made or qualified for the control of particulates, temperature or humidity.
2. **Controlled Not Classified (CNC):** Areas where HVAC systems are specifically designed to reduce airborne contaminants below the level of the ambient environment and both temperature and Relative Humidity (RH) are controlled more tightly than in the ambient environment although there is no monitoring of airborne particulate size. Qualification is common. No claim is made or qualified for the specific control of particulate. Typical systems will have heating, cooling and filtration meeting MERV 13 or better.
3. **Controlled Not Classified with Local Monitoring (CNC+):** These areas are typically qualified to meet ISO 8 requirements at rest only, to control temperature and humidity within a specified band. These areas are generally aligned with PIC/S designation "Grade D."
4. **Anteroom (APF Suite):** See Section 13.5.7. Anterooms/airlocks shall be provided to allow personnel to enter the APF suite and proceed through multiple stages of gowning protocols, as appropriate, for the level of risk.

   Airlocks at the entry and exit to the facility, for personnel gowning and de-gowning, provide buffers between different ISO classifications. Entry airlocks shall be the same ISO classification as the aseptic processing room they serve, while return airlocks may be lower. Anteroom/ airlocks provide a transition area that ensures that pressure relationships are maintained during normal disturbances to the HVAC (such as door openings), and mitigates the impact of large disturbances in the HVAC system, such as power outages, or equipment failures. An airlock shall be required between lower classified spaces and ISO 8 space.
5. **ISO 8:** A classified space that satisfies U.S. FDA requirements for ISO 8 classification measured via airborne 0.5µm particulate in the "in-operation" state, as well as EMA and PIC/S requirements to meet ISO 8 measured via airborne 0.5µm and 5.0µm particulate in the "in-operation" state and meet ISO 7 measured via airborne 0.5µm and 5.0µm particulate in the "at-rest" state.
6. **Anteroom (ISO 7):** An anteroom is required for a transition between ISO 8 and ISO 7 spaces. The air quality within these anterooms may need to meet ISO 7 or 8 requirements, depending on airflow. See Section 13.5.7.
7. **ISO 7:** A classified space that satisfies U.S. FDA requirements for ISO 7 classification measured via airborne 0.5µm particulate in the "in-operation" state, as well as European Medicine

Agency (EMA) and Pharmaceutical Inspection Cooperation/Scheme (PIC/S) requirements to meet ISO 7 measured via airborne 0.5µm and 5.0µm particulate in the "in-operation" state and meet ISO 5 measured via airborne 0.5µm and 5.0µm particulate in the "at-rest" state.

8. **Anteroom (ISO 5):** An anteroom is required for a transition between ISO 7 and ISO 5 spaces, although typically ISO 5 is only provided within PECs. The air quality within these anterooms may need to meet ISO 5 or 7 requirements, depending on airflow. See Section 13.5.7.

9. **ISO 5:** A classified space that satisfies U.S. FDA requirements for ISO 5 classification, measured via airborne 0.5 µm particulate in the "in-operation" state, as well as EMA and PIC/S requirements to meet ISO 5 measured via airborne 0.5 µm particulate and ISO 4.8 measured via airborne 5.0 µm particulate in the "in-operation" and "at-rest" states. An ISO 5 environment is typically achieved in a Primary Engineering Control (PEC), while less restrictive environments are generally created and maintained by the design, mechanical systems, and procedures followed by staff. All open process tissue work is performed in an ISO 5 environment.

In addition to the above design considerations, which impact the organization and relationship of spaces within the APF, there are certain design elements which are generally consistent across various types of APF. See Section 13.4 for design elements that are specific to Biologics Facilities and Section 13.5 for design elements that are specific to Pharmacy Facilities. Other common APF design elements include:

B. Equipment: All equipment and furniture shall be non-permeable, non-shedding, cleanable and resistant to regular exposure to cleaning chemicals and processes without degradation. All surfaces should be “smooth, impervious, free from cracks and crevices, and non-shedding.” Equipment and furniture installed in an APF must be specifically designed, fabricated, and marketed for use in ‘Cleanroom’ environments. Some typical cGMP equipment includes:

1. **Biological Safety Cabinets (BSCs):** BSCs are among the most important equipment in the GMP facility. BSC’s provide open front and inward and downward HEPA filtered air HEPA exhaust. The overall design shall enable one or more BSCs to remain in use should the other(s) become inoperable. The appropriate selection of BSC type shall be substantiated via the QRM (Risk Assessment) process.

   Most Aseptic Processing Room BSCs will be Class II Type A2. Access to these rooms shall be through an ISO 7 anteroom. The overall design shall enable one or more BSCs to remain in use should the other(s) become inoperable. Class II Type B2 (ducted exhaust) BSCs are generally unnecessary for manufacturing Cell Therapy products but are generally required for the safe manufacture of products in USP <797> facilities.

2. **Centrifuges:** These are typically located in equipment or Tissue Culture Rooms.

3. **Incubators:** Incubators are located in Tissue Culture Rooms and will be used for the product currently in production in that room at that time. CO_2 will be required.

4. **Laminar Air Flow Workstation (LAFW):** LAFWs provide ISO 5 unidirectional environment with horizontal HEPA air flowing from the back of the LAFW toward the open front. Vertical LAFWs shall not be used.

5. **Pass Throughs:** See Section 13.6.5.

6. **Refrigerators and Freezers:** Refrigerators and freezers shall be used for storage of intermediate and long-term products. These will be mechanical refrigerators and freezers including cryo-freezers. Under counter refrigerators can be used for daily storage. Controlled rate freezers will be housed in clean freezer rooms.

C. Cross-Contamination Prevention: A system of airlocks and pass through(s), designed to provide separation of spaces, buffer between HVAC zones and, provide areas for cleaning and gowning/de-gowning between areas of different classification or contamination risk. These elements, including personnel and cleaning flows, assist in addressing the risk of product cross-contamination

D. Primary Engineering Controls (PEC): The basic design for the compounding space shall consist of an ISO Class 5 Primary Engineering Control (PEC) located within an ISO Class 7 room, such as a buffer, intravenous (IV), or chemotherapy (chemo) room. Access to these rooms shall be through an ISO Class 7 anteroom. Proper placement of PEC is critical to ensuring an ISO 5 environment for compounding.

PECs shall be located out of traffic patterns and away from circulating air currents. Both Laminar Air Flow Workstations (LAFW) and BSCs may be used.

E. Secondary Engineering Controls (SEC): In an APF facility, the environments leading to the ISO 5 Primary Engineering Control (PEC) are referred to as the "Secondary Engineering Controls." Under USP terminology, these are referred to as "Buffer Areas." These rooms have specific air supply, exhaust, differential pressure, airflow direction, temperature, relative humidity and other requirements. These environmental performance requirements will be listed in the URS. The SEC areas must maintain their ISO class under dynamic working conditions.

F. Controlled Not-Classified (CNC): CNC areas are those within the aseptic manufacturing facility which are designed to support the manufacturing process, but which do not require the level of control and monitoring required to maintain a specific ISO Classification. A CNC area must be cleanable, access-controlled, and supplied with HEPA filtered air (typically systems will have heating, cooling and filtration meeting MERV-13 or better), where the HVAC systems are specifically designed to reduce airborne contaminants below the level of the ambient environment and both temperature and Relative Humidity (RH) are controlled more tightly than in the ambient environment. Qualification is common. No claim is made or qualified for the specific control of particulates.

G. Gowning and Changing Rooms: These may be in a dedicated room or an area of a multipurpose room, and provide space for donning and doffing PPE. There should be a transition area that ensures appropriate pressure relationships are maintained during normal conditions and during large disturbances in the HVAC system. The ante area further segregates the aseptic processing rooms and other cleanrooms from less-clean areas of the facility. The ante area should have a rectilinear footprint, without offsets for achieving uniformity of airflow.

During the predesign phase, criteria should be established for the following (refined as required during the design phase):

1. Understand and define the number of people at one time in use and the maximum capacity per code.
2. Gowning (on and off) procedure
3. Frequency of replacement, storage, and disposal of needed equipment
4. Disposable vs. cleanable for multi-use PPE
5. Hand hygiene equipment
6. Instructional aids

Sufficient space for donning/doffing PPE is essential, with attention given to unidirectional, non-crossing movement. A generic process flow for this action follows:

Entry:

1. Enter controlled area suite
2. Walk-off adhesive mat
3. Use lockers for securing personal property
4. Use shoe covers, or rack for housing cleanroom shoes.
5. Use hands-free hand hygiene station
6. Collect PPE, as needed:
    a. Under-glove or glove dispenser
    b. Medical face mask and beard cover (as required) dispenser
    c. Non-shedding hood/headcover dispenser
    d. Non-shedding coverall PPE dispenser
    e. Bootie/shoe cover dispenser
7. Don PPE
8. Use waste receptacle for PPE wrappings
9. Step over Line of demarcation (LOD) when

donning shoe covers/cleanroom shoes

10. Use an inspection mirror with poster of properly donned PPE, with adjustment, as required
11. Collect additional PPE, as needed:
    a. Safety glasses dispenser
    b. Over-glove dispenser
12. Don additional PPE
13. Use waste receptacle for PPE wrappings
14. Use adhesive walk-off adhesive mat
15. Enter aseptic area

Exit:

1. Use adhesive walk off mat
2. Exit aseptic processing area
3. Use waste receptacle for disposable PPE
4. Return to start to stow cleanroom shoes
5. Retrieve personal property
6. Leave controlled area

The site-specific donning and doffing process shall be codified by users, into an SOP, which will stipulate training and certification requirements for operators, and other NIH staff who frequent the facility (i.e., DFOM, DTR/FCIS, etc.). Provisions for training infrequent site visitors should be incorporated into the SOP. Site-specific procedures may change due to modifications in programs, regulations, and availability of appropriate PPE. The facility should be large enough to accommodate such changes. Provide waste receptacle wherever PPE is removed from packaging. Provide ergonomic lean-rails, benches, etc., to facilitate safely donning/doffing PPE.

During construction, the clean build requirements require the contractor to develop, per user approval, a PPE entry/exit plan, commensurate with the work being performed. To the extent practicable, it should utilize the existing gowning and changing areas.

H. Equipment Rooms: These are areas within the aseptic manufacturing facility which support the manufacturing process. The program use of the space will determine whether the equipment can be housed in CNC (typical) or requires higher ISO classification. Some equipment rooms may require environmental containment as well.

The type and number of required support equipment is program-driven and may include incubators, controlled rate and low/ultra-low temperature freezers, centrifuges, shakers, bead baths, autoclaves, and other equipment for specialized functions requiring isolation, containment, or separation. Sufficient size must be programmed for equipment rooms to allow for air circulation around equipment and for adequate cleaning between and behind.

I. Freezer Room: Freezer rooms are a specific, and common type of APF equipment room. Cell Therapy manufacturing facilities generally use liquid nitrogen (LN_2) storage freezers and ultralow temperature (-80°C) mechanical freezers. In addition to storage freezers, programmable (controlled-rate) freezers are located in clean freezer rooms. Liquid nitrogen freezers (storage tanks) and mechanical freezers shall be on emergency power and will require IT drops.

Liquid nitrogen should be supplied from an external bulk supply tank or from locally stored supply liquid cylinders. Liquid nitrogen supply cylinders should be located to facilitate change-out without entering classified space. Where necessary to accomplish this safely, the cryogenic supply cylinders shall be connected to the LN_2 use points via a DRM compliant piping system, which shall be vacuum jacketed. Provided Oxygen depletion monitors tied to BAS in LN_2 freezer rooms.

J. Quality Control (QC) Laboratory: The QC lab contains flow cytometry and other assay testing equipment and associated computers and is located outside the classified areas, so the technologist does not need to be fully-gowned. Consideration shall be given to high-density storage systems in storage rooms.

K. Supply Rooms: Supply rooms may be designated as "dirty" for the receiving of quarantined materials, breaking down and reducing packaging, etc., or "clean" for receiving materials released for use in the facility. Clean supply rooms shall be constructed to meet the requirements of a classified space, as appropriate.

L. Housekeeping Room: Housekeeping room (or

Janitor's Closet) may be used to store cleaning equipment and supplies, specific to the APF to which it is associated. It is permissible to centrally house equipment and supplies and deploy to numerous separate APFs, only under approved SOP, due to contamination risks. Access to this space (frequency, timing, and personnel) shall be clearly defined by the program during programming level, to ensure that the design addresses any need for mechanical controls. A janitor's closet may be classified as "clean" or "dirty" depending on the location and function. See Section 2.4.5.5, Section 6.1.13.3, Section 6.1.14, and Section 8.2.11.

1. **Clean Janitor's Closet:** Typically located within the classified zone of the APF. A sink may be provided in the Clean Janitor's Closet for the preparation of site mixed/diluted cleaning agents but is not recommended due to environmental monitoring concerns.

2. **Dirty Janitor's Closet:** Typically located in non-classified zones of the APF. A sink and/or floor drain may be provided for the approved disposal of waste cleaning solutions. The traps for these drains must be part of a trap maintenance program to control biological growth and contamination.

M. Administrative Areas: Administrative areas may include an office area for cell processing staff and any other office areas required for records, reports, accounting activities, and patient storage.

N. Mechanical Rooms: The design of mechanical support spaces for cGMP APFs require a fundamental shift in the typical approach which defers much of the final placement and alignment of components. Because of the high frequency of calibration, certification, and verification, a higher level of intentionality to facilitate this ongoing work is required. The designer should strive to make the systems as simple as possible, with gauges, sensors, valves and other control points organized to promote this higher level of service. Access ways and "swim lanes" must be planned and maintained.

APF mechanical rooms shall be designed to be brightly lit, painted, and have waterproof, seamless, durable floors with 152 mm (6 in.) integral base. Floors of mechanical rooms shall be designed to contain leaks. Penetrations through the floor shall be protected, via sealed raised curbs and sleeves. Housekeeping pads shall be provided where deemed beneficial for major equipment. Where housekeeping pads are not provided, consider elevating equipment through the use of corrosion-resistant bases to mitigate the risk of damage due to flooding and to maintain clean-ability.

All mechanical rooms with wet equipment or water storage tanks, whether plumbing or HVAC related, shall be provided with not less than two industrial-grade water flood alarms that shall alert to the BAS, and alarm locally if water is detected. The number and location of sensors provided shall be sufficient to monitor the room for flood issues.

Entry to mechanical rooms shall be independent/ separate from the APF. A high level of MEP component labelling is required in these spaces, including directionality.

O. Interstitial Areas: Similar to mechanical rooms, the interstitial areas supporting a cGMP APF are highly trafficked for maintenance and operations activity, so accessibility of gauges, sensors, valves, etc. is important. Access ways and "swim lanes" must be planned and maintained. Where these are located directly above the APF, it is recommended that the floor plate below be painted on the floor of the interstitial for ease of pinpointing relative position, floor-to-floor.

Floors of interstitial rooms shall be designed to prevent leaks. Exposed pan-deck, form-deck or similar is not an acceptable interstitial floor finish. Penetrations through the floor shall be protected, such as raised curbs and sleeves. All mechanical rooms with wet equipment shall be provided with room flood monitoring, reporting to the BAS.

13.3.5 Design Review and Design Qualification

A. Design Review: The review process should include considerations of constructability, maintenance, and testing.

B. Design Qualification: Review of compliance of design documents with GMP which needs to be demonstrated and documented. The process of design review and approval for GMP compliance may be integrated into the overall design review process.

13.3.6 Value Engineering (VE) and Sustainable Design Requirements

Section 1.7 describes the mandatory requirement for VE in projects where the construction cost exceeds a maximum value per OMB Circular-131, and Federal Procurement Policy Notices, Value Engineering shall be considered. Further, integration of sustainable design features into construction projects is mandated by law, regulation, executive order, and policy. The DRM shall not be used to abridge these requirements. Although the robustness and redundancy requirements in APFs are generally not compatible with such measures, all associated analyses and reports are to be performed as required.

A. Value Engineering Proposals (VEP): For all APF VEPs, a fully reviewed and accepted risk analysis must be prepared. The proposed value engineering shall not increase the risk to the product, patient, or worker; likewise, VE or sustainable features which increase the difficulty of O&M or reduce the robustness or resiliency (such as reducing the [n+x] redundancy of critical systems) shall not be considered.

B. Guiding Principles of the Federal Leadership in High-Performance and Sustainable Buildings Memorandum of Understanding (MOU): The guiding principles shall be incorporated into the planning, design, construction, operation, and maintenance of APFs to the extent practicable. Although neither U.S. Green Building Council's Leadership in Energy and Environmental Design (LEED) nor the Green Building Initiative's Green Globes System are designed to consider facilities of the nature of an APF, the guiding principles still need to be considered and documented. See Section 1.8.2.

13.3.7 Commissioning and Validation Activities (Design)

The Commissioning Agent (CxA) or the Qualification Validation Agent (QVxA), or the integrated Commissioning, Qualification, Validation (CQV) Services Agent should be engaged early in the design phase. If the project utilizes a CQV approach, the agent will be responsible for both the VxA and CxA activities, as listed below.

A. CxA Activities:

1. **Schematic Design Phase Activities:**
    a. Participate in the Integrated Project Team (IPT)
    b. APF design review collaboration
    c. Develop testing matrix
    d. Begin Commissioning Master Plan (CMP)
    e. Document requirement matrix
    f. Document control and management
2. **Design Development (DD) and Construction Document (CD) Phase Activities:**
    a. Develop Cx Specifications
    b. Review and comment on the following:
        - PVMP
        - Component level assessments (direct impact systems only)
        - Equipment specifications
        - Vendor documentation
        - Construction Quality Plan
        - Change Management
        - Construction and Startup Integration Planning
        - Design Submittals
        - FAT/SAT, as applicable
    c. Good Documentation Practices
    d. Confirm that the DQ has been fully executed

B. QVxA Activities:

1. **Schematic Design Phase Activities:**
    a. Participate in the IPT
    b. APF design review collaboration

c. Understanding the product manufacturing basis:
    - Identification of critical quality attributes (CQAs)
    - Critical process parameters (CPPs)
    - Critical materials/components (CMAs)
    - Critical aspects

d. System list

e. Process user requirements

f. System boundaries

g. Quality Risk Assessment (QRA)

h. System Level Impact Assessments (SLIA)

i. Develop testing matrix

j. Begin Project Validation Master Plan (PVMP):
    - Design Qualification (DQ)
    - Commissioning Master Plan (CMP)
    - Qualification Plan (QP)
    - Installation Qualification (IQ)
    - Operational Qualification (OQ)
    - Performance Qualification (PQ)
    - Cleaning Validation (CV)
    - Computer System Validation (CSV)

k. Document requirement matrix

l. Document control and management

2. **Design Development and Construction Document Phase Activities:**

a. Participate in the IPT

b. APF design review collaboration

c. Develop the PVMP

d. Component level assessments (direct impact systems, only).

e. Equipment specifications

f. Vendor document requirements

g. Construction Quality Plan (CQP)

h. Design qualification

i. Change management

j. Construction and startup integration planning

k. Good Documentation Practices (GDP)

l. Development of Factory Acceptance Test (FAT) and Site Acceptance Test (SAT), as applicable

m. Verify that the DQ has been fully executed

13.3.8 Document Change Control

Good Documentation Practice (GDP) describes the standards by which documents are prepared, reviewed, approved, issued, stored, maintained and archived. The control of documents related to the operation and maintenance of and within the APF, is particularly important, and in many cases, are codified by regulatory bodies.

Both the user group and ORF are required to develop, implement, and maintain systematic procedures, Standard Operating Procedures (SOPs), on a program and/or facility-specific process, procedures and requirements.

Document change management/change control procedures shall be developed and implemented during design and adhered to strictly, during design, construction and beyond. Each project develops its own change control and is subject to review and approval by the FCIS, DTR. The Document Change Control requirements shall be specified in the Project Execution Plan (PEP).

13.3.9 SOP for Construction

APFs which are intended to remain wholly, or partially in operation, or which will have operations temporarily suspended for construction or maintenance work shall have SOPs developed, reviewed and approved by DFOM, DTR, and the user. Any impact to the material, equipment, or personnel flows of a degree or duration, at the discretion of the user's QA, shall also update the record flow diagrams.

13.3.10 Non-Inspection FDA Meetings

The FDA describes two types of optional (non-inspection or filing) interactions with design teams working on prospective facilities. The NIH scientific program, in conjunction with the ORSC, CC will determine which FDA meetings are required and, will be the sole point of contact with the FDA on APF projects. The types of meetings include:

A. Pre-operational Reviews of Manufacturing Facilities (FMD 135 Meeting): According to Field Management Directive (FMD) 135, these meetings serve to provide field guidance when responding to requests from industry for reviewing plans for the construction of new or, modifications of facilities prior to commercial production. This meeting is generally between an interested party and the responsible district office. This type of meeting is often undertaken to familiarize the district with a facility they will later inspect and to obtain feedback from the agency regarding possible errors or design defects. The review is a general discussion of the facility design and intended construction. The district may engage SMEs from the Center for Drug Evaluation and Research (CDER). The recommendations and other feedback are not binding on the FDA. FMD 135 reviews may occur at any or all of the following stages:

1. Design Review
2. Pre-Construction Review
3. Construction/Equipment Installation and Qualification Review
4. Pre-Production Review

B. Type-C Meeting: A Type-C meeting is any meeting other than a Type-A or Type-B meeting (Type-A and B meetings are generally non-facility related) between CBER or CDER and, a sponsor or applicant, regarding the development and review of a product. The Type-C meeting is scripted and scheduled per FDA policy. A designated NIH representative shall be the sole point of contact between the project team and the FDA. The project team shall generate a package of the necessary information to submit to the FDA, per the FDA document, "Formal Meetings Between the FDA and Sponsors or Applicants of Prescription Drug User Fee Act (PDUFA) Products Guidance for Industry." These materials shall be developed, reviewed and approved by NIH, prior to the FDA established due date which is typically 30 days prior to the formal meeting date. The Type-C meeting is generally scheduled when the planning and design are sufficiently mature for review and comment, but prior to initiating construction-phase activities. The APF user group and ORSC shall coordinate the timing, nature, and number of requested meetings and other contacts with the FDA.

13.3.11 Deliverables (Design)

The following required deliverables may vary based on size and complexity of individual projects. Not all of the following will apply to every APF project.

Note: These are above and beyond Appendix E, A/E Submission Requirements, which addresses typical requirements, such as design drawings, specifications, calculations, etc.:

1. Updated feasibility study report(s)
2. Updated QRM & risk analysis report(s)
3. Updated GxP harmonization report
4. Updated project execution plan (PEP)
5. Updated user requirement specifications (URS)
6. Updated room data sheets (RDS)
7. Updated process flow diagrams with narrative
8. Updated equipment schedule

9. Updated FDA meeting document packages
10. Meeting minutes
11. Updated validation master plan (VMP)
12. Updated construction quality plan
13. Updated SAT/FAT protocols

Other documents may be updated and submitted for review as required, as specified in the PEP.

13.3.12 Document Review and Approval (Design)

There are many documents and processes that are specific to APF projects. Some of these documents are subject to validation (approved by a signature from appropriate parties), and some are subject to review by parties above and beyond those specified in Section 1.5.3.3, NIH Technical Review Staff. Table 13.3.12, below, provides a typical framework for the documents associated with this phase, although there will be some facility and project-specific variations, so this table should be considered as general and informative, but not exhaustive or inclusive of the document requirements of a specific project. Those specific requirements should be developed during this phase and documented in the PEP.

Table 13.3.12 APF Document Review and Approval (Design)

Document	Signed	Controlled	PO/COR	Per DRM Section 1.5.3.3	FCIS	ORSC	DFOM	NIH Program (User)	User QA	External Regulatory Agencies
Project Execution Plan (PEP) by Final Design	•		IRS		R	R		RS	R	
Basis Of Design (BOD)	•	•	IRS	R	RS	RS		RS	R	R
Program Questionnaire	•		IRS	R	R	R		R	R	
Room Data Sheets (RDS)			IRS	R	R	R		R	R	R
Process Flow Diagrams (PFD)	•		IRS	R	RS	RS		RS	RS	R
Equipment Schedule	•		R	R	R	R		IRS	IRS	
Piping and Instrumentation Diagrams (P&ID)			IRS	R	R			R	R	
GxP Harmonization Report	•	•	R	R	RS	RS		IRS	RS	R
User Requirement Specifications (URS)	•	•	R	R	RS	RS		IRS	RS	R
Feasibility Study Report(s)	•		IRS	R	RS	RS	R	RS	RS	R
Quality Risk Management (QRM) Report	•		R		RS	RS		IRS	RS	R
Final Design Contract Documents (Dwgs., specs., etc.,)	•	•	IRS	R	R	R	R	RS	RS	
Validation Masterplan (VMP)	•	•	IRS	R	RS	RS	R	IRS	RS	
Project Validation Masterplan (PVMP)	•	•	IRS	R	R	R	R	RS	RS	
Commissioning Masterplan (CMP)	•	•	IRS	R	RS	R	R	RS	RS	
VE and Sustainable Design Analysis			IRS	R	R	R		R	R	R
Change Management (Project) SOP	•	•	IRS	R	RS	R		RS	R	
FDA meeting document package(s), if applicable	•		IRS	R	R	R		RS	R	R
Test Protocols as applicable per Section 13.17	•	•	IRS	R	RS	R	R	RS	RS	
SAT/FAT Protocols, where applicable	•	•	IRS	R	RS	R	R	RS	RS	
SOPs for Construction Phase	•	•	IRS	R	RS	R		RS	RS	
Construction Quality Plan (CQP), if D/B	•	•	IRS	R	R	R		R	R	

I *Initiated By*
R *Reviewer*
S *Signatory*

Note: Unless indicated otherwise, PO/COR is responsible for the management of the above document(s).

Section 13.4

Biologics Facilities

Contents:

13.4.0 Introduction

Biologics production facilities at NIH manufacture cell therapy products, including live cellular materials such as stem cells, T-Cells, for autologous or allogeneic administration to patients as part of Phase I and II clinical trials. Cell therapy involves the transplantation of these live cellular materials into patients, primarily for treatment or prevention of diseases, by repairing a lost or defective function. Regulations require that cell therapy products, intended for patients, be done in a cGMP facility. Cellular therapy products are thus manufactured in compliance with 21 CFR 1271 (Good Tissue Practices), 21 CFR 211, and related cGMP expectations.

These facilities are typically designed for the manufacture of multiple products, either concurrently, or sequentially (campaigned), although there are some dedicated, single-product facilities. Known infectious biological material is processed in BSL-2, ISO 7 cleanrooms, separate from biological material that has tested negative for infectious diseases.

Based on discussions with the user, the A/E shall document, the following minimum information about the intended manufacturing processes in the BOD:

1. Nature of the starting material – primary human cells vs. cell line(s).
2. Nature of the process: Infectious vs non-infectious vectors or other materials present that will impact design decisions.
3. Nature of processes to be performed: Ex vivo expansion culture, cell selection, gene modification, etc., noting any open vs. closed process steps, in particular.
4. The number of products to be produced: Dedicated (single product) vs. multiple product (Concurrent or campaigned) production.
5. Nature of the temporal segregation of processing activities, in multiple product facilities. Note approximate duration of process steps, particularly open process steps. Note temporal segregation of processing activities, including periods of active processing and inactive intervals (e.g., product in incubator).
6. Whether the production is a single, or multiple room process.
7. Dedicated vs. shared equipment.
8. Whether cells from multiple patients/donors be processed in the same cleanroom contemporaneously?
9. Flow pathways for personnel, raw material, processed material, and waste (Unidirectional flow is preferable), etc.
10. Whether the product will ship extra jurisdictionally, particularly to EU-located partners?

13.4.1 General Plan Arrangement

Good Manufacturing Practices dictate a progression of spaces that lead from unclean and uncontrolled spaces to, progressively cleaner spaces. The transition between these spaces is maintained by design of the facility, the mechanical systems supporting the facility and by adherence to SOPs. Conformance to these requirements is carefully monitored to ensure ongoing compliance.

The FDA regulations, specifically CFR 211, calls for the segregation of activities/operations to prevent cross-contamination and mix-ups. Contamination, including microbiological and by endotoxin(s) can result from environmental conditions, personnel, handling of materials, and/or crossed contamination with other products prepared within the same suite (but in separate rooms). Thus the design of a GMP facility, its engineering controls along with, procedural controls can mitigate the risks associated with contamination of the product being produced at the facility.

Potential sources of contamination may include but are not limited to:

A. Personnel Issues:

1. Inadequately trained personnel
2. Personnel not following SOPs
3. Donning/Doffing improper, inadequate or contaminated PPE

4. Direct contact between the operator's hands and starting materials, primary packaging materials or product

5. Defective/improperly released raw materials (including packaging materials)

B. Facility Issues:

1. Inadequate facility design in terms of unidirectional flow, adequate steps between ISO classification changes, etc.

2. Contamination of ventilation air, water, compressed gasses, or other utilities

3. Inadequate lighting

4. Improper architectural finishes and details

5. Excessive noise and vibration

6. Non-unidirectional airflow

7. Inadequate hand hygiene, toilet, and locker facilities to allow for sanitary operation

C. Combination Personnel and Facility Issues:

1. Insufficient size and inadequate organization of the space leading to selection errors like mix-ups or cross-contamination between consumables, raw materials, in-process materials, and finished products

2. Insufficient size and/or inadequate organization of PPE donning/doffing spaces

3. Improperly maintained and/or operated production equipment

4. Cross-contamination or mix-ups with finished or semi-finished material; and others.

5. Improper cleaning procedures and/or materials

6. Improper pest management

7. Known infectious biological material is processed in BSL-2, ISO 7 cleanrooms, not kept separate from biological material that has tested negative for infectious diseases.

13.4.2 Biologics APF Design Recommendations

A. Changing/Locker Room: Changing rooms are for the donning and doffing of street clothes to a uniform base garment, typically scrubs, for entry into the APF as well as upon exit. Sufficient space shall be allocated for this process. Changing rooms are typically CNC. Equipment and furniture in a changing room often include scrub dispensers, lockers, benches, and provision for hand hygiene.

Locker rooms, where separate from changing rooms, shall be located near the changing rooms. Equipment and furniture in a locker room often include lockers, benches, and provision for hand hygiene. Locker rooms with CNC Toilet facilities are generally not co-located with APF changing/locker rooms to mitigate the risk of contamination. Locker rooms are typically provided only at larger facilities.

Where hand hygiene is performed, follow the below design requirements:

1. Provide a hands-free hand washing/hygiene sink of adequate dimensions to allow for washing up to the elbow.

2. Locate the sink near the entry door when possible (i.e., closer to the dirty-side).

3. Provide an eyewash located at the sink or an eyewash station.

B. Gown-In Room: Gown-In Rooms are generally, part of the entry anteroom sequence. If not performed in the CNC areas, ISO class 8 can be used for personnel, garbing (donning 1st or 2nd layer of PPE), staging of components, and other activities that potentially generate high levels of particulates. A rectilinear footprint is preferred, without offsets for achieving uniformity of airflow. Sufficient area for donning/doffing PPE is essential, with attention given to single direction, non-crossing movement. In bidirectional facilities, segregate the flow to the extent practicable. See Section 13.3.3.

Design recommendations:

1. A bench for PPE garbing may be provided.

2. Full-length mirror for visual inspection of PPE.

C. Clean Corridor: The clean corridor typically connects the changing/locker room, via an airlock, to the entry airlock(s) of one or more aseptic processing rooms. Often, a material airlock to the clean storage is provided to move materials and supplies to the aseptic processing rooms. Clean corridors are typically ISO 8 or better. In a unidirectional flow facility, there will be corresponding material pass throughs to move this material into the entry airlocks, or directly into the aseptic processing rooms.

D. Airlock/Anteroom: Airlocks shall be provided as buffers to allow personnel to proceed through multiple stages of gowning protocols, as appropriate, for the level of risk. Airlocks are typically provided at the entry and exit of processing rooms, for personnel gowning and de-gowning. Entry airlocks shall be the same ISO classification as the aseptic processing room they serve, while return airlocks may be lower. See Section 13.8.9 for additional information.

E. Aseptic Processing Room: An aseptic processing room (often referred to as a tissue culture room or cleanroom) shall serve as the processing room for cell therapy products in Biologics APFs and is the most critical of the rooms. Aseptic processing cleanrooms commonly house the PECs (i.e., BSCs), associated cell processing equipment (i.e., incubators, centrifuges, etc.), and mobile casework. These rooms may be equipped with small refrigerators or freezers within the clean classified environment for intermediate storage of materials during processing. Water sources, such as sinks or floor drains, are not permitted in Aseptic Processing rooms. Communication devices such as intercoms and cameras should be used to minimize traffic between areas. Aseptic Processing rooms are typically ISO 7 but may be ISO 8 if all work is performed in isolators.

For Biologics APFs using viral vectors or other infectious, or potentially infectious materials, the Aseptic processing suite shall be ISO 7, but negative to adjacent space. This requires an ISO 7 anteroom, because the air from the anteroom will move into the aseptic processing room. A second anteroom, an ISO 8, is generally utilized beyond the ISO 7 anteroom, as a cascade, to transition to adjacent spaces.

Return Corridor: A return corridor is similar to an exit corridor, but is typically ISO 8 or better and configured to allow a return to the clean corridor, after some proscribed donning and doffing of PPE and other steps as required to mitigate the risk of cross-contamination. Return corridors also typically allow access to storage and/or freezer rooms, then out of the suite. In a unidirectional flow facility, there will be pass throughs to then move processed material and waste into the exit corridor.

Bidirectional Anteroom: Provide dedicated gowning rooms for entering and exiting processing rooms to reduce the risk of residual contamination on a dirty (exiting) garment from contaminating clean (entering) garments. SOPs shall disallow the non-concurrent donning and doffing of PPE in bidirectional anterooms. Bidirection flow traffic in shared gowning rooms may be allowed in small APFs and only based on risk assessment and at the approval of NIH.

Freezer Room: Freezer Rooms are common in Biologics APFs. Freezers shall be used for storage of intermediate and long-term products. These may consist of liquid nitrogen (LN_2) storage freezers, ultralow temperature (-80°C) mechanical freezers. Programmable (controlled-rate) freezers typically located in freezer rooms. Under counter refrigerators may be used for daily storage. LN_2 freezers (storage tanks) and mechanical freezers shall be on emergency power and will require IT drops. LN_2 should be supplied from an external bulk supply tank, or from locally stored cryogenic liquid cylinders. Where necessary to safely facilitate supply change out without entering classified space, LN_2 supply should be located outside classified space and connected to the use points via a DRM compliant piping system, which shall be vacuum jacketed. LN_2 freezer rooms shall be provided with O_2 depletion monitors tied to the BAS.

Logistics Rooms: Within the CNC areas, each Biologics APF will typically have space for pickup, receiving, reviewing, recording and storage (quarantined/dirty and released/clean) of raw materials, finished product, cleaning supplies, etc. Sufficient storage area for carts shall be provided along with space for bulk storage, active storage, supply storage, etc. There shall also be areas for packaging, labeling and storage of finished product. Adequate space shall be provided for these activities to minimize the chances of mix-up.

Pass Through Boxes, Chambers, or Cabinets: Refer to Section 13.6.5.

See Section 13.3.4 for additional rooms and requirements.

Section 13.5

Compounding Pharmacy Facilities

Contents:

13.5.0 Introduction

A compounding pharmacy refers to a facility or suite that, under license and by prescription by a physician or other legally authorized prescriber, mixes or "compounds" chemical ingredients into a finished medication that is ready to use by an individual patient.

NIH Compounding Pharmacy facilities are part of the Aseptic Processing Facilities (APF) portfolio where medications used for NIH clinical trials are manufactured, stored and dispensed. The products dispensed shall be sterile (if so specified), of correct identity (ingredients), purity (free from contaminants), and strength. The products must be dispensed into sterile, accurately labelled containers, and stored in carefully monitored and controlled environments, appropriate for the products being stored.

Compounded sterile preparations (CSPs) may be stored for extended periods before use, during which time it is possible for contaminating microorganisms to grow, particularly if appropriate compounding and storage conditions are not met. Contaminated CSPs can cause patient health complications or even death and, negatively impact clinical trial data quality. Mitigating these risks is the principal purpose behind the requirements described in this chapter.

The combined effort of appropriate engineering and administrative controls through facility design, construction, and O&M ensures that the facility environment can be operated in a state of control, produce the appropriate environment for CSP preparation, storage and dispensing.

In all APF Pharmacy facilities, airflows are controlled and monitored such that air flows from clean to dirty areas while control of staff, equipment, and material flow increases from dirty to clean. Generally this is accompanied by a positive pressure cascade to keep the product isolated from the surrounding environment, but in a hazardous compounding area (described in more detail in Section 13.8), air flow shall be negative to the adjacent room with appropriate engineering and administrative controls for the contamination risk levels defined in USP <797>. In all APFs, consideration shall be made for relationships between the anteroom(s), buffer, gowning, segregated and storage areas in workflow patterns as they will affect air quality.

13.5.1 Pharmacy: Compounding Regulations

USP is a scientific nonprofit organization that sets public standards for the identity, strength, quality and purity of medicines. The federal Food, Drug and Cosmetic Act (FDCA) specifically references and mandates USP standards for compounding. Parties responsible for compounding medicines are required to comply with USP's Chapters and Monographs:

1. USP <795> Pharmaceutical Compounding Nonsterile Preparations
2. USP <797> Pharmaceutical Compounding Sterile Preparations (CSP)
3. USP <800> Hazardous Drugs – Handling in Healthcare Settings
4. USP <823> Radiopharmaceuticals for Positron Emission Tomography (PET)
5. USP <1160> Pharmaceutical Calculations in Pharmacy Practice
6. USP<1163> Quality Assurance in Pharmaceutical Compounding
7. USP<1176> Prescription Balances and Volumetric Apparatus Used in Compounding

USP Chapters for Compounding Facilities define where sterile or non-sterile preparations are performed. Sterile compounding differs from nonsterile compounding primarily by requiring the maintenance of sterility when compounding exclusively with sterile ingredients and components and, the achievement of sterility when compounding with nonsterile ingredients and components. A primary difference between nonsterile and sterile compounding is that clean conditions, not aseptic conditions, are required for non-sterile compounding. Some other differences between standards for sterile compounding and those for nonsterile compounding in Pharmaceutical Compounding Nonsterile Preparations (795) include, but are not limited to: ISO classified air environments; person-classified air environments; personnel garbing and gloving; personnel training and testing in principles and practices of aseptic manipulations and sterilization; environmental quality specifications and monitoring; and disinfection of gloves and surfaces of ISO Class 5 sources.

13.5.2 Compounded Sterile Preparations (CSP) USP <797> Risk Levels

USP <797> shall be followed when preparing compounded sterile human and animal drugs to ensure the sterility of any CSPs. CSPs consist of injections; aqueous bronchial inhalations; baths and soaks for live organs and tissues; irrigations for internal body cavities; ophthalmics; implants, etc.

USP <797> categorizes contamination risk in the preparation of CSPs. A determination of the level of risk should be made for each facility where CSPs are compounded to assure that policies and practices established for the area respond to the risk level present.

The risk to the sterility of the product, associated with a CSP depends on a number of factors. CSP microbial risk categories are assigned primarily according to the potential for microbial contamination. They are distinguished primarily by the conditions under which they are made and the time within which they are used. They are categorized into two (2) categories, (per the USP <797> proposed revisions:

1. **Category 1 CSP:** This is a CSP, assigned a Beyond Use Date (BUD) of 12 hours or less, at controlled room temperature or 24 hours or less, refrigerated. A PEC may be placed within an unclassified, segregated compounding area.

2. **Category 2 CSP:** This is a CSP assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours, refrigerated. Category 2 CSP must be prepared in accordance with all applicable standards for Category 2 CSPs per USP <797> which dictate a cleanroom environment with separate buffer and Anteroom. PEC shall be placed in an ISO 7 classified buffer room.

Urgent-Use USPs: Urgent use USPs are utilized in situations where there is a need for emergency or immediate patient administration of a CSP (e.g., pulmonary resuscitation) for:

1. A single patient AND when preparation under Category 1 or 2 would subject the patient to additional risk due to delays in therapy.

2. Compounding procedure must be a continuous process not to exceed 1 hour AND administration of the CSP must begin immediately upon completion of preparation of the CSP.

3. During preparation, aseptic technique is followed AND procedures must be in place to minimize the potential for contact with non-sterile surfaces, the introduction of particulate matter or biological fluids, and mix-ups with other CSPs.

13.5.3 Hazardous Drugs (HD) as CSPs USP <800>

Any antineoplastic Hazardous Drug (HD) requiring manipulation and HD Active Pharmaceutical Ingredients (API) on the "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings" current edition, must follow USP <800> for the preparation and storage of HDs. HD preparation and storage shall be designed to protect the healthcare workers and other personnel in the preparation, handling, and storage of HDs.

HD shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure; however, sterile and non-sterile HDs may be stored together. Many HDs have sufficient vapor pressures that allow volatilization at room temperature. Because of this, storage is preferably within a negative pressure containment area. The storage area should have sufficient general exhaust ventilation, at least 12 air changes per hour, to dilute and remove any airborne contaminants.

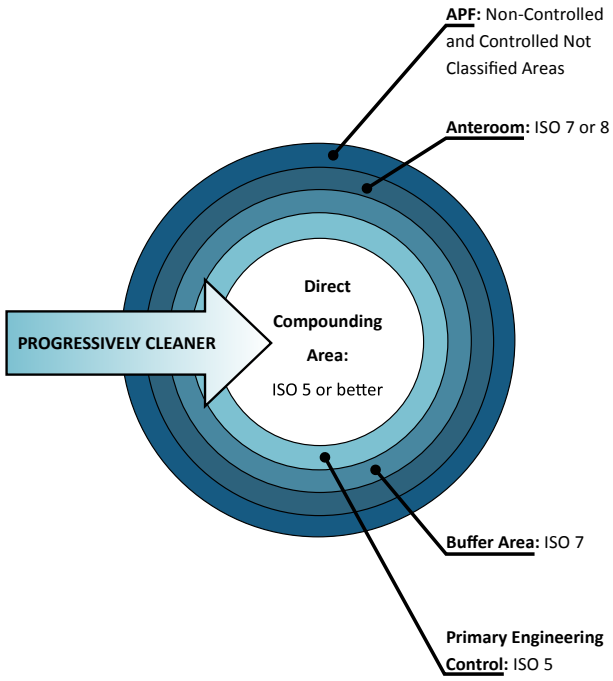
13.5.4 Direct Compounding Area (DCA)

The DCA is the critical area within the ISO 5 Primary Engineering Control (PEC) that is exposed to unidirectional HEPA-filtered first air. This may consist of the following:

1. ISO 5 HEPA-filtered Biological Safety Cabinet (BSC) within an ISO 7 (or better) buffer room.
2. Isolator, within an appropriate ISO level buffer room
3. An ISO 5 (or better) room

See Figure 13.5.4.

Figure 13.5.4 Diagram indicating progressively cleaner sequence of compounding pharmacy facilities



13.5.5 Primary Engineering Controls (PEC)

The basic design for the compounding space shall consist of an ISO Class 5 Primary Engineering Control (PEC) located within an ISO Class 7 room such as a buffer, intravenous (IV), or chemotherapy (chemo) room. Access to the ISO Class 7 rooms shall be through an ISO Class 7 anteroom. Proper placement of PEC is critical to ensuring an ISO 5 environment for compounding PECs. PECs shall be located out of traffic patterns and away from circulating air currents (See Appendix A, Biological Safety Cabinet (BSC) Placement Requirements for New Buildings and Renovations). Both Laminar Airflow Flow Workstations (LAFW) and BSCs may be used. LAFWs provide an ISO 5 unidirectional environment with horizontal HEPA air flowing from the back of the LAFW toward the open front. Vertical LAFWs shall not be used. BSCs provide open front and inward and downward HEPA filtered air HEPA exhaust. The overall design shall enable one or more BSCs to remain in use should the other(s) become inoperable.

A. Containment Primary Engineering Control (C-PEC): This is an externally vented Class II or III biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI) with HEPA filtered exhaust, as required by the program. Such a device is not required for manipulations of intact, final products unless they produce aerosols, gases, or powders. All C-PECs used for manipulation of sterile HDs shall be externally vented. A C-PEC does not have to be within an ISO 7 space but should be in a separate negative pressure room. The C-PEC is designed to minimize worker and environmental HD exposure when directly handling HDs.

The C-PEC may be placed in an ISO Class 7 buffer room that has a negative pressure between 2.5 and 7.5 Pa (0.01 and 0.03 in. w.g.) and has a minimum of 30 ACPH of HEPA-filtered supply air.

B. Compounding Aseptic Isolator (CAI): When a CAI is used for compounding, in lieu of the Intravenous (IV) solutions area, it may be prepared within the pharmacy provided it complies with the following:

1. The CAI shall provide isolation from the room. The CAI provides ISO Class 5 levels during dynamic/operating conditions, including transferring raw materials, ingredients, components, and devices into and out of the CAI and during the preparation of CSPs.
2. The particle counts sampled shall be 152 to 305 mm (6 to 12 inches) upstream of the critical exposure site within the CAI.
3. The CAI shall maintain ISO Class 5 levels during compounding operations.

13.5.6 Buffer Areas

A Buffer Area is an ISO 7 area where the PEC is physically located. During operations, the Buffer is continually monitored for viable and non-viable particles, to ensure that the concentration of airborne particles is controlled. Environmental Monitoring (EM) of the air, personnel, and surfaces are conducted per SOP (as mandated by USP <797>) to ensure that allowable microbial levels are not exceeded. Activities in the Buffer Area include the preparation of CSPs, and the staging of ingredients, components and other supplies for the product being produced.

All CSPs (except possibly Category 1, if supported by risk analysis and approved by Pharmacy QA) must be compounded in the clean area with buffer and anteroom.

Water sources, such as sinks or floor drains, should not be immediately adjacent to segregated compounding areas outside of a buffer area, and are not permitted in the buffer area. This area may include a limited amount of shelving and/or carts for the staging of compounding (not for storing stock). Moving in and out of the buffer area may increase airflow interruption. Communication devices such as intercoms and cameras should be used to minimize traffic between areas. This is generally true of all APFs, but particularly important in this application. There shall be a systematic process of entering and exiting the various areas to minimize contamination.

A. Containment Secondary Engineering Control (C-SEC): A C-SEC is a room in which the C-PEC is placed. Hazardous drugs shall be prepared in an area that is physically segregated (a different area from the other CSP areas). C-SEC must be externally ventilated via a HEPA filter. Sterile HD compounding must be performed in a Containment PEC (C-PEC) that provides an ISO Class 5 or better air quality (e.g., a Class II or III BSC or CACI), and Class II BSC types A2, B1, or B2 are acceptable).

B. Containment Segregated Compounding Area (C-SCA): Under USP <800> a C-SCA is intended to house a CACI (that meets the requirements listed in USP <797>) for the compounding of low or medium risk sterile hazardous drugs and must exhaust a minimum of 12 ACH. C-SCA is not acceptable for high-risk HD compounding. C-SCA areas must be cleanable, access controlled, and supplied with HEPA filtered air.

C. Intravenous (IV) Solutions Room: A sterile work area shall be provided for Intravenous (IV) preparation, where required by the program. The IV solutions room work area shall consist of a preparation room, PEC room and a separate chemo PEC room, where required. Access to the preparation room shall be through the pharmacy only; while access to the PEC room or chemo PEC room shall be through the preparation room only.

The associated preparation room shall provide ample work counter, gowning area, and shelving. A hand hygiene fixture with hands-free controls shall be in the preparation room and within 1.5 m (5 ft.) of each entrance to the PEC or chemo rooms. Hand hygiene fixtures and floor drains are not allowed inside the PEC or chemo rooms.

13.5.7 Anteroom Requirements

The anteroom is an ISO class 8 or better area which provides space for personnel to perform hand hygiene, garbing (donning PPE), staging of components, order entry, CSP handling, and other activities that potentially generate high levels of particulates. It is also a transition area that ensures pressure relationships are maintained between designated areas during normal and conditions of large disturbances in the HVAC system. The ante area further segregates the buffer area from less-clean areas of the facility. The ante area should have a rectilinear footprint, without offsets for achieving uniformity of airflow.

Design requirements:

1. Provide a hands-free hand washing/ hygiene sink of adequate dimensions to allow for washing up to the elbow.
2. Locate the sink near the entry door when possible (i.e., closer to the dirty-side).
3. Provide an eyewash located at the sink or an eyewash station.
4. A bench and storage facilities or lockers for personnel garbing shall be provided.
5. Full-length mirror for visual inspection of PPE.

13.5.8 Pharmacy Support Areas

The pharmacy support areas, described in this section are outside the ISO classified areas, however, they are essential to the function of the pharmacy. The specific composition and room requirements for these spaces will be dictated by the facility program, but may include all or some of the following:

A. Material Receiving/Breakdown: This room/ area should be located at the perimeter of the APF, with good access to the loading dock, and shall have sufficient space for receiving, breakdown, inspection, storage of supplies/materials intended for use within the pharmacy areas. Materials from this room are moved to the appropriate storage room(s) and reduced to minimum packaging (i.e., no cardboard). Initial checks are performed here to begin the quality inspection of the product and its paperwork.

B. Storage Rooms: Ideally located within the pharmacy suite, this room shall have adequate space for pickup, receiving, reviewing, recording and storage of sterile supplies. There should be areas for carts; space for bulk storage, active storage, and refrigerated storage; a fire safety cabinet or storage room that is constructed under the requirements for protection from hazardous areas in accordance with NFPA 101, Chapter 12, for volatile fluids; a secure vault, safe, or double locking wall cabinet for narcotics and controlled drugs; and space for general supplies and equipment not in use. There shall also be areas for quality assurance activities. Storage of hazardous drugs shall be segregated from all other inventory.

There shall be separate "cleared" and "quarantined" storage areas/rooms as defined by the program. If these areas are in the same contiguous space, there shall be a demarcation line between "clean" and "dirty" areas of the space.

13.5.9 Radiopharmacy Design Requirements

Radiopharmaceuticals are associated with the risk of radiation exposure to personnel. The radiopharmacy facilities shall comply with all appropriate pharmacy requirements and Nuclear Regulatory Commission (NRC) regulations. Radiopharmaceutical CSP must be prepared in a cleanroom environment with separate buffer and anteroom. PEC shall be placed in an ISO 7 classified buffer room.

A radiopharmacy shall be designed to have a multilayer system of protection, such that a failure at one layer is compensated for by subsequent layers, for the purposes of:

1. Preventing accidents that may cause exposure
2. Restoring safe conditions after an accident
3. Mitigating the consequences of any such accident that does occur

The radiopharmacy facilities shall additionally have the following special features in the radioactive substances preparation area:

1. Provide a secure, shielded storage area for radioactive substances. This may be a room, area, or a locked cupboard, safe, refrigerator, or freezer, situated in the work area.
2. Shielded temporary storage of solid radioactive waste and places designated for the disposal of liquid radioactive waste, and in no cases, directly connected to the main sewer.
3. Shielding to protect workers where significant external exposure may occur; a wash-up area for contaminated articles, such as glassware.
4. Subject to approval by the ORS Division of Radiation Safety (DRS), and the ORF Division of Environmental Protection (DEP), drains from radiopharmacy sinks shall route as directly as practicable to the main building sewer and should not connect with other drains within the building. The intent of this requirement is to minimize the possibility of a 'backup' contaminating other, non-controlled, areas.
5. All drains that carry potentially radioactive waste shall be labeled, and accurately depicted on the record of work as constructed documents.
6. Pipes through which radioactive materials flow

shall be marked to ensure that monitoring precedes any maintenance.

7. Where waste piping is required to be routed to any type of storage vessel (including for short-term half-life reduction) and for other conditions required by DRS or DTR, such radwaste piping shall be double contained Type 316 L stainless steel pipe or tubing of not less than Schedule 10 wall thickness (except that applications with high levels of chlorides shall be Hastelloy C22), and with radius pattern fittings. Piping joints for the internal carrier pipe shall be smooth and crevice-free, with complete joint penetration (CJP) ASME BPE type weld design (including or similar to autogenous orbital) for the primary carrier. Post-weld pickling and passivation is required for stainless steel systems. The containment annulus shall be of approved stainless steel, PVDF, or polyolefin material appropriate to the application and exposure, joined by a thermal fusion process and provided with automatic, segmented low-point leak detection.

8. Pressurized fluid piping containing radioactive liquids shall be double contained Type 316 L stainless steel of not less than Schedule 10 wall thickness. Piping joints for the internal carrier pipe shall be smooth and crevice-free, with ASME BPE type autogenous orbital weld design for the primary carrier and post-weld system pickling and passivation is required. The containment annulus shall be joined by heat fusion or weld methods and shall be provided with automatic, segmented low-point leak detection. Bundling of multiple compatible pressurized lines into common containment shall be approved at the discretion of DTR and DRS.

Additional Radiopharmacy Design Requirements:

1. Provide an entry/gowning/locker room area donning and doffing of PPE, and where washing and contamination monitoring can be performed. Provide a wash-up sink adjacent to the work area, out of the main traffic flow, as practicable. Faucets shall be operable without direct hand contact and lint-free disposable hand towels should be available. An emergency eyewash shall be installed near the hand washing sink.

2. There should be nearby access to an emergency shower for decontamination of persons in or near the laboratory. Do not provide a floor drain in this location. The temperature setting of this emergency decontamination fixture shall be confirmed with DRS for each application. Provide dedicated emergency fixture mixing valves where higher temperatures than otherwise permitted in Section 8.3 are required.

3. Radiopharmacies which will fill phantoms shall have deep sinks and foot pedal or knee controlled faucets in lieu of sensor controlled faucets.

4. Signage shall be per the requirements set forth in Appendix M, Interior Signage Manual. Confirm the program requirements and with DOHS. Additional information required to be posted includes:

    a. Access restrictions (on applicable doors)

    b. Name and telephone number of lab director on entry/exit door(s)

    c. Special requirements such as the required use of PPE, personnel access (on applicable doors)

    d. Signage material shall be resistant to degradation by decontaminants. Fully seal sign to the mounting surface.

5. The surfaces (i.e., bench tops, tables, seats, etc.) of the room where radionuclides are used or stored shall be smooth and non-absorbent so that they can be cleaned and decontaminated easily.

6. The outlets for supplies (e.g., gases, electricity, and vacuum equipment) shall be mounted on walls or stands (not on bench tops) unless otherwise dictated by program need.

7. The floor and benches, including worktops, shall be strong enough to support the weight of any necessary shielding materials or of radionuclide (Tc) generators, or other heavy, shielded equipment. The need for lifting equipment for radionuclide generators should be assessed.

8. If radioactive aerosols or gases may be produced or handled, provide an ventilation system that includes an appropriate PEC (fume hood, laminar airflow cabinet or glove box). The working surface of the PEC should have a slightly raised lip to contain any spills.

9. The ventilation system shall be designed such that the suite is at a negative pressure relative to surrounding areas, except where required to contain radioactive powders, gases, or similar materials. The airflow shall be from areas of minimal (lower) likelihood of airborne contamination to areas where such contamination is likely.

10. All air from the suite should be exhausted through a PEC or LSW exhaust grill to the exhaust system and shall not be recirculated either directly, in combination with incoming fresh air in a mixing system, or indirectly, unless approved by DRS and DTR.

11. Some radiopharmacy spaces may require a positive, rather than a negative pressure, relative to the surrounding rooms. In this case, the pressure gradient can be obtained by a sink anteroom separating the ISO 7 compounding room (Cleanest and with its own exhaust), from another workroom, preceded by a bubble anteroom, or similar arrangement to promote asepsis.

12. Controlled access is required to gain entry to the source storage and preparation areas.

There shall be adequate provisions for the calibration, quality assurance, and operation of diagnostic and therapeutic equipment. This may include, but not be limited to maintaining adequate service and use clearances around the equipment; accessible test ports; and other provisions to facilitate these activities.

Section 13.6

APF Design Requirements: Architectural

Contents:

13.6.0 Introduction

Architectural finishes and details are a critical system for the overall performance of APFs. The design and selection of APF architectural surface finish systems, materials and details must promote cleaning, maintenance and proper operations. All surface finishes shall be selected to be compatible with the anticipated agents and methods used for cleaning, disinfection or sterilization and protocols used by the program without damage or degradation, including discoloration. See Section 4.4.5.

Surface finishes shall not be selected based on a first-cost, but on a life-cycle cost basis for the facility. Systems shall be impact resistant and shall have smooth, sealed joints and transitions, eased outside corners and coved inside corners.

Surface finish selection shall take into consideration the following factors:

A. Material: Finish material shall be non-particle generating; inert; impervious, non-absorptive; not harbor or sustain mold or microbial growth; all joints and penetrations properly detailed and constructed; configured without recessed areas and voids that are difficult to access for cleaning and pest management (See Section 1.12 and Section 13.15.4).

B. Cleanable: Architectural finishes shall be seamless/monolithic; easily cleaned, sanitized, and maintained; smooth; monolithic; designed such that sharp corners (particularly inside corners), joints, crevices and other conditions that can collect dirt shall be eliminated to the extent practicable; horizontal surfaces (i.e., large horizontal surfaces, including bench tops, floors, seats, etc., as well as small horizontal surfaces such as window ledges, electrical raceways, etc.) shall be minimized.

C. Durable: Material shall be able to withstand regular exposure to aggressive cleaning and sanitizing chemicals and cleaning processes without degradation, abrasion, impact, and overpressure damage resistant. Existing materials which can be damaged by anticipated use and maintenance must not be reused or shall be protected (i.e., wall protection panels, etc.).

Some typical cleaning agents used individually, sequentially, or in combination at APFs include, but are not limited to:

1. Sodium hypochlorite
2. Hydrogen peroxide
3. Peracetic acid
4. Isopropyl alcohol

Material selections shall be laboratory tested against the agents and methods used for cleaning and sanitization as well as all agents identified by the program that will be used at the facility. Testing shall be performed for agents individually and in sequential combination. It is recommended that testing is performed for failure to adequately remove/neutralize exposure to peracetic acid. If a record of performance with agents is not available, then a mock-up test shall be conducted, documented, and passed prior to selection.

Test reports shall be submitted to document the suitability of material specifications for all locations subject to an APF cleaning program. Standard DRM details and materials may be utilized in other areas of the APF. Mockups shall be fabricated and tested as a system and incorporated into the construction of the facility.

13.6.1 Ceilings

APF ceiling design considerations shall include, but not be limited to:

A. Structure: Ceiling structures must be designed to resist sagging and deflection due to room pressure gradients, including pressure reversals, without damage to their supported finishes. Therefore, a rigid, self-supporting ceiling system directly attached to structure is preferred; suspension of structure by threaded rod is allowable; suspension of structure by hanger wire is disallowed for classified and non-classified areas within APFs.

B. Systems: Acceptable APF ceiling systems include:

1. **ISO 7 or better:**
    a. Monolithic ceilings with high-performance finish systems are preferred in rooms with ISO level classifications of 7.
    b. Where monolithic systems cannot be

provided (due to existing conditions, etc.) and suspended panel systems are selected, a panelized system composed of fiberglass reinforced polymer (FRP) or uPVC are preferred so long as the system is gasketed with hold down clips to create a fully sealed system.

c. Monolithic composite panelized ceilings are preferred.

d. Fully-sealed, cleanroom suspended tile system with cleanroom ceiling tiles gaskets and hold down clips are allowable.

e. High-performance epoxy-coated drywall systems are allowable, but should be minimized to the extent practicable.

2. **ISO 8, CNC, and NC:**

a. Monolithic composite panelized ceilings are preferred.

b. Fully-sealed, cleanroom suspended tile system with cleanroom ceiling tiles are allowable.

c. High-performance epoxy-coated drywall systems are allowable, but discouraged.

C. Additional Design Considerations: All APF ceilings shall be an integrated system with the walls, or shall have a flush, smooth sealed ceiling/wall joint. Acceptable materials/ systems shall be "smooth and impervious", and:

1. **Monolithic composite FRP, uPVC and other moisture and chemical-resistant panel systems:**

a. Panel system can either be walkable (preferred) or non-walkable (acceptable).

b. Shall be adequately supported to prevent sagging and/or delamination under loads, including air pressure-driven deflection (hyper-negative/positive).

c. Joints should be flush and smooth, and preferably batten-less.

d. All components shall be tested for resistance to the cleaning materials and methods and as a system.

e. Refer to Section 4.4.5 Wall and Ceiling Finishes for Aseptic Facilities, BSL-3, ABSL-3, and Similar Facilities for additional requirements.

2. **Cleanroom suspended tile systems shall meet or exceed the following criteria:**

a. Designed and built per manufacturer's requirements and recommendations for not less than one ISO classification level better than the design requirement of the room.

b. Where accessible, suspended tile panel systems are used, provide heavy-duty corrosion-resistant, gasketed grid and hold-down clips that result in compression of the gasket around the entire perimeter of each panel. Hold-down clip design shall allow for panel removal without damage to the ceiling system in areas where utility access is required.

c. All components shall be tested for resistance to the cleaning materials and methods and as a system.

3. **High-performance epoxy-coated drywall systems shall meet or exceed the following criteria:**

a. Composition and thickness of coating systems are dictated by the functional requirements of the space they serve. Gypsum wallboard within an APF shall be specialized high impact moisture resistant systems appropriate for APF environments. Standard commercial systems are not acceptable. Consideration should be given to protecting gypsum wallboard partitions with abuse-resistant glass fiber reinforced finish system. A level 5 gypsum drywall finish system is not permitted.

b. Total minimum wet-film thickness after substrate preparation shall be 0.25 mm (10 mils), but not less than manufacturer's recommendations for the specific application.

c. Dry film thicknesses are difficult to ascertain, so DTR prefers recorded wet film thicknesses during installation, per

ASTM D4414 – 95 Standard Practice for Measurement of Wet Film Thickness by Notch Gages.

d. Substrate shall have a noncombustible (fire-rated, Type-X, where required), moisture and mold-resistant core; and shall have a moisture resistant fiberglass mat faces, or similar.

e. All components shall be tested for resistance to the cleaning materials and methods and as a system.

D. Access Panels/Doors: Access panels must be minimized within aseptic facilities. MEP systems shall be specifically designed to locate all items requiring maintenance, service, and adjustment outside of the facility perimeter to the greatest extent practicable. The number of access panels should be minimized; a single, larger panel is preferred to multiple small panels.

If access doors must be located in an APF they shall be flush stainless steel, fully welded, and gasketed. Access doors must have multi-point concealed latches, positively latch and provide an airtight, fully gasketed seal (watertight, where required by the application). See Section 1.15.1, Common Engineering Systems' Requirements for Service Access and Service Access Panels.

Where required, access panels shall have the following characteristics:

1. Flush, fully welded and closed-cell gasketed stainless steel frames with concealed hinges are preferred.
2. Airtight/Watertight/Bubble-tight access doors are required within APFs.
3. Screwdriver operated cam latch is preferred; Key locking-type latches shall not be permitted.
4. Where required for pressurization, bubble-tight access panels shall be utilized.

E. Sprinkler Heads: The selection of sprinkler heads shall take the cleaning process/protocol into consideration and vice versa. Concealed, flush-mounted sprinkler heads are preferred (the cleaning SOP, shall consider and address the potential for buildup of cleaning residue between the cover and ceiling).

F. Ceiling Penetrations: Light fixtures, HVAC components, sensors, and other ceiling mounted devices must be sealed or gasketed to ceiling finish material. Piping, ductwork, electrical boxes, conduits, and other penetrating items shall be firmly anchored to resist movement that could damage seals.

G. Ceiling-Wall Interface: All finish transitions shall be smooth, flush and sealed. Radiused inside and outside corners are preferred for cleanability.

13.6.2 Walls

APF wall design considerations shall include, but not be limited to:

A. Structural: Wall construction shall be designed to provide the required strength to support the imposed loading and with sufficient stiffness, to minimize deflection and movement, and eliminate finish cracking and sealant failures. Wall construction and materials must be selected to ensure compatibility with finish systems, and to provide a smooth, void-free substrate. All seams and fasteners must be fully sealed, and the system adequately supported to prevent sagging, deflection or delamination. See Section 4.3.2, Laboratory Partitions for additional requirements.

B. Materials: Provide impact-resistant wall system, including protection and components. Following is a listing of finish materials for APF walls:

1. Monolithic composite panelized systems are preferred.
2. They shall be adequately supported to prevent sagging and/or delamination under loads, including air pressure-driven deflection due to hyper-negative/positive over-pressurization).
3. Joints shall be flush and smooth, and preferably batten-less.
4. All components shall be tested for resistance to the cleaning materials and methods and as a system.
5. Modular cleanroom wall systems are also preferred.

6. They shall be designed and built per manufacturer's requirements and recommendations for not less than one ISO classification level than the design requirement of the room (preferred).

7. They shall incorporate windows, doors, and other accessories, as required for a complete installation, including all accessories and rough-ins.

8. Primarily glazed cleanroom wall systems that are modular cleanroom wall systems are also preferred, but have special wall protection requirements (i.e., floor-mounted crash rails, etc.). These are additionally preferred due to enhanced observation and communication capacity.

9. High-performance epoxy-coated drywall systems are allowable, but not preferred (See Section 13.6.1, Ceilings, high-performance epoxy-coated drywall systems for additional requirements).

10. Filled concrete/masonry/plaster surfaced with high-performance coatings are disallowed for APFs.

C. Details: Detailing requirements for APF walls include, but are not limited to:

1. The tops of hollow partitions shall be sealed to exclude pest infestation.

2. Walls shall be sealed to door frames, cover plates and all other openings and penetrations.

3. They shall be coved in the wall-ceiling, wall-wall, and wall-floor transitions to promote cleaning.

D. Wall Penetrations: Windows, doors, pass through chambers, HVAC components, sensors, and other wall mounted devices must be sealed or gasketed to wall finish material. Piping, ductwork, electrical boxes, conduits, and other penetrating items shall be firmly anchored to resist movement that could damage seals. All seams and fasteners must be fully gasketed and sealed.

E. Wall Protection: Wall finishes shall be protected from impact and wear; see Section 13.6.5, Wall Accessories for additional information.

F. Wall-floor Interface: All finish transitions shall be smooth, flush and sealed. An integral cove base is required to transition from the wall to the floor.

13.6.3 Doors & Hardware

Doors play a critical role in the overall design as they function to maintain pressurization and, prevent contamination. As in labs at NIH, pocket doors, bi-fold doors and accordion doors are not permitted in APF due to the crevices that are difficult to clean as well as issues related to pest management and maintaining control. Specialty doors such as automatic operating sliding doors may be allowed only if fully cleanable and do not promote dirt collection and require approval by the PO/COR, DFM and DTR/FCIS. High-quality doors, door frames and hardware are to be selected for high use due to durability, maintenance and operations issues. The following criteria are to be applied in the selection of doors and associated hardware.

A. Frames:

1. All door frames shall be fabricated from type 304 stainless steel or extruded aluminum.

2. Fully welded, mitered stainless steel or FRP frames are preferred.

3. New knock-down hollow metal (KDHM) frames, included welded, filled and ground, are disallowed in APFs.

4. Existing to remain (ETR) KDHM frames are discouraged in ISO classified areas for construction projects.

5. Frames should be flush with the adjacent walls to present as few horizontal surfaces as possible.

6. Frame shall be well anchored to minimize deflection/distortion, to avoid abrasion (particle generating).

7. Door frames shall accommodate replaceable, closed-cell bubble gaskets. Bristle sweeps are not permitted in APFs.

B. Doors:

1. Doors shall be designed and fabricated for cleanroom applications from stainless steel (low carbon), or FRP with half or full glass vision panels for high visibility.
2. Door panels shall be fully flush on all sides with no recesses or openings on any side. Top rails must be flat on top, not channel construction.
3. Doors should present as few horizontal surfaces as possible.
4. Doors, frames and hardware shall not create voids, crevices or cracks which require caulking.
5. Preferred cleanroom door slabs include:
    a. Minimum 16 Ga., type 304 stainless steel, with a solid polyurethane core.
    b. Minimum 3/8" thick (9.5mm), fully-glazed tempered glass with smooth-polished edges on all sides.
    c. Seamless molded fiberglass, with solid polyurethane core.

C. Door Hardware:

1. All door hardware should be fabricated from type 304 stainless steel.
2. High load lift-off (pivot) hinges are preferred over knuckle hinges.
3. Handles and locks shall be smooth, non-snagging and cleanable.
4. Hardware, such as latches, locks, hinges, and door/frame interfaces shall be closely adjusted to minimize abrasion (particle generating).
5. Automatic door operators should be considered for hands-free operation, and if used, infrared motion detector activation is preferred over push plates.
6. Door position switches may be provided on doors monitored for differential pressure, and tied to the BAS for collecting door position data (for BAS alarm response and management).
7. Thresholds should be avoided to the extent practicable.
8. Provide sloped top shrouds for door closer power units, where the unit cannot be fully recessed into the wall.
9. Drop-down sweeps should be avoided in favor of solid, adjustable, fixed sweeps.
10. Bristle-type sweeps and astragals are prohibited inside APFs, but may be considered for perimeter doors.
11. Provide door plates.
12. Door systems shall be fully integrated with automatic openers, emergency egress overrides, door interlock systems, door status indicator lamps, door position switches, electrified mortices/mag-locks, etc. that are appropriate for the following characteristics:
    a. Resistance to the cleaning materials and methods.
    b. Ability to fully compress the bubble gasket and latch/unlatch and unseal through the entire range of motion, as designed, against the 2x the full design pressure differential and reversal of that condition.

D. Door Configuration:

1. Doors should be configured to open to the higher pressure-side where practicable, and/or provided with mechanical operators.
2. Where the design pressure on the door exceeds .04 in. w.c., a mechanical door operator shall be provided.
3. Doors in series, functioning as a vestibule or anteroom, shall be physically or operationally interlocked. Interlock function can be via electromagnetic locks, red light/green light indicators, or through other administrative controls, established by the users and documented in SOPs or, some combination of systems. The interlocking scheme shall be reviewed and approved during design.

E. Doors in Series: Particular to anterooms, but common in APFs, are the feature of doors in series. An NIH APF is not a place of public accommodation and is an access controlled area within a federal facility, so the Architectural Barriers Act Accessibility Standard (ABAAS) is the governing regulation for accessibility.

The ABAAS does not contemplate a condition where the doors are required by procedure or physical interlock to be incapable of simultaneous operation. NIH cannot grant a variance on the ABAAS requirements, and an Access Board waiver may be required where it is desired to treat this condition as conforming to ABAAS 404.2.6, or other interpretation which seeks to shorten this distance due to space constraints.

13.6.4 Windows

Exterior windows are not desirable within APFs and should be avoided, particularly in ISO classified spaces, due to the possibility of moisture migration as well as air infiltration and the resulting bioburden to the space. However interior windows are desirable within APFs for safety, visual inspection, aesthetics, and to provide borrowed light.

A. Frames: APF window frame considerations shall include, but not be limited to:

1. Fully flush, frameless stainless steel or FRP construction are preferred in ISO classified spaces
2. Knock-down frames including welded, filled and ground, are disallowed in APFs.
3. Glass stops and other components shall be integral with the frame, sealed or concealed.
4. Frame surface shall be sloped or otherwise detailed to eliminate horizontal surfaces. The perimeter of frames shall be flush with and sealed to adjacent wall finish for ease of cleaning as to prevent settling of dust.

13.6.5 Wall Accessories

In APFs, wall accessories include components affixed to the wall; made of durable materials; resistant to the cleaning chemicals, designed to minimize caulking while maintaining cleanability; and able to resist differential pressures without leakage. Caulking/sealing shall be done all-around wall accessories. See Exhibit 13.6.

Within APF, non-classified areas, normal DRM compliant wall accessories may be provided, but it is recommended that these also comply with the stricter requirements listed here. The following requirements apply to all other areas within APFs.

A. Crash/Bumper Rails: Crash/bumper rails shall be heavy duty stainless steel (304 or 316 L); tubular style; floor or wall-mounted with countersunk/concealed and sealable fastening hardware (typically flat bar posts with circular baseplate); corners pre-formed; standards should suspend the rail not less than 76 mm (3 in.) off the face of the wall to facilitate cleaning all-around. Provide suitable structural backing to support mounting.

B. Corner Guards: Corner guards shall be heavy duty stainless steel (304 or 316 L); pre-formed to the angle of the outside corner; fully adhered using 2-part epoxy; full-height; and gapped 13 mm (½ in.) from other wall accessories to facilitate caulking all-around. The width can vary, depending on the location, but should be not less than 51 mm (2 in.).

C. Scuff Plates: Scuff plates are heavy wall protection plates that are fully adhered and sealed to the wall. They shall be heavy duty stainless steel (304 or 316 L) or FRP-type panel, not less than 1.905 mm (0.075 in.); fully adhered using 2-part epoxy, and gapped 13 mm (½ in.) from other wall accessories to facilitate caulking all-around. The width can vary, depending on the location, but should be not less than 152 mm (6 in.). The centerline of the mounting height shall align with the contact point of the carts, shelves, tables, etc. that are anticipated to impact the wall in these locations.

D. Shelves and Standards: APF shelving should be cart-mounted where practicable (furniture/cart shelving is preferred to wall-mounted for clean-ability). Where shelves and standards must be wall mounted, the standards shall be heavy duty stainless steel (304 or 316 L); mounted rails on stand-off shelf bracket supports that have an adjustable tubular standard suspended

between. Where KV-style brackets are necessitated, due to load considerations, they shall be provided with covers and closures to seal the ends of the standards as well as any unused holes in the standard. All shelves shall be heavy duty stainless steel (304 or 316 L), or epoxy-coated plated steel wire shelves. Provide suitable structural backing to support mounting.

E. Cleanroom Clocks: Cleanroom clocks shall be specially designed and manufactured for the cleanroom environment. The clocks shall be recess mounted; stainless steel (304 or 316 L). The clock features and color shall be selected by the facility owner. Clocks may be hard wired or battery powered (but not less than a 10 year battery).

F. Cleanroom Telephones: Cleanroom telephones shall be compatible with NIH telephone hardware requirements, and shall be designed and built for cleanroom applications, including oversized buttons, smooth and impervious front panel, and shall be water resistant.

G. Fire Extinguisher Cabinet (FEC): FECs shall be fabricated from stainless steel (304 or 316 L), with a frameless glass door. The cabinet shall be designed to install flush with the wall in a prepared cavity.

H. PPE Dispensers (Built-In): Shall be fabricated from stainless steel (304 or 316 L), or other compatible material. Provide suitable structural backing to support mounting.

I. Signage: All APF signage shall be non-permeable, non-shedding, cleanable and resistant to regular exposure to cleaning chemicals and processes without degradation. All surfaces should be "smooth, impervious, free from cracks and crevices, and non-shedding".

APF signage should be formed from a single reinforced plastic or aluminum blank, fully adhered and caulked to the wall (not door), per the Architectural Barriers Act Accessibility Standard (ABAAS) guidelines. Sign headers and colors on safety signs shall comply with OSHA and ANSI specifications to designate the severity of the hazard. Signs that are pre-drilled for mechanical fasteners should be avoided in favor of continuous sign blanks, fully-adhered. ABAAS-required braille and raised numbers should be considered exempt from the "smooth" requirement (e.g., braille and raised lettering is allowed).

Paper-based certification labels on equipment, such as BSC certifications are prohibited in APF areas. Debossable aluminum self-adhesive labels are the preferred solution to this issue.

J. Pass Through Chambers: Pass through boxes/chambers/cabinets shall be used where material (or carts with or without materials, in the case of cart pass-through chambers) must transit between rooms of differing risk, classification, and/or differential pressure in order to reduce the risk of contamination. Pass through assemblies shall be constructed of welded stainless steel; flanges and mounting brackets are necessary for a flush, sealed installation in the wall. Doors shall be interlocked, positively latched, and gasketed to provide an air-tight seal and maintain pressure differentials, and should have full lite glass doors for visibility.

All pass through chambers in APFs shall be active. See Section 13.8.9 for additional information.

Cart pass through chambers must be sized to accommodate the largest anticipated cart, including the cart's anticipated load. Material pass through chambers must be sized to accommodate the largest anticipated containers but shall not be less than 460 mm x 460 mm x 460 mm (18 in. x 18 in. x 18 in.) and shall be structured to support no less than 23 kg (50 lb.).

Floor flatness at and around cart pass through chambers (i.e. extending not less than 2x the door swing for existing facility renovation projects) must be adequate to create and maintain pressurization between the seal and the floor. See Section 13.7.2 for additional information on floor flatness requiremenets.

K. Other Accessories: Other accessories shall be of appropriate materials suitable for the APF environment. Interface points to the wall shall be caulked to eliminate gaps, cracks, and edges. Where practicable, the accessories shall be installed flush with the surface of the wall. The wall should be bumped out as required to facilitate this condition. Large accessories should be flashed to the wall with not less than 51 mm (2 in.) wide stainless steel flashing. Accessories that are not flush should be gapped from perpendicular wall surfaces not less than 305 mm (1 ft.) to facilitate cleaning. Where this spacing is not achievable, instead minimize the gap and bridge the resulting/remaining gap with not less than 51 mm (2 in.) wide stainless steel flashing.

13.6.6 **Floors**

Finished flooring in the APF shall be monolithic and seamless with integral coved base (152 mm [6 in.] minimum height) and shall be extended wall-to-wall, including under equipment and casework systems. It shall also have radiused inside corners. Transitions of flooring with the wall, door frames, and all other elements shall be smooth, flush and sealed. All transitions shall be detailed in the drawings.

The following criteria shall be taken into consideration for APF flooring design.

A. Structure: Floor construction shall be level and adequately strong to support the anticipated loads without deflection, cracking or movement. Floors, including finishes, shall be capable of withstanding impacts and heavy wheeled traffic without damage.

B. Floor Preparation: Prior to installation of the finish system, the manufacturer must inspect the floor and certify that all required conditions for the finished floor installation have been met.

C. Materials: Finish flooring material shall be selected based on cleanability, level of traffic (foot and wheeled), loading, use of cryogenics and resistance to chemicals and disinfection agents. Selection of floor finish shall take into consideration shoe covers worn by the user, as part of the gowning process, to ensure that selected finish has sufficient slip resistance. To the extent practicable, the same flooring material should be used throughout the APF, including classified and non-classified areas. Acceptable finish materials for APF floors include, but are not limited to:

1. Welded seamless sheet vinyl:
    a. The sheet vinyl cleanroom flooring system shall be designed and installed per manufacturer's requirements and recommendations for not less than one ISO classification level than the design requirement of the room (preferred).
    b. Sheet vinyl shall be heavy-duty, commercial cleanroom grade, non-porous, abrasion resistant, easy to clean, resistant to damage under both static and dynamic loads.
    c. User group shall provide electrostatic characteristics during design (if applicable).
    d. All components shall be tested for resistance to the cleaning materials and methods and as a system.
    e. Installation shall use heat welded seams.
    f. Use of factory formed, reinforced inside and outside cove corners is preferred, top form an integral cove base.
2. Cold-Welded Rubber:
    a. Cold-welded rubber sheet cleanroom flooring systems shall be designed and installed per manufacturer's requirements and recommendations for not less than one ISO classification level than the design requirement of the room (preferred).
    b. Sheet rubber shall be heavy-duty, commercial cleanroom grade, non-porous, abrasion resistant, easy to clean, resistant to damage under both static and dynamic loads.
    c. User group shall provide electrostatic characteristics during design (if applicable).
    d. All components shall be tested for resistance to the cleaning materials and methods and as a system.
    e. Use of factory formed, reinforced inside and outside cove corners is preferred, top form an integral cove base.
3. High-Performance Resinous Coatings:
    a. High-performance resinous coating flooring systems, typically urethane-based, shall be designed and installed per manufacturer's requirements and recommendations for not less than one ISO classification level than the design requirement of the room (preferred).
    b. High-performance resinous coating flooring systems are allowed, but not preferred.
    c. Careful attention shall be paid to friction-enhancing components to reduce slips and falls, to avoid creating conditions that damage cleaning mops, or impair thorough

cleaning.

4. Other Flooring Materials:

    a. Vinyl composition tile (VCT), raised access flooring, and other non-monolithic flooring systems are not appropriate for the APF environment.

D. Line Of Demarcation (LOD): These are lines/markings on the floors that indicate step-over lines, cart excursions at cart pass throughs and other administrative controls that limit the range of movement allowable in areas within an indicated area of the APF. There is a range of options available for permanent marking of these lines:

1. **Change in Floor Material Color:** This should only be utilized where there is a high level of confidence that the LOD will remain fixed for a long time, especially for epoxy-type flooring.

2. **Inset Lines:** Preferred method, based on impact to change, and maintenance impacts.

3. **Floor Marking Tape:** This is the most flexible approach where the program is subject to change, however, it poses the highest risk of failure due to adhesion issues, or difficult to maintain. Mockup testing is therefore essential prior to deploying a tape solution.

13.6.7 Furnishings

Moveable, cleanroom specific furniture should be used in lieu of built-in, wherever possible. Items should be easily removable or moveable for flexibility and, to allow for cleaning and decontamination.

If built-in items are required, they shall be cleanroom specific, sealed to the wall and floor (where allowed by regulation) and be welded stainless steel or other APF-appropriate seamless material that can withstand the cleaning regimen of the facility.

13.6.8 High-Performance Coatings

The composition and thickness of coating systems in APFs are dictated by the functional requirements of the space it serves. High-performance reinforced multi-coat resinous paint finish on anti-microbial and mold-resistant gypsum board may be considered when there are functional advantages over modular, panelized systems and if approved by ORF and the program. In the APF, high-performance coatings on masonry and other surfaces which are not impervious, flat and smooth are not permitted.

A. Testing/Mock-Ups: Where epoxy paint and other specialized high-performance coatings are selected as floor, ceiling or wall finish, selected system and surface finish coating shall have been verified for compatibility with the cleaning chemicals identified by the program, for use in the facility. When data is not available and/or is questioned, coupon testing of selected finish and/or mockup with finish product shall be tested to ensure compatibility.

The following requirements are in addition to the manufacturer's installation requirements.

1. **Installer Qualifications:** Coating applicators shall be minimum Society for Protective Coatings (SSPC) Coating Application Specialist (CAS) Level II Certified, and must be trained and approved by the coating system manufacturer for the application of the specified products and techniques, required for the application of products per the manufacturer's recommendations and requirements.

2. **Independent Inspection:** All high-performance resinous coating system applications must be inspected by an independent third-party Coating Inspector Program (CIP) level-III certified inspector (approved similar qualifications may be considered) throughout the preparation and installation. The inspector shall then prepare and submit a detailed report on the installation.

13.6.9 Modular Components

Modular wall and ceiling panelized systems provide significant performance advantages over stick-built and coated systems, including uniformity, high resistance to degradation, and incorporation of cleanroom detailing.

A. Wall and Ceiling Panels: Pre-e ngineered wall and ceiling panels constructed of Fiber-Reinforced Plastic (FRP), Chlorinated Polyvinyl Chloride (CPVC), High Density Polyethylene (HDPE) with polyester gel coat, or other material that has been tested to demonstrate non-shedding, cleanable, and resistant to regular exposure to cleaning chemicals and processes without degradation properties. The panels shall be tested and certified to meet or exceed the ISO cleanliness of the room in which it is to be installed, per ISO 14644-1. The system shall not outgas post installation.

Surface finishes shall not be selected based on first-cost, but on the life-cycle cost basis for the facility. Systems shall be impact resistant and shall have smooth, sealed joints and transitions, eased outside corners and coved inside corners.

All materials shall resist damage due to exposure to cleaning materials and methods, heat, humidity, and other abuse that will reasonably be anticipated to be encountered in the life cycle of the facility, without degradation below minimum service level for the application.

All finish material selections shall exhibit mold and mildew resistance properties. Products shall be installed over cellulose-free (inorganic-faced) substrates only.

Provide impact-resistant wall system, including protection and components.

The joint systems should be batten-less, with concealed fasteners, and coved at all inside corners, including wall-wall, and wall-ceiling joints. All joints should be filled, smooth and continuous with equal or better resistance to degradation than the field panels (i.e., chemically welded). The finish of modular panels should be smooth, glossy, and white. The panels should be the largest size practicable. All wall-wall and wall-ceiling interfaces should be coved with pre-manufactured components designed for that purpose. All wall-floor interfaces should be coved utilizing the flooring system and terminated to the wall panels with a smooth, cleanable condition that does not create a horizontal surface.

Panelized composite wall and ceiling systems are preferred due to their controlled-environment manufacturing, design versatility, chemical resistance, pressure/airflow resistance, and pre-engineered details. Selected panel systems shall be resistant to the chemicals listed in the Cleaning and Sanitizing SOP for the APF.

Installation must be by certified installers. Substrate material and detailing must be inspected and certified as acceptable by the manufacturer. Adhesives, sealants and all other system components must be as chemical resistant as system panels. Panel Systems shall be Class "A" Fire Rated both as a composite assembly and for the surface alone.

Mechanical, Plumbing, Process Piping, Electrical Power, Electrical Low-Voltage, and other systems should be integrated into wall and cavity spaces behind the panels using metal stud framework. Integrated openings, such as for service panels, fire extinguisher cabinets, etc. should be planned and detailed to ensure continuity of the room envelope. Wall protection should consist of stainless steel corner guards and scuff plates, fully adhered to the wall panels, gapped 13 mm (½ in.) and caulked.

Modular panelized ceiling systems may be fully adhered to a structural joist system, suspended by clips to a threaded rod hanger, or a specially designed, gasketed, cleanroom lay-in ceiling grid, suspended by threaded rods from the structure above. Cable supported ceiling structures are not permissible in APFs.

B. Windows: The interior windows should be provided as part of the modular panel system to the extent practicable. There should be no exterior windows in APFs. These components should integrate with the wall system such that they produce a completely flush condition, without horizontal ledges or joints.

Generally windows will be the full depth of the wall to create flush surfaces on each side of the wall, and should be hermetically sealed and include a desiccant or other means to prevent condensation within the window unit. All windows in APFs should be tempered.

C. Doors, Frames & Hardware: The door systems should be specialty cleanroom doors, smooth, easy to clean, non-shedding, non-porous, resistant to microbial growth, and resistant to regular exposure to cleaning chemicals and processes without degradation. Except

where precluded by the program, all interior APF doors should have half-lites or larger to promote visual communication and safety.

13.6.10 Caulks and Sealants

For APF projects, all joints, gaps, seams, penetrations and voids in and within the facility, shall be completely sealed, forming a continuous monolithic and impermeable infiltration barrier, to enhance sanitation, facilitate gas and/or vapor decontamination, and maintain pressure differentials. APF sealant requirements are different from other project types, as described in the, see Exhibit 13.6 for the APF sealant table. Other areas that require sealant include:

1. All fixtures, furniture, and devices (including fixed equipment, casework, shelving systems, mechanical and electrical devices) shall be completely sealed, including, but not limited to, all conditions listed in the Sealant Table.

2. All penetrations into, and through partitions, floors, and ceilings, listed in the Sealant Table, shall be in addition to, and not a substitute for, rated sealants.

A. Sealant Selection: Confirm compatibility between sealants and the material to which they are applied. Sealant must have chemical resistance, flexibility, durability, adherence, mold resistance and other characteristics appropriate for its use. Opaque sealant shall be utilized to verify full coverage and highlight imperfections in application.

B. Sealant Types: All sealant used in the APF shall be 100% silicone (i.e., JS-5 100% Silicone ASTM C920) and mildew resistant. Use aluminum finish silicone sealant when sealing stainless steel equipment, fixtures and assemblies.

Stainless steel to stainless steel joints shall be sealed with clear silicone. All other joints shall be white silicone.

C. Sealant Installation: Sealant shall be applied in accordance with the manufacturer's requirements and recommendations, without drips or excessive material, uniform, smooth, and continuous manner, resulting in a finish free of voids, pinholes, sharp edges, or excess sealant. Sealant must be full coverage, without gaps or voids.

Sealant must be compatible with all material that it is in contact with, including other sealants. Previously sealed items shall be cleaned of old sealant and properly prepared for resealing.

Sealant shall not adversely impact the operation of sprinklers or other devices. All items shall be firmly anchored, and wall and ceiling construction designed to resist movement that could damage seals.

D. Sealant Details:

1. All joints between materials and systems will be flush wherever possible and will be gasketed and/or sealed.

2. Penetrations shall be visible for inspection and maintenance.

3. Penetrations in rated assemblies shall be appropriately UL listed and approved by the DFM. Finish sealants, listed in the sealant table, shall be in addition to, and not a substitute for, rated sealants. Seams between walls, floors, and ceilings, and between all dissimilar materials shall be fully sealed. Sealant at movement joints shall be applied after installation of finishes to resist cracking.

4. Where escutcheons are provided, they shall consist only of a flat, non-corrosive plate, free of concealed or inaccessible voids, fully embedded in sealant and completely sealed to the penetrating item.

E. Sealant Installation Execution Plan: The Sealant installation execution plan shall be provided and approved by the PO/COR, DTR/FCIS, DTR and the ORSC, OD prior to installation. The Execution Plan shall indicate the responsible party for installing all sealants, including their experience and qualifications.

F. Sealant Mock-Up: The sealant mock-up shall be constructed for approval of the PO/COR, Pest Management Representative and DTR/FCIS. The mock-up shall include all typical conditions and materials, and shall remain in place as a basis of comparison and approval of the final installation.

13.6.11 Mock-ups

Mock-ups are required for all aseptic facility projects. The mock-ups shall be constructed with the same conditions, using the same materials and techniques as the final installation. Mock-ups shall include sections of all finish materials and systems (coatings, floor, wall and ceiling finishes, sealants, door frames, access panels, cover plates, wall protection, etc.), in all typical conditions (inside and outside corners, base/wall junction, wall/ceiling junction, wall and ceiling-mounted devices, etc.). Mock-ups shall be approved by the PO/COR, program personnel, DTR and other stakeholders, and shall be maintained as a reference for the minimum level of acceptable quality and workmanship.

Mock-ups may be used for chemical and other testing if required performance records for materials are not available, or deemed necessary for facility users or DTR.

13.6.12 Finish Cleaning Schedule

The construction contractor shall furnish a table of all finishes, including caulks and sealants, potentially exposed to cleaning. This table shall be predicated on a triple clean (meaning sequential cleanings with germicidal detergent, sporicidal, phenolic disinfectant, hydrogen peroxide and/or other oxidizing cleaners). The table should describe the various manufacturer's minimum curing schedule prior to exposure to the site-specific triple cleaning protocol.

Section 13.7

APF Design Requirements: Structural

Contents:

13.7.0 Introduction

Structural design is crucial to the performance of an APF. Critical assessment of proposed structural framing should reflect current planned as well as future needs. The Office of Research Services (ORS), Division of Physical Security Management (DPSM) may provide additional structural requirements, including, but not limited to progressive collapse and hardening. See Section 5.2.1, Structural Design.

Perform early planning and coordination with the entire design team. The PO/COR shall ensure that the structural engineer learns the needs of all disciplines, resolves issues, and develops a multi-discipline-coordinated structural system.

13.7.1 Structural Capacities

The total weights of APF trailers and modular buildings shall be transferred to supporting structures, within the live load capacity of the supporting structural framing. APFs shall not be subject to live load reduction.

A. Live Loads:

1. The general live load capacity of a new APF floor shall be not less than 6 kPa (125 PSF).
2. Walkable ceiling, with light traffic only (i.e. changing filters, lamps, and similar light work) = 1.0 kPA (20 PSF).
3. Snow Loads: See Section 5.4.5.
4. Wind Loads: See Section 5.4.5. Additionally, tie-downs or their equivalent shall be provided sufficient to resist uplift and overturning force(s).

B. Dead Loads:

1. The APF shall be designed to support the actual weights of all materials. These include structural materials, finishes, ceilings, partitions, shielding, electrical wiring and conduits, piping, and ductwork.
2. Assumed weights shall be indicated on the design documents.
3. See Section 5.2 for additional structural load requirements.

13.7.2 Floor Flatness

APF Design documents shall specify minimum floor flatness and floor levelness tolerances when the installations of finish materials, functional conditions, or equipment dictate tight control of concrete slab substrates. This is of particular importance where cart pass throughs are utilized, due to their required seal to, and door swing interactions with the floor surface.

Avoid raised thresholds, steps, or ramps in corridors and other areas used for material transport to the extent practicable.

See Table 13.7.2 for a summary of these requirements.

Table 13.7.2 Recommended Floor Flatness

Minimum Recommended F numbers for APF Floor Profile Categories:

Area	Character	Random Traffic Floor				Defined Traffic Floor
		Specified Overall Value		Minimum Local Value		
		F_F	F_L	F_F	F_L	F_{MIN}
Critical APF Areas	Flat	50	33	25	17	50
General APF Areas	Good	38	25	19	13	38

13.7.3 Vibration Control

The structural system shall be stiff to the extent that any transmitted vibration occurs at high frequencies, as high frequencies can be dampened with instrumentation vibration dampening systems and isolation tables rather than vibrations occurring at lower frequencies. The recommended floor vibration velocity limits of a modular system APF is 100 (μm/s) and 3,200 Kipps/In-S.

See Section 5.2.2, Vibration and Section 6.5.4, Ductwork and Fan Sound Control.

Section 13.8

APF Design Requirements: HVAC

Contents:

13.8.0 Introduction

The purpose of Heating, Ventilation and Air Conditioning (HVAC) in APFs is to provide safe and effective products to the patients, provide personnel comfort, and protect both workers inside and the environment outside the facility from airborne materials that could be hazardous.

This is achieved when these systems are appropriately designed, built, commissioned, qualified, operated and maintained. The most important HVAC parameters for the APFs include airborne particles (filtration), temperature, humidity, and pressure differential. The HVAC requirements addressed this section are in addition to Chapter 6, Mechanical Design.

13.8.1 Cleanroom Classification System

The concentration of total airborne particles and microbial contamination within the space is a key indicator of the room environmental conditions for Pharmacy and Biologics facilities. This target maximum is referred to as "classification" of the space.

Several classification systems exist for the classification of space. FDA follows ISO 14644 standard for assigning ISO levels (5, 7 and 8), but provides values only in-use and adds bio-burdens values for each ISO class. Other systems such as the European Union (EU) uses the term Grade followed by A, B, C and D. For example, ISO 7 looks similar to Grade B, but the EU standard also has at-rest limits. See Table 13.8.1.

Table 13.8.1 Cleanroom Classification Table

ISPE GRADE	FDA - IN OPERATION		PIC/S GRADE	EU AND PIC/S				ACTIVE AIR ACTION LIMITS
	ISO	USP 0.5 MICRON PARTICLES/ CU FT		IN OPERATION LIMIT (particles/m³)		AT REST LIMIT (particles/m³)		
				≥0.5µ	≥5.0µ	≥5.0µ	≥5.0µ	(cfu /m³)
Grade 5	ISO5	100	A	3,520	20	3,520	20	1
Grade 6	ISO6	1,000	N/A	35,200	290	3,520	29	7
Grade 7	ISO7	10,000	B	352,000	2,900	3,520	29	10
Grade 8	ISO8	100,000	C	3,520,000	29,000	352,000	2,900	100
CNC+	N/A	N/A	D	N/A	N/A	3,520,000	29,000	200
CNC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Notes:

1. *Values may be averages; EU and PIC/S require measurement of particles up to and including 0.5 micron and 5 micron; the US require 0.5 micron, hence the table incorporates both to ensure compliance with the most stringent requirement.*
2. *Samples from Grade 5 areas should normally show no viable organisms.*
3. *Recovery from the "In Operation" to the "At Rest" state should be verified to occur within 15-20 minutes for ISPE grades 6, 7 and 8. The recovery test as defined in ISO 14644-3 may be carried out to verify a one or two log reduction test. Recovery testing may also be performed for informational purposes.*
4. *"At Rest" figures are given to support Recovery and "Static" Room Classification testing. Maintenance of these Levels during idle (not in use) periods is not intended.*

13.8.2 Outdoor Design Conditions

The outdoor design conditions for Bethesda shall be per Section 6.1.7 and Table 6.1.7.

13.8.3 Indoor Design Conditions

Room temperature and humidity requirements depend on process, equipment, material and product requirements, and operator comfort.

Personnel in the space produce fewer particles when comfortable. Also, high humidity increases microbial and mold growth on surfaces.

The compounding pharmacy USP regulations, require room temperature to not exceed 20°C (68°F) and room humidity to not exceed 60% RH. For NIH APFs, pharmacy compounding room temperature shall be designed to between 18 and 19°C (64.4-66.2°F) for classified rooms (with room temperature not to exceed 20°C [68°F]) based on the gowning requirements and type of work being performed. Also, the room humidity shall be designed between the 50% and 55% RH for the classified areas during summer months with room humidity not to exceed 60% RH. During winter, the minimum room humidity shall be designed to 25% RH. The A/E shall consult with User and DTR/FCIS prior to design.

In GMP, when human comfort is the only requirement, temperature shall be designed between 18.3 to 20°C (65 to 68°F) for classified rooms based on the gowning requirements and type of work being performed. Also, the room humidity shall be designed between the 50% and 55% RH for the classified areas during summer months while holding the room below 60% RH. During winter, the minimum room humidity shall be designed to 25% RH. The A/E shall consult with User and DTR prior to design.

For CNC spaces, the design temperature may be slightly higher than classified spaces. A/E shall consult with user for indoor design requirements.

13.8.4 Dedicated HVAC Systems

Dedicated air handling systems (including exhaust system) are recommended to serve the APFs and to maintain room environmental conditions including space pressurization at all times, even during non-working hours. This segregation should be extended to other systems including chilled water pumps, reheat systems, pre-heat systems, humidification, heat exchangers and controls to the extent feasible.

13.8.5 Redundancy

Provide minimum n+1 redundancy for AHUs, exhaust fans, pumps, heat exchangers, chillers and boilers serving APFs. APF systems are designed to operate 24 hours/day, 7 days/week. Redundancy allows systems to be properly serviced and maintained and work as backup during emergencies.

13.8.6 Ventilation Criteria

Unlike laboratories and animal facilities which require 100% outside air (OA), APFs do not require 100% OA, unless potent or hazardous compounds are to be used. Through a process of risk assessment and user requirements, the A/E shall determine if 100% OA or recirculating systems are appropriate and propose a system early in the design phase for NIH review and approval. NIH may choose to elect a 100% OA system based on multiple factors, including varied types of products, the unique population of patients that are served by these products, and the risks of contamination and cross-contamination during operation and changeover. If multi-recirculated units are used in classified spaces, return from these spaces shall not be recirculated in areas where there is risk of cross-contamination.

Due to large ACH requirements for the classified spaces compared to typical laboratory and animal facilities, 100% OA systems for APF, pose significant spatial, utility and energy requirements, including the risk of freeze ups, all of which should be carefully evaluated early in design.

In support areas, the minimum OA shall be in conformance with ASHRAE 62.1 or, as necessary to maintain pressure relationships.

13.8.7 Air Change Rate

In GMP, there is a common understanding of a minimum 20 ACH in classified spaces. The Compounding Pharmacy USP regulations require a minimum of 30 ACH for ISO 7 spaces. Pharmacy non-sterile hazardous rooms and hazardous drug storage rooms require a minimum of 12 ACH per USP regulations. Setting actual air change rates in classified spaces is complex and includes multiple factors such as:

1. Ability of the room to maintain and recover the airborne particle counts from an upset condition according to the room classification system
2. Number of occupants
3. Tasks they are doing
4. Donning/doffing PPE (and the type/level of PPE)
5. The delivery of supply air, including means, efficiency, and coverage
6. Heat and moisture gain from internal and external influences
7. Process and its particle generation rate
8. Cleanliness of supply air
9. Airflow required to achieve required Differential Pressures (dPs)

The higher the ACH, the higher is the recovery of the room from in-use to at rest. Also, viable particles are fewer in number than non-viable, but they travel with the non-viable, therefore controlling non-viable is critical. Setting arbitrarily high air changes rates can have significant cost implications although they may improve particle counts in the room.

At NIH, the following room air change rates (air changes per hour-ACH) shall be applied for APFs in order to maintain the desired room cleanliness classification. Particle dilution calculations shall be used to determine air supply rate (or ACH) to ensure it meets the maximum airborne contaminations specified for its ISO class. The calculation shall be based on particle dispersion rate at steady state and concentration over time. This includes using the effect of the combination of filters and their removal efficiency on the make-up air, leakage rate, rate of particles emitted from equipment, rate of particles generated from cleanroom personnel and type of gowning used. The calculation shall be based on concentration of particles equal to 0.5 micron. Particle tracking using Computational Fluid Dynamics (CFD) to predict particle transport in an enclosed space is not cost-effective. CFD may be used for evaluating air flow velocity, volume, and temperature uniformity, recovery test as well as room pressurization in transient (as use) state. The ACH rate is typically based on supply air (first air) to the room.

1. ISO 7 spaces - 40 ACH minimum
2. ISO 8 spaces – 24 ACH minimum
3. CNC spaces – 12 ACH minimum
4. Non-Classified Spaces – 6 ACH minimum

Recirculated BSCs may be used to dilute airborne particles in the room and may accelerate the recovery time of the room. The airflow from the hood may not be included in the air change calculation rate because the added dilution only affects the area near the BSC's airflow path, not the entire room. The benefit of having recirculated HEPA is limited to improve the room recovery time.

13.8.8 Pressurization

Room relative pressurization is critical in controlling the migration of contaminants. The air distribution systems are designed to attain desirable pressure level within each room relative to all adjacent areas. The A/E shall establish a pressurization scheme early in design so it can be integrated with the architectural features of the facility. Door swings, type of doors, door gaskets, wall openings, and pass throughs all factor into the design of the pressurization system.

In general, directional airflow will be the targeted design criteria, with airflow cascading from clean to less clean areas with design differential pressures between adjacent spaces with the same ISO classification and shall be 10 Pa (0.04 in w.g), but not less than 7.5 Pa (0.03 in w.g.) and between 10 (0.04 in w.g.) and 15 Pa (0.06 in wg) for adjacent spaces with different ISO classification.

In a cleanroom, the processing suite is typically at the highest pressure relative to outside corridor and so it is important that each space is evaluated against relative pressure to outside corridor or to an alternate reference location such as interstitial space to make sure pressure differential across doors is not set too low or is too excessive. Differential pressures of greater than 25 Pa (0.1 in. w.g.) can cause difficulty in opening or closing doors against pressure and whistling through the cracks. Pressurization values on plans shall be shown both as represented "across the door" and "in relation to common reference point".

All cleanrooms shall remain positive to adjacent areas. Exceptions include:

1. Hazardous Drug (HD) sterile and non-sterile preparation rooms
2. HD Drug storage rooms (some conditions, such as oral solid dosage storage may require local exhaust vents (LEVs)
3. Radiopharmacy buffer rooms for compounding pharmacies
4. Infectious or viral vector rooms in Cell Processing suites

These “exceptional” rooms shall be negative to the entry airlock, but positive to the exit airlock in a unidirectional layout. Entry airlocks should be designed as “bubbles” and exits as “sinks”. See Section 13.8.9.

Where recirculating systems are used, central AHUs shall be sized to provide outside air to maintain the space pressurization and to provide the makeup air to support exhaust requirements in the space.

Pressurization of the rooms will be maintained via primary air, delivered to each room via a constant volume terminal unit with reheat.

The A/E shall evaluate the following types of pressurization control including active pressurization control (direct pressure control systems shall not be used):

1. Flow tracking control with fixed user selectable offset
2. Cascade flow tracking control with pressure based reset of offset

Space pressure differential will be actively controlled through the Building Automation System (BAS), and airflow control devices will be provided on the supply air inlet to, and exhaust/return air outlet from, each space. Differential pressure transmitters for all rooms will be mounted outside the classified room or outside the cGMP area in a central panel. Space pressurization, supply airflow and door open duration (where feasible) will be recorded and alarmed via BAS. This system will also record any additional identified Critical Process Parameters in the HVAC system. Room pressurization shall not be affected by the energizing or de-energizing of central AHUs or terminal units or recirculation units.

Pressurization will be also be monitored via a validated Environmental Monitoring (EM) system.

13.8.9 Airlocks

Airlocks are designed to effectively control airborne contamination between rooms of different classification. Airlocks maintain pressure differential and integrity of the controlled space during entry and exit. If there is no airlock, room differential pressure (dP) will drop to near zero when the door is opened. Donning and doffing PPE generates large numbers of particles in the small volume of the airlock, therefore these spaces should be highly ventilated (above the ISO class ACH minimums) to allow for quick recovery and flushing.

Airlocks are required between ISO 7 and ISO 8 spaces and recommended between ISO 8 and lower class spaces (CNC or unclassified). There are three kinds of airlocks:

1. **Cascade:** Airflows from high pressure to lower pressure through airlocks
2. **Bubble:** Airlock is higher pressure then/to adjoining rooms

3. **Sink:** Airlock is at negative pressure then/to adjacent areas

The determination of whether the airlocks are "bubbles", "sinks", or "cascades" will be based on the specific activities taking place within the relevant/connected spaces.

For pharmacy rooms, all entry to sterile non-hazardous areas will be designed with "cascading" type airlocks. All entries to sterile hazardous and radiopharmacy rooms shall be designed as "bubble" type airlocks with the same ISO classification as the processing room to provide both cleanliness and containment. If there are exit airlocks in the layout, then the exit airlocks can be designed as "sinks" with lower ISO classification to the processing room.

In a fully unidirectional flow APF (material and people), the airlocks entering the processing suites shall be "bubble", (i.e., positively pressurized with respect to both the supply corridor and the suite), and the airlocks exiting the hazardous areas shall be "sink", (i.e., negatively pressurized with respect to both the suite and the return corridor). The "sink" airlock at the room exits will protect the processing areas from the dirty return corridor, and will protect the return corridor from contamination.

Supply and return corridors shall be separate from airlocks for entry or exiting the processing suites.

Gowning entrances to suites designed as "bubble" will help maintain the cleanliness of the personnel gowning step taking place by ensuring that air from the corridor and the processing suite is inhibited from entering the airlock.

The airlocks will be designed with administrative or engineering controls (i.e., physical interlocks) to prevent doors on either side of an airlock being opened simultaneously. Clear, unobstructed lites in both doors shall be considered to provide a line of sight view. Red/green indicator lamps are highly recommended to show when both doors are adequately sealed. A time delay may be considered to extend the time from the door position switches indicating the doors are in the closed-position before indicating a green light (i.e., "Go") condition, to allow for greater recovery time of the anteroom.

Airlocks shall have their own dedicated supply and exhaust/return outlets and terminal units. Supply is typically entered "high" at the clean end and exhaust/return, "low" at the dirty end.

A material pass through chamber is a type of airlock designed for the transfer of materials between rooms of differing risk, classification, and/or differential pressure in order to reduce the risk of contamination. A cart pass through chamber is installed at the floor level. All pass through chambers in classified spaces shall be active, and the type of pass through chamber selected (i.e. supply air only, exhaust air only, supply and exhaust air, or HEPA-filtered recirculating) shall be approved by DTR/FCIS. Passive pass through chambers shall not be allowed unless otherwise approved by NIH and supported by risk analysis.

HEPA-filtered recirculating pass through chambers shall both intake air from and exhaust air to the less clean side of the pass through.

Ducted pass through chambers shall require dedicated, pressure-independent supply and/or exhaust terminals in order to minimize pressurization impact on adjacent classified spaces, and to allow for constant airflow as pass-through filters load.

See Section 13.6.5 Wall Accessories.

13.8.10 Air Distribution System

Numerous, equally-spaced air outlets, shall be used to create an airflow pattern that generally moves uniformly downwards from ceiling to floor. Air to classified spaces shall be supplied through ceiling mounted terminal HEPA filters. The terminal filters become part of the direct impact boundary. The use of remote HEPA filters in the supply duct shall not be allowed.

All supply terminal grilles shall be of a non-aspirating type, of stainless steel construction. The return/exhaust air outlets in classified spaces shall be located at or near the floor level preferably on at least two walls along the long dimensions of the room to ensure maximum uniformity of airflow. Exhaust outlets in rooms housing LN_2 freezers or controlled rate freezers shall be located within 300 mm (12 in.) of the floor to improve ventilation effectiveness and prevent accumulation of vapors.

On recirculated systems, exhaust outlets (not returns) may be located at the ceiling if the exhaust airflow is small relative to the return air. Equipment and furniture shall not block return/exhaust openings. Return/exhaust outlets shall be avoided under BSCs because this may affect airflow patterns around the BSC. Return/exhaust outlets on ducted systems can be louvered stainless. Where engineered cleanroom return wall systems are used, returns/exhaust may be open-ended near the floor level if the opening is hidden behind the wall. Placement of air walls on only one side of the cleanroom is not recommended.

All supply/exhaust/return ducts shall be directly connected to air outlets. Although permitted in the APF, the use of plenums as a passage for delivery of supply air is not recommended unless the plenum can be tested and meet the requirements for pressure and leakage of the associated duct. Where plenums are used/allowed for supply air, provide HEPA FFU. The use of ceiling plenums for exhaust/return is prohibited.

Each area shall be provided with supply and return dampers to allow proper balancing. Isolation dampers on supply and exhaust shall be used to isolate rooms from other rooms. Bubble tight dampers shall be specified, unless the airflow terminals are selected that can perform dual functions of control and bubble tight isolation.

13.8.11 Air Handling Capacity

The air handling capacity for systems serving APFs shall follow Section 6.2.1.

13.8.12 Ductwork Design

The ductwork design shall meet the requirements of Section 6.2.2 except:

1. Flexible supply ductwork should be minimized or avoided due to risk of restricting air from compression and possibility of flexible ductwork unfastening.
2. Supply ductwork shall be galvanized up to the terminal unit and then minimum of 304 stainless steel. All exhaust and return ductwork shall be minimum of 304 stainless steel. The elbow and the first section of connecting duct shall be 316 L stainless steel. This will allow the ductwork to be resistant to harsh cleaning agents or decontamination gases.
3. A total percentage leakage method is recommended in accordance with SMACNA. Ductwork leakage shall be no more than 1%. For hazardous exhaust on the positive pressure side, leakage shall be 0%. 100% of supply/return/exhaust ductwork serving classified areas shall be tested. Leakage from internal components is included in the total leakage test criteria.
4. Provide adequate access to service components such as dampers and reheat coils.
5. Ductwork shall be wiped and cleaned of oil (interior), dirt and metal shavings prior to installation. After ductwork is cleaned, cover the opening with plastic sheeting.
6. Use of self-drilling screws shall be avoided as they generate large amounts of metal chips.
7. All penetrations of ductworks should maintain interior cleanliness.

13.8.13 Air Intake/Exhaust

The outdoor intake and exhaust discharge shall meet the Section 6.2.3 requirements.

13.8.14 Air Handling Units (AHU)

The air handling unit (AHU) shall meet the requirements of Section 6.2.4.2, except aluminum or stainless steel material shall be used in lieu of galvanized steel. All AHU sections require drainage capability for wash down. All hardware shall be corrosion resistant (304 or 316 L stainless steel is preferred). Multiple smaller

direct drive plug fans arranged in an "array" may be used instead of centrifugal fans. Each AHU shall be provided with air flow measurement on supply and return (if applicable). Fans and motors shall be provided with vibration sensors to provide early warning of bearing failure.

The maximum number of rows for cooling coils may be increased to 10 rows to improve performance. The main AHU's chilled water coil dew point temperature shall be designed at a maximum of 8.9 °C (48°F), to allow the necessary dehumidification needed to maintain room temperature and humidity.

Freeze protection for AHUs (particularly 100% OA) shall be provided and shall meet the requirements of Section 6.3.8.

The AHU location should allow sufficient space for servicing its utility connections and internal components. On units that are disassembled after factory testing and reassembled on-site, a pressurized leak test shall be performed to ensure joints/connections are properly aligned and the AHU is not leaking in excess of the specified value.

13.8.15 Air Filtration

Air filtration is the primary method to reduce the contaminant levels in an air stream. Air filtration is used at various locations within the HVAC system. Filtration shall meet Section 6.2.5 requirements, unless indicated otherwise herein.

Pre-level filtration of outside air is typically located within the AHUs. Final filtration (not to be confused with terminal filters), located on or after the final discharge section of the AHU, is used to extend the life of the terminal filters and keep the supply ductwork clean, and shall meet the requirements of Section 6.2.5. HEPA final filters in the discharge section of the AHU are required on recirculating units serving multiple rooms to prevent cross contamination. HEPA final filters in the discharge section of the AHU on 100% OA units are typically not required as they are serve no additional purpose other than possibly extending the life of the terminal filters.

Filters shall be front loaded so the airflow pushes them into the mounting frame to eliminate bypass. Filter frames shall have closed cell rubber/neoprene type gaskets to prevent shedding. Provide at least 25 mm (1 in.) gap between filter banks in the pre-filter section to permit pressure measurement.

Terminal filters located at the room ceiling shall be HEPA filters (minimum of 99.97%) and shall be generally rated for Class 2 in accordance with UL 900. Terminal HEPA filters shall be designed for maximum of 0.5 m/s (100 fpm). Filter performance shall be specified at the intended face velocity as filter velocity has a significant impact on filter performance (Higher filter velocity, more particles will pass).

Filters shall have silicone gel seal to form a positive seal and eliminate air bypass around the filter edge. Filter housing shall be stainless steel or aluminum welded construction and exposed stainless steel trim with pressure test ports, damper adjustment, and ability to introduce aerosol challenge. The filter shall be capable of being replaced room side.

Fan-filter unit (FFU) is a self-contained filter assembly with fan and speed control and a shallow HEPA filter sealed into a stainless steel or aluminum enclosure.

FFUs used to augment ACH should be avoided in classified spaces especially where they do not use low returns. They may be used in smaller spaces such as gowning or airlocks to provide the extra capacity as long as they have inlets ducted from floor level. Consideration shall be given to service life, replacement of filter, electric wiring and heat generated by fans. Since FFUs are self-powered they may be used where a central air handling system do not have requisite static pressure to overcome pressure drop from the HEPA filter.

FFUs are typically connected in series to the primary AHUs. The FFU fan motors can have premature failures if they are operated when primary air systems are down for long periods of time. However, the use of room bypass duct at each FFU shall be avoided because it creates additional complexity to the overall system.

Poly Alpha Olefin (PAO) shall be used for aerosol challenge for leak testing of HEPA filters. The filter efficiency test in the field shall be based on filter's Most Penetrating Particle Size (MPPS) and not the standard efficiency test that is carried out at the factory (typically using pneumatic Laskin-nozzle type generator at 0.3

micron). Dioctyl Phalate (DOP) is an old aerosol that was used in the past to challenge filters and will not be used due to safety concerns.

HEPA filter gel seal may degrade with time as silicone gel seal material reverts to a liquid state. If this occurs, the gel may begin to drip out the gel track. This may pose a sterility and safety problem. All miter joints in the filter gel channel shall be completely sealed with silicone gel. Gel seals shall not be used since they are affected by cleaning chemicals and aerosol challenge materials such as PAO.

HEPA bleed-through is a phenomenon where a filter fails a filter integrity test (FIT) that had been previously passed at the factory. This occurs mainly with paper-based HEPA filters. Where HEPA bleed-through poses a problem, ULPA or ePTFE filters may be specified. Both ULPA and ePTFE filters are more expensive than HEPA and they may present their own challenges during testing. DTR and DOHS shall be consulted before specifying or replacing the filters with ULPA or ePTFE filters, their use shall be justified.

HEPA filters shall be handled with care and special consideration during shipping and checked for damage during shipment. A thorough inspection is required prior to installation. Filters shall be stored indoors in dry conditions, to prevent damage, or water intrusion, and stored in conditions between 4.4 and 37.8°C (40 and 100°F) and 25% to 75% RH. Filters should be stored in their installed orientation to prevent crushing. Filter housing shall be cleaned using appropriate NIH-approved chemicals and procedures prior to installation of filters.

Carbon filters shall not be allowed in the air handling system serving APF, due to risk of bleed-off.

Temporary filters shall be provided during construction to protect the AHU, ductwork and the space from accumulating dirt. These will be replaced with new filters prior to commissioning and qualification

13.8.16 Exhaust Air Systems

Exhaust air systems shall meet Section 6.1.22 requirements. Dedicated exhaust systems shall be provided for APFs and shall not tie into the building exhaust system. Ducted BSCs handling hazardous or potent exhaust shall be independent of the general exhaust to allow proper control of BSC exhaust.

Exhaust fans shall comply with Section 6.2.7 requirements. The exhaust fans shall operate as constant volume; however, each fan shall have all the necessary components to be capable of variable volume operation. Fans and motors shall be provided with vibration sensors to provide early warning of bearing failure.

Exhaust filtration is not typically required on any exhaust (including hazardous exhaust tied to ducted BSCs, since hazardous air is HEPA filtered at the BSC before it is discharged outdoors).

Exhaust air discharge velocity and stack height shall follow laboratories and animal facilities requirements as described in Section 6.2.3, Outdoor Air Intakes and Exhaust Air Discharge. Each exhaust fan stack shall be equipped with a Variable Geometry Nozzle (VGE) to allow the exhaust fans to modulate airflow and still maintain a discharge velocity of 15.24 m/s (3,000 fpm). As an alternative, an outdoor air intake hood and bypass damper shall be installed or "strobic" style high induction exhaust fans may be employed.

Air dispersion modelling shall be provided as described in Section 6.2.3 for re-entrainment of the general and infectious exhaust discharge air with the intake air to confirm the location of the exhaust discharge.

13.8.17 Humidification System

Steam injection type humidifiers providing dry steam (without downstream condensate droplets) is required for APFs because it is bacteria free. Plant steam and RO water for make-up (and potable water for backup) shall be used to provide chemical-free steam via steam-to-steam redundant (provide option for pressurized or atmospheric). This chemical free low-pressure steam should be piped to a short absorption distance dispersion manifold assembly which will be installed inside AHUs, upstream of the cooling coils, which will allow the cooling coil to double as a moisture eliminator, mitigating nuisance smoke detection alarms and reducing the risk of water damage to the fans and APF spaces. Humidifiers shall have automatic isolation valves to

remain closed during cooling mode.

Humidifiers located within ductwork, or downstream of the supply fan shall be avoided because of risk of flooding of ductwork.

13.8.18 Chilled Water Systems

Chilled water to APF AHUs shall be provided from central utility plant (CUP) and shall meet Section 6.3.6 requirements. To help mitigate discharge air temperature and dew point fluctuations of AHUs due to varying chilled water temperatures from the CUP, supplemental air-cooled chiller shall be provided. n+1 redundancy of this supplemental chiller is not required; however, pumps shall be redundant. Typically, designs provide an indoor insulated storage tank between the supplemental chiller and AHU trim coil to allow the supplemental chilled water system to respond quickly to sudden changes in CUP supply chilled water temperature. The supplemental chiller design shall be based on CUP supply temperature rising 2°F (from 45°F to 47°F). The chiller shall be piped to separate AHU trim coil. AHU trim coils shall also be piped to the plant chilled water loop, but would remain isolated closed during normal operation when the supplemental chiller is operational.

For small APFs such as modular trailers where CUP chilled water is not available in close proximity, n+1 redundant air-cooled chillers shall be provided.

13.8.19 Heating Water Systems

Heating water systems shall meet Section 6.3.5 requirements. Preheat system shall be glycol preheat water. Provide glycol concentration per DRM requirements for freeze protection. See Section 6.1.24. Direct steam heating systems should be avoided, unless reviewed and approved by DTR.

13.8.20 Steam System

Steam systems shall meet Section 6.3.7 requirements. Where monographed pure steam is required for direct impact process applications, steam shall be produced from RO water (typically single pass) that has been produced directly from potable water as described for Pharmaceutical Water WFI production in Section 13.10.3. Membrane contactors should be considered for degasification.

13.8.21 Piping

Piping shall meet Section 6.3.9 and Exhibit 6.3, Piping Designation, Material, Fittings and Joints requirements. Use stainless steel piping for pure clean steam with sanitary weld joints post-fabrication passivation. Valves and components for all clean/ high purity systems shall be sanitary type with no lubricants or other contaminants that may contaminate the process fluid. All components, instrumentation types and connection arrangement serving high purity system application shall be free of dead legs, and contamination-prone fouling area in contact with the system fluid.

Fluid piping over APF spaces shall be limited to that required specifically to serve such spaces. Utilities serving other areas of the facility shall not be located above ceilings or within walls serving APF spaces unless unavoidable, justified, and subject to approval. Fluid piping over APF spaces shall be limited to that required specifically to serve such spaces. Utilities serving other areas of the facility shall not be located above ceilings or within walls serving APF spaces unless unavoidable, justified, and subject to approval. In some cases, DTR may require fluid services to be double-contained and provided with automatic leak detection.

13.8.22 Service Access Panels, Mechanical Spaces and Maintenance Consideration

Access panels in the classified boundary areas shall be avoided, since they could become a source of contamination or air leakage. To the extent possible, piping,

valves, dampers, and air terminals shall be located outside the classified boundary. Major equipment, valves, dampers, and terminal units serving classified spaces shall be located in interstitial or mechanical penthouse or mechanical spaces to allow for maintenance staff to have easy access to equipment and devices. Access to field calibration, testing and repair should be considered. Access for removal of large motors and equipment shall be considered. Where piping must be exposed within APF spaces, it shall be mounted to walls or ceilings with manufactured, non-corrosive 316 stainless steel sanitary (hygienic) piping supports of the rounded ASME BPE compliant type, with silicone, PTFE, or approved equivalent inserts. Supports shall be free of entrapment areas, smooth and polished, and arranged to ensure piping stands-off from finished walls or ceilings at least 25 mm (1 in.).

Where insulated piping is required within APF areas, the insulation and joint system shall be specifically manufactured to be particle-free (including during cutting or impact), suitable for routine wash-down, sanitary, chemical-resistant, fully sealed, and readily cleanable for use in clean room applications. Alternatively, insulated piping may be fully encased in an approved durable and sanitary containment annulus of not less than Schedule 5 wall thickness, with approved sanitary termination fittings. Insulation shall be halogen free, closed-cell, non-fibrous, and dust-free. Examples of suitable products may include closed-cell white PVDF foams, however melamine insulation and insulation with PVC jacketing is not acceptable.

13.8.23 Emergency Electrical Power

Supply air fans, exhaust fans, controls and BAS and all devices and equipment serving APFs shall be connected to an emergency power system. Emergency loads shall be able to transfer standby power in 10 seconds, but not more than 20 seconds.

Following a power outage, and initiation of emergency electrical power, all VFDs associated with supply and exhaust fans shall restart into a coasting motor (catching motor on the fly) without delays and without damaging the motor.

13.8.24 Equipment, Ductwork, and Piping Identification

Equipment, ductwork and piping systems shall be accurately identified. Services specific to APF shall clearly designate function and direction to avoid cross connections, service disruptions and aid in maintenance and operations.

Section 13.9

APF Design Requirements: HVAC Controls

Contents:

13.9.0 Introduction

This section describes the general building automation systems (BAS) design considerations, as well as the specific requirements for control sequence design and construction document submittals. APFs shall meet all the requirements of Sections 7.1-7.6 and meet additional requirements as outlined in this section. These additional requirements provide a greater level of safety and reliability of operation. Refer to Section 13.8 for additional mechanical requirements and controls related to this chapter.

13.9.1 General Requirements

HVAC and building system parameters shall be monitored and controlled on an appropriately commissioned and tuned BAS control system. Critical HVAC control parameters (including: space temperature, humidity and room differential pressure) shall be monitored, recorded, and alarmed on a validated Environmental Monitoring System (EMS). Refer to Section 13.14 for details on EMS.

All field devices for critical BAS and EMS shall be co-located and have similar accuracy, repeatability, stability and tolerances to the extent possible. These field devices shall also be maintained under a quality change control and calibration system because they are mimicking the validated EMS.

Based on the System Level Impact Assessment (SLIA), NIH may elect to manage other HVAC or other systems or components or control devices under the quality change control and calibration system. As an example, terminal units controlling the critical parameters in classified rooms could be determined as direct impact and be maintained under the quality change control system.

13.9.2 Terminal Units

Supply and exhaust systems shall be controlled by one single controller with stand-alone capability. All programming shall be provided via a single programming language. All units serving APF areas shall be controlled by a primary controller, preferably the same controller which manages the supply (this shall be limited by size). Refer to Section 6.6.2 and Section 6.6.7 for requirements for supply and exhaust terminals. All controllers in APF spaces shall provide stand-alone capability at the suite level. The A/E shall clearly indicate both tracking relationships between airflow terminals and clearly indicate the classified boundaries of a collection of rooms (suite) that shall be controlled by the same controller.

13.9.3 Isolation Dampers

Automatic dampers in the exhaust shall fail-open. Automatic dampers in the supply shall fail-closed if another means is not provided to prohibit reverse pressurization in the time specified below in the event of applicable failures. If the supply automatic damper is not providing this reverse pressure protection, it shall fail-open. The position of automated isolation dampers shall be monitored (make contact on close). Refer to Section 6.6.9 on specification requirements for the isolation dampers.

Isolation damper closing rates shall be tuned to isolate the lagging system more quickly than the leading system, to ensure airflow in the correct direction.

13.9.4 Differential Pressure Monitors

The BAS shall provide differential pressure monitors on classified spaces to indicate the room differential pressure and shall alarm when the pressure goes beyond adjustable thresholds and time durations established in concert with DFOM, DTR/FCIS, ORSC and IC.

Classified space may be equipped with a sensor indicating the status of the door (open or closed). This sensor shall provide an input to the room differential pressure monitor in order to disable or provide a delay on the alarm parameter as appropriate to the door's position.

Differential pressure monitors for all rooms should be mounted outside the entrance door to the room being monitored (in unidirectional personnel flow); provide

an additional red/green indicator lamp on the opposite side of the door (in bidirectional personnel flow); or placed in a central panel, so long as the panel location is in line of sight of the rooms being monitored.

13.9.5 Critical Parameter Control and Sensors

Critical HVAC parameters are particular to individual products and processes. Main factors to consider for a monitoring system include:

A. Accuracy and Repeatability: Control set points should be selected to assure that errors (drift, hysteresis, accuracy) do not combine to allow a condition outside acceptable operating range. This is very important in systems where multiple instrument signals are used to calculate a control response. All sensors shall be NIST traceable or to a industry standard.

Common monitored environmental parameters include:

1. Airflow
2. Differential pressure (dP) between spaces
    a. dP will be electronic pressure transducers with indicator readouts to allow operators to see the measured value. Accuracy will be ±1.25 Pa (±0.005 in. w.g.).
3. Temperature
    a. All temperature sensing for the HVAC systems will be accomplished using either electronic 100-ohm platinum RTD sensors with 4-20 mA transmitters or 1,000-ohm platinum RDT elements without transmitters (cGMP areas) or thermistors (non-cGMP areas). Sensor accuracy will be 0.06°C (0.1°F). Sensor shall be compatible with hydrogen peroxide, peracetic acid and sodium hypochlorite.
4. Relative Humidity (RH)
    a. Room humidity sensors (for monitoring only) will be industrial, capacitance type and compatible with hydrogen peroxide, peracetic acid and sodium hypochlorite. Sensor accuracy will be ±2% RH.

B. Long-term Stability and Failure Modes: Some instruments are prone to drift out of calibration sooner than the others. Maintenance and recalibration frequency should be based on manufacturer's recommendations. Failure modes should be considered by designers. A failure mode should be chosen that is safer for the product and personnel and maximizes the probability of detection.

C. Sensor Location: All field devices for critical BAS/EMS should be co-located, mounted for easy access, calibration and replacement. Potential lack of uniformity throughout a space should be considered for mounting space temperature and humidity sensors. For example, temperature sensors shall not be placed next to BSCs or heat producing equipment where they may impact temperature control and uniformity.

Co-location of temperature sensors shall be interpreted to mean installed at the same elevation, on the same wall plane, within 914 mm (3 ft.) of each other. Co-location of RH sensors shall be interpreted to mean installed on the same plane, within 914 m (3 ft.) of each other. Co-location of dP sensors is not as critical, but the displays should be installed at the same elevation, on the same wall plane, within 914 m (3 ft.) of each other.

Location of heat and humidity producing equipment shall be considered in the placement of room sensors. Where practicable, sensors shall be located outside the controlled space, but accessibility for maintenance must be considered. Temperature and humidity sensors located in return or exhaust ducts can also provide a reasonable reference for the room conditions as long as they are located close to the room and can be accessible for maintenance and calibration.

D. Alarm Requirements: It is considered good practices to set the action alarm at the extreme acceptance conditions and have an engineering "alert" at conditions just outside the normal operating range to alert engineering personnel of a potential unusual condition. Differential pressure (dP) can change very quickly, and therefore, has potential to create nuisance alarm whenever a door is opened. DP alarms should have time delays. The duration of the time delay should be sufficient (not less than 120 seconds) to permit the normal passage through an open door and for the system to recover.

E. Sensors Resistant to Damage: All sensors in contact with cleaning chemical shall be compatible with hydrogen peroxide, peracetic acid, and sodium hypochlorite. A stainless steel hat, sensor configuration, and/or sensor design should be resistant to wetting during cleaning, and consequent damage.

F. Record Requirements: The frequency of data collection is dependent on the parameter being measured.

1. Differential pressure data should be collected at 1 minute intervals due to rapid changes in value, such as door openings.
2. Temperature and RH data may be collected at intervals up to 15 minute intervals because these values tend to change slowly.
3. The sensor data archiving requirement shall be designated by latest facility BOD and SOP.

G. Ease of Maintenance and Calibration: The selection of sensors and other field devices should be considered in order to select the most effective type of sensor and method of calibration.

13.9.6 Room Pressurization Control

To control the migration of contaminants, the air distribution systems shall be designed to attain pressure level within each room relative to all adjacent areas. In general, the design shall provide airflow cascading from clean to less clean areas.

APFs require multiple levels of room pressurization. Pressures shall be maintained to ensure proper directional airflow between zones. Passive cascading flow tracking (fixed offset) pressurization control system is the most commonly used method in APFs. Active pressurization control may be considered by the A/E based on cascade flow tracking control with pressure based reset of offset. See Section 13.8.8.

Direct pressure measurement based active pressurization control is not allowed in APFs.

To the extent possible space pressurization for each classified room shall be controlled by a single pair of supply and exhaust terminals. No space shall be pressure controlled using only a single terminal unit (supply or exhaust), or have a single unit serve multiple rooms.

To the extent possible, pressure differentials between rooms shall be achieved using gaps around doors and door undercut. The use of pressure stabilizers or relief vents for maintaining pressure differentials between rooms shall be avoided due to a number of concerns, including a heightened risk of contamination during an air reversal condition, difficulty to clean and maintain, etc. Such devices may be considered in special cases and shall be reviewed and approved by NIH on a case by case basis.

See Section 13.9.4, Differential Pressure Monitors.

13.9.7 Controllers and Supply / Exhaust Interlock

Controllers monitoring and adjusting the HVAC in APF areas shall be primary controllers.

Terminal controls shall be panel-based (instead of having controllers for each unit). Controllers on terminal units requiring frequent calibration (such as every 12 hours) are NOT allowed, even when they are provided with Auto Zero Modules (AZM). This is because frequent calibration using AZM could upset pressure differential dynamics in the space.

Provide an interlock (between the supply controller and the exhaust controller) indicating exhaust system status and supply system status, such that the lagging system can confirm operation of the leading system in the absence of the controller local area network (LAN) communication. Where multiple controllers are controlling the supply and exhaust systems, status outputs shall be wired in parallel.

The interlock between the exhaust and supply shall be designed to keep positive or negative pressure to the adjacent rooms at all times per the program requirements. Components shall be selected so that in any realistic failure scenario, the supply airflow rate will decrease more quickly than the exhaust for negative spaces or vice versa for positive spaces. This requires that the A/E consider the control sequence and actual/

required responses of all drives, sensors, fans, dampers, and damper actuators. Based on this, the A/E shall confirm that all practical measures have been implemented to ensure maintenance of required pressure at all times.

13.9.8 Loss of Pressurization

The A/E shall analyze the potential for loss of space pressure control due to power loss, generator testing, or controller failure and design the controller configuration to minimize risk. Fail positions (fail in last position) of the air valves shall be such that classified space pressurization is maintained to the extent possible. Upon main system failures (such as loss of AHU or exhaust fan), the valves shall fail-closed to ensure pressurization is not reversed.

13.9.9 Cross-Limiting Loop

In APF spaces, as the spaces are constructed to have minimal leakage, a cross-limiting loop shall be provided (the control sequence shall automatically reset the flow-rate set point in the lead terminal box upon detection of excessive flow differential) to restrict the leading system from exceeding the lagging system by a specified value that shall be set to prohibit excessive door-opening forces. Values shall be set such that the control loops do not interact under normal operation. Cross-limiting does not apply to chemical fume hoods, biological safety cabinets (BSCs), canopy hoods, or other safety equipment. As an example, if the normal offset is to have the exhaust volume 75 L/s (160 cfm) lower than the supply, another control loop shall restrict the exhaust to no less than 150 L/s (320 cfm) below the supply, otherwise it could be difficult to open the space door.

13.9.10 Airflow Tracking

Airflow tracking control shall maintain differential pressures between adjacent spaces. There shall never be a condition in which the control system goes outside this range for more than 2 minutes (adjustable) and designed directional airflow must be sustained. The APF spaces shall be designed such that under failure conditions the airflow will not be reversed. This has significant implications for the central systems serving the APF concerning starting, power outage, rotation, and proof logic and hardware. The monitoring requirements include:

1. Space temperature
2. Space differential pressure with local indication (where required)
3. Alarm conditions and strobe in associated rooms, outside of all entry doors
4. Humidity (where zone-level humidity is required only)
5. Supply/exhaust velocity (total/static differential) pressure.
6. HEPA-filter pressure (refer to component) (when provided)

13.9.11 UPS and Emergency Power

Central system controllers shall also be on an uninterruptable power supply (UPS) and emergency power, and must detect power interruptions and take appropriate action locally. This in effect means providing a three-phase monitor as an input to the controller.

Zone terminal-unit controllers shall be on emergency power so they can continue to control through power interruptions.

13.9.12 Terminal Damper Actuators

Terminal damper actuators shall be "fast-acting". Damper fail positions shall be selected to fail in last position or fail-closed (for both exhaust and supply) depending on the type of failure. If the failure is at the local actuator level then fail in last-position actuators may be used, otherwise fail-closed shall be utilized.

13.9.13 Interface on Variable Frequency Drives (VFDs)

The interface between the BAS controller and VFD shall be hard-wired directly, point-by-point from the BAS to the VFD interface board. Interface shall not be done through digital communications except as provided supplementary to the hard-wired interface. See Table 13.9.13.

13.9.14 Fan Failure

The supply system status indication to be used in failure and restart logic shall consistently indicate a change in status within 10 seconds. Status indications shall further be capable of distinguishing belt breaks from normal operation at minimal load. Either current switches or differential pressure switches will be used. The current switches minimum operating amperage draw shall exceed that of the no-load motor at 60 Hz. Upon a supply fan failure, either a redundant supply fan shall start, or if the redundant fan is running, then it shall ramp up. If ramp up is not achieved or there is no redundant fan, both the supply and exhaust fan(s) shall shutdown. Similar sequence shall be used for exhaust fan failure.

Pressure cutout switches shall be tuned to trip the unit when extended beyond normal pressure, but shall have an adequate delay to avoid nuisance trips due to short transient excursions. Trips from excessive pressure shall be manually reset.

Under failure conditions, the airflow will not be reversed.

13.9.15 HVAC Controls Resilience and Recovery

Controllers shall have the capability to automatically restore their volatile memory upon loss of power.

13.9.16 Additional BAS Quality Requirements

Controls contractor shall submit all programming code for review and approval by DTR and DFOM. Code shall be clean and devoid of unused or "Junk" code which will be verified via commissioning of the BAS system.

Table 13.9.13 Minimum Instrumentation Requirements

Instrumentation Certification Type							
Air	**Hydronic**	**Function**	**Minimum Range**		**Accuracy**	**Resolution**	**Calibration Interval**
•	•	Rotational Measurement	0 to 5,000 RPM		± 2% of reading	± 5 RPM	12 Months
•	•	Air Temperature Immersion Temperature	-40 to 115C	-40 to 239 F	± 1% of reading	± 0.1 C ± 2.18 F	12 Months
	•	Contact Temperature					
•	•	Volts AC	0 to 600 VAC		± 2% of reading	1 V	12 Months
•	•	Amperes	0 to 100 Amps		± 2% of reading	0.1 Ampere	12 Months
•		Air Pressure	0 to 2,500 Pascals	0 to 10 in. w.g.	± 2% of reading	2.5 to 250 Pa 0.1 to 1.0 in. w.g.	12 Months
•		Air Velocity (not for Pitot traverses)	0.25 to 12.5 m/s	50 to 2,500 fpm	± 5% of reading	0.1 m/s 20 fpm	12 Months
•		Relative Humidity	10 to 90% RH		± 2% RH	1%	12 Months
•		Direct-Reading Hood	50 to 1,000 L/s	100 to 2,000 cfm	± 5% of reading ± 2.5% L/s (5 cfm)	Digital: 0.5 L/s (1 cfm) Analog: N/A	12 Months
•		Pitot Tubes (2 of adequate length for intended use)	45 cm min.	18 in. min.	N/A	N/A	N/A
	•	Hydronic Pressure Measurement (Pressure Gauges)	-760 mm hg to 400 kPa 0 to 700 kPa 0 to 1400 kPa	-30 hg to 60 PSI 0 to 100 PSI 0 to 200 PSI	± 2% of reading	± 3.3 kPa ± 0.5 PSI ± 6.7 kPa ± 1.0 PSI ± 16.7 kPa ± 2.5 PSI	12 Months
	•	Hydronic Pressure Measurement	0 to 25 kPa 0 to 300 kPa	0 to 100 in. w.g. 0 to 100 ft. w.g.	± 2% of reading	250 Pa 1.0 in. w.g. 3.0 kPa 1.0 ft. w.g.	12 Months

Table based on NEEB TAB Procedural Standards, Table 4-1 NEEB Minimum Instrumentation Requirements.

Instrumentation with multiple capabilities shall be accepted for more than one function when documented as each separate function meets these requirements. Calibrations of all instrumentation requiring calibration shall be traceable to current NIST Standards for US-based facilities or equivalent organizations in other countries.

The minimum calibration intervals listed on this table do not necessarily reflect the risks associated with APFs. Often particularly with Temperature, Relative Humidity, and Differential Pressure sensors, the interval set in the URS according to risk analysis to shorter periods. The EMS and BAS sensors should be recalibrated contemporaneously, and to the extent practicable using the same NIST calibrated devices.

Section 13.10

APF Design Requirements: Plumbing

Contents:

13.10.0 Introduction

This section addresses additional specific requirements for all plumbing and process piping systems in APFs. Refer to Chapter 8 and Chapter 12 for baseline requirements.

13.10.1 General Requirements

Systems that are considered direct impact in APFs will receive full testing, commissioning and validation throughout the construction process including but not limited to materials, equipment and methods verification, and any items that may affect fluid quality, reliability, initial purity, or potential for contamination.

Isolation valves for pressurized piping penetrations as well as components requiring routine service shall be located outside the classified spaces. To the extent possible, pressurized water and waste piping in ceilings over classified spaces shall be avoided to limit damage to spaces from leaks.

Fluid piping over APF spaces shall be limited to that required specifically to serve such spaces. Utilities serving other areas of the facility shall not be located above ceilings or within walls serving APF spaces unless unavoidable, justified, and subject to approval. In some cases, DTR may require fluid services to be double-contained and provided with automatic leak detection. Pipe penetrations through clean room walls and ceiling shall be constructed of 316 stainless steel (SS) mounting rings and flexible while silicone boots.

Where piping must be exposed within APF spaces, it shall be mounted to walls or ceilings with manufactured, non-corrosive 316 stainless steel sanitary (hygienic) piping supports of the rounded ASME BPE compliant type, with silicone, PTFE, or approved equivalent inserts. Supports shall be free of entrapment areas, smooth and polished, and arranged to ensure piping stands-off from finished walls or ceilings at least 25 mm (1 in.).

Where insulated piping is required within APF areas, the insulation and joint system shall be specifically manufactured to be particle-free (including during cutting or impact), suitable for routine wash-down, sanitary, chemical-resistant, fully sealed, and readily cleanable for use in clean room applications. Alternatively, insulated piping may be fully encased in an approved durable and sanitary containment annulus of not less than Schedule 5 wall thickness, with approved sanitary termination fittings. Insulation shall be halogen free, closed-cell, non-fibrous, and dust-free. Examples of suitable products may include closed-cell white PVDF foams, however melamine insulation and insulation with PVC jacketing is not acceptable.

Lab water may not be used as a source of water supply for any APF since lab water may be subject to a variety of hazards that may compromise the quality of water introduced in APFs.

13.10.2 Domestic Cold and Hot Water Systems

APFs are sensitive to microbial and chemical contamination which may be present in incoming domestic water. While incoming municipal water includes chlorine residual from source water disinfection to reduce microbial contamination, there is no guarantee that it will be free of microbial contamination at the point of use. For this reason, domestic water should only be present at the early stages of gowning and late stages of de-gowning for hand washing and as a water source for non-sterile equipment processes (e.g. autoclave vacuum pumps and wash equipment). Sink traps can become a source of mold or pathogens and may require a significant cleaning and disinfection control regimen to control contamination. Generally, domestic water should be avoided in ISO 8 areas. Domestic water is inappropriate for use in ISO 7 or ISO 5 areas, except where required for scientific use and where additional approved treatment is provided.

Where domestic cold and hot water is required in the classified areas, the A/E shall review the building domestic hot and cold water system, prior to designing the system for APFs, at a minimum:

1. Cold water systems shall maintain and deliver to the use point potable water at a temperature not to exceed 18.3°C (65°F). Hot water systems shall maintain and deliver potable hot water to the use point at a temperature of not less than 51.7°C (125°F). Where possible, hot water should be delivered to the use point between 56.7°C and 60°C (134°F to 140°F)

with final temperature control integral with the faucet or immediately at the point of use without dead legs.

2. The quantity and length of dead legs in hot and cold water piping shall be minimized. Distribution systems shall be arranged to ensure daily fresh water turnover via normal passive operation and without sections of stagnation. To the extent possible avoid reliance on the use of any single fixture to achieve daily water turn-over.

3. Recirculation shall be provided for hot water systems. The maximum permissible length of uncirculated piping shall be limited to that which produces a 15 second wait time to achieve full hot water distribution system design temperature at the use point. In no case shall the length of any hot water system uncirculated piping section exceed 6.1 m (20 ft.) developed pipe length.

4. Where feasible, the use of faucets with integral thermostatic/ mixing controls and 60°C (140°F) hot water supply direct to the faucet should be utilized. Sensor faucets that incorporate a thermal disinfection mode are favored provided the discharge outlet is located immediately at or adjacent to the mixing valve and with minimal or no tempered water outlet dead leg. The use of wall mount mixing arrangements that drain completely with each use (e.g. wall mount digital mixer faucets) should be considered. Laminar flow outlets shall be utilized instead of aerators. Serrated tip outlets and submersible hose attachments shall be avoided.

5. The mixing valve at the sink shall be located immediately at the exposed faucet supply where integral mixing faucets are not used. The intent is to absolutely limit the dead leg distance downstream from the mixing valve outlet where water can stagnate. Self-draining arrangements (e.g. wall mount digital mixers and spouts) are preferred, but not mandatory.

6. The use of disinfectant injection (catalytic-generated or procured ANSI/ NSF-60 chlorine dioxide) or water filtration should be evaluated on a case by case basis and, be based on a full risk assessment and, life cycle costing and, shall be reviewed and approved by DTR. Due to risk of damaging the stability of pipeline corrosion inhibiting films, (even where disinfectant residuals are elevated within Safe Drinking Water Act levels) as well as potential efficacy, by-products and potability concerns, the injection of additional chlorine is unacceptable.

7. The use of water filtration is not recommend for microbial control due to the required frequency of filter replacement, as well as pressure and flow issues associated with suitable filters. If filters are not rigorously maintained, microbial conditions could get worse both upstream and downstream. Though certain Point of Use (POU) filters may be beneficial in some applications, POU water filters should not serve as a primary microbial control device, and their selection and application requires justification and pre-approval. The maintenance of appropriate hot and cold water temperatures, avoidance of stagnation, and (if necessary) supplemental water treatment (catalytic generated or ANSI/ NSF-60 procured chlorine dioxide) is preferable to other means of domestic water system microbial control, however the use of any water treatment process requires water supply analysis, confirmed continued potability validation, and DTR pre-approval, including implementation of procedures to maintain operation and monitor water quality.

8. Zone-level filtration shall not be utilized for microbial control due to long-term efficacy concerns, potential routine-maintenance, and induced contamination associated with routinely depressurizing, opening, and re-pressurizing components, and potential for upstream or downstream contamination associated with inadequate maintenance. High purity water is not a recommended alternative for this application due to significant infrastructure cost necessary to ensure reliable microbial-controlled water.

9. Water supply branch piping to APF spaces shall include “Aseptic Facility” or similar application-specific text in their pipe line identification nomenclature. This is to avoid unrelated

tapping or disruption of pressurized services, which could induce contamination.

10. Solvent cemented joints, natural rubber, hydrocarbon cutting oils, and other sources of contamination that may substantially elevate TOC shall be avoided in the water supply serving APFs. Refer to Section 8.3, Water Systems for further requirements to maintain system microbial control, including requirements for water heaters/ source equipment.

13.10.3 Pharmaceutical Water

The term "Pharmaceutical Water" is intended as a generic descriptive term to be inclusive of purified waters of various qualities. The specific water application shall be identified by nomenclature as utilized in the USP monograph (e.g., USP Purified Water, Water or Injection, etc.). Pharmaceutical waters in APFs have multiple uses including:

1. Ingredient in preparation of parenteral compounding
2. Sterile diluent for parenteral products
3. Solvent in preparation of intermediates
4. Preparation of cleaning solutions/rinsing
5. Analytical laboratory as analytical reagents

Pharmaceutical water can be either produced at site (bulk) or procured as packaged. Due to complexity and cost of design, maintenance and validation, on-site pharmaceutic water systems should be avoided in APFs where possible. Where demand, storage space, cost and logistics of procuring and handling packaged water is too prohibitive, pharmaceutical water(s) may be produced at site for both monograph and non-monographed water applications. Any pharmaceutical water intended to be packaged must additionally meet the STERILE monographed water requirements as non-sterile waters and waters that do not contain adequate contaminant restriction may result in quality degradation.

Water that is used as a dosage form ingredient or parenteral must be compendial (monographed) water. Any pharmaceutical water whose variability may have an impact on a critical quality attribute (CQA) shall be provided as fully controlled, independent, dedicated and validated compendial water. Compendial water is typically (but not exclusively) associated with parenteral compounding or a sterile diluent for parenteral products (including cleaning of certain parenteral contact components) and shall comply with USP requirements for Water for Injection (WFI). WFI is injected directly into patients bypassing the body's primary defensive systems. WFI water is subjected to regular testing according to the USP monograph.

Pharmaceutical water systems shall comply with the most current USP compendium as a primary requirement as well as any more restrictive and supplemental requirements as addressed in Chapter 12 and Appendix N. Site produced (Bulk) pharmaceutical water shall be sourced directly from potable water supply and shall be completely independent of laboratory or other process purified water systems. Pharmaceutical water systems shall be located in secure areas which facilitate reliable operation and service activities to occur without contamination. Deionization methods utilized in pharmaceutical water shall be electrodeionization (EDI) type.

Bulk WFI water shall have total microbial count of less than 10CFU/100ml, conductivity of less than 1.3 mS/cm referenced to 25°C (77°F), less than 10 ppb TOC and less than 0.25 EU/ml Endotoxin. Low design TOC levels are essential to maintaining system microbial control and shall be complied regardless of means of disinfection.

Subject to evaluation of all fluctuations of source water conditions and design to confirm reliable compliance with water quality specifications, the Bulk WFI water system shall include at least:

1. **Pretreatment:** Ion-exchange type softening, redundant carbon sorption, and a sanitary RO system (at least single-pass) with appropriate bio-fouling control.
2. **Primary Treatment:** Either multi-effect still or the second pass from a two-pass hot water sanitizable, FDA sanitary (full-fit type) RO system.
3. **Final Treatment:** Distillation based systems shall be circulated and maintained as high temperature systems (80°C [176°F]) and incorporate point of use sanitary heat exchangers.

Final filtration is not required for distillation based systems, but may be utilized to limit build-up of cell fragments and non-replicating particles. Membrane based systems (two pass RO without distillation) shall incorporate ultrafiltration or final microfiltration compliant with Chapter 12. The final filtration system and storage tank shall be either hot water or ozone sanitizable and so-configured. Where membrane-based systems are not maintained and distributed at high temperature, the final filtration (including the final permeate storage tank) shall incorporate electrolytic generated ozone-based sanitization and ozone destruct in conformance with Chapter 12. Where ozone is used, it shall be continuously present in the storage tank and utilized at least weekly for the distribution loop.

Where necessary to reliably achieve required conductivity, electrodeionizaton (EDI) may be used in the treatment process but only if positioned upstream of the primary treatment (second pass RO) process. Oxidizing UV (185nm) may be used only for minor TOC polishing applications (after primary TOC removal). The restriction of UV to minor polishing applications is to ensure continued efficacy and to prevent generation of hazardous byproducts. Oxidizing UV and other polishing equipment shall not be used in place of either (a) RO followed by distillation or (b) two-pass RO configurations. Where dissolved gas (e.g. CO_2, oxygen, or ammonia) removal is required, such may be accomplished through use of ultra-pure water membrane contactors or EDI prior to 2nd pass RO (or for CO_2 removal by technical-grade pH adjustment prior to 2nd pass RO). Where both membrane contactors and EDI is utilized, the membrane contactor shall be located prior to the EDI. EDI may be utilized only for CO_2 reduction only where determined sufficient (typically applications with less than 10 mg/L concentration. EDI shall not be used without prior RO treatment.

Tanks for WFI shall be 316 L stainless steel, electropolished and maximum 15 Ra, and shall include a clean sterile filtered monographed either argon (preferred) or nitrogen blanket, except that heat-sterilized, heat traced sterile gas vent filtration may be utilized for some applications. Sanitary rupture disk tank arrangements are required. Where monographed argon is available it is preferred for inherent purity and avoidance of nitrogen-fixing bacteria.

WFI water shall be continuously recirculated in a 15 Ra and electropolished 316 L stainless steel pickled and passivated distribution system with autogenous orbital welds, except that for low temperature, non-heat sanitized systems infrared fusion nature PVDF piping may be utilized. Where heat exchangers are utilized, the system shall be designed such that the WFI or USP water is always at a higher pressure than the process fluid, and double wall, ultrapure type is required. All components shall be arranged to maintain system sanitation and suitable for clean-in-place/sterilization in place (CIP/SIP). Strict controls shall be established for system-design quality control, all wetted materials, elastomers, installation, inspection, and handling processes, and for all component and equipment selections that will be in contact or could impact product water quality or reliability. Dedicated serpentine distribution is required for WFI.

Bulk USP Purified Water shall have total microbial count of less than 100 CFU/100 ml, conductivity of less than 1.3 mS/cm referenced to 25°C (77°F), and less than 20 ppb TOC. Preferred method of production is filtration, ion-exchange type softening, carbon sorption and two-pass RO with final filtration (Refer to Section 12.1), however similar arrangements that include single pass sanitary grade RO, EDI, final filtration, and ozonation may also be utilized where TOC can be reliably maintained below 200 ppb. High temperature distribution is not utilized for USP Purified Water and there is no specified endotoxin requirement. The increase in TOC (from 20 ppb to 200 ppb) is permissible for this USP Purified Water application where distribution systems are routinely (at least weekly) ozonated as a means of microbial control; however it is generally recommended to maintain the lower TOC levels. Where EDI is utilized with two-pass RO, it should be located before the second pass.

Non-compendial high purity water may (depending on application suitability) be used for facility washing/cleaning/rinsing and for tests and in assays used in analytical laboratories as well as, formulations of bulk active pharmaceutical ingredients (APIs). Non-compendial water is validated in a manner consistent with compendial water.

Non-compendial water should be as appropriate to the application, however the treatment process shall include

(at minimum) filtration, ion exchange softening, carbon sorption, either two-pass RO or single pass RO plus EDI, disinfecting UV, and final filtration. Such water should have less than 100 CFU/ml, less than 2 mS/cm referenced to 25°C (77°F), and in no case more than 500 ppb TOC. There is no endotoxin requirement for non-compendial water. With the exception of non-compendial water utilized only for general cleaning applications of non-critical surfaces, it is recommended that water be produced and maintained with TOC below 20 ppb, except that TOC levels up to 200 ppb may be acceptable where routine ozonation is incorporated.

For WFI water, an alert level of not to exceed 25 ppb and an action limit of not to exceed 100 ppb shall be utilized for TOC. Action limits for other parameters or for other compendial applications shall be determined by system design and application, but in no case exceed 80% of the monographed water quality requirement or values indicated in Table 12.1.1, whichever is more stringent and as updated (but not to exceed these values) based on trend data of properly operating systems. Conductivity values in Table 12.1.1 are stated as resistivity. There is no lower limit to conductivity (upper limit for resistivity) for pharmaceutical waters, except that pharmaceutical waters supplying incubators and certain other scientific equipment may have manufacturer-imposed limits (typically conductivity values that are not permitted to be less than 0.2 mS/cm referenced to 25°C (77°F) are acceptable). The establishment of alert and action levels must allow for monitoring of a parameter that may be trending out of control and corrective action prior to detecting an excursion.

The term "High Purity Water", "HPW", "HPWS", and HPWR" shall not be used without modification for pharmaceutical water supplies serving APFs due to potential conflict with water applications and systems in other areas of facilities. For example, where USP High Purity Water is utilized, "USP HPW" or "Pharmaceutical HPW" should be used for system identification.

Refer to Chapter 12 for details on the pre-treatment options which shall be utilized for pharmaceutical water systems, including multimedia filters, carbon filters, softeners, cartridge filters, RO systems, EDI systems, UV systems, storage tanks, distribution system, sanitization systems, quality control and quality assurance and system startup. Refer also to Appendix N for additional guidance related to water testing and start-up.

For WFI applications, off-line conductivity test shall not substitute for on-line conductivity and Anion/ Cation/ Metals/ Ammonia analysis. Comprehensive Installation Qualification (IQ) is mandatory for all compendial systems, including but not limited to use of qualified ultra-high purity (UHP) piping system contractors and 3rd party UHP piping system quality assurance during construction, and testing and to verify proper materials, purge gas, calibration reports, personnel and machine welding qualifications, test sample chain of custody documentation, etc. Where specified in compendium, the sampling and testing methods for specific parameters shall comply with the listed validation methods

Once IQ, OQ and initial PQ activities are complete, sufficient sampling and monitoring of compendial systems shall continue throughout the duration of an approved trend period sufficient to prove system stability. This trend period should typically not be less than 3 months, and at minimum shall be sufficient to include proven performance throughout upstream supply system source water changes, inclusive of at least 3 consecutive successful sample tests conducted over not less than a 6 week period for each water supply source. Example municipal sources that seasonally change from ground water to surface water, rotate supply sources for capacity issues or otherwise materially and routinely change their supply source or treatment process in a matter that may potentially effect source water composition. Subsequent off-line testing frequency and instrument calibration shall be defined on a site specific basis. Testing of compendial systems shall include off-line TOC, microbial, anions, cations, ammonia, and trace metals testing at least annually. At minimum, quarterly off-line testing shall occur throughout the first year, though monthly should be considered to establish trend stability. Presence of on-line instrumentation (e.g. TOC monitors) shall not substitute for off-line testing, or vice versa.

13.10.4 Drain and Vent System

APFs are sensitive to contamination which is common in drainage systems. For this reason, drains should only be present at the early stages of gowning and late stages of de-gowning, and in equipment/glass wash areas.

Generally, drains should be avoided in ISO 8 areas. Drains are inappropriate for ISO 5 or ISO 7 areas, except where required for scientific use and approved by DTR. Where indirect waste drains are required and for any application where a floor drain is permitted, they shall be of sanitary, accessible, and readily cleanable design, constructed of not less than 316 stainless steel, with smooth surfaces and radius corners, self-draining without any retained wastewater, and shall be factory passivated.

Wherever possible, drains required for equipment and systems should be placed in a segregated routinely occupied and unconcealed area under negative pressure and accessible from outside the clean room. If the space cannot be accessed from outside the clean room, space should be provided for over-gowning and sanitization for entry and exit. Proper air-gaps shall be provided.

Where drains are required, they shall be provided with solid gas-tight gasketed covers. The drain and traps should be subject to a "drain/trap management program" which will include periodic sanitization and swabbing to assure control. Automatic electric trap seal priming is required, trap seal liquid shall be readily visible from the drain opening, and the use of mechanical or elastomeric trap seal devices (barrier type trap seal devices) is unacceptable.

High purity water sampling port drain and valve shall be located within clean space to mitigate contamination risk.

All traps shall have smooth, self-cleaning interiors (free of flat areas) to minimize the risk of soil accumulation and microbial growth. Deep seal traps are preferred to minimize risk of cross-contamination.

13.10.5 Sinks and Faucets

Drain-waste-vent (DWV) systems are a known source of contamination in APFs. For this reason, sinks should only be present at the early stages of gowning and late stages of de-gowning for hand washing, and in equipment wash areas. Sinks are inappropriate for use in ISO 7 or ISO 5 areas, except where required for scientific use and approved by DTR.

Hand washing/hygiene sinks for APFs should utilize "hands-free" operation for water, soap and drying. Sensors, knee, and foot pedal operations may be acceptable, depending on site-specific requirements.

Sinks shall be not less than Type 316 stainless, NSF type, and without overflows. There shall be no sound deadening material applied to sinks in APF spaces. Faucets shall meet requirements of Section 8.2 and Section 13.10.2, however they shall be furnished without vacuum breakers unless specifically required for the application or risk (e.g. janitor faucets shall incorporate vacuum breakers). All faucet outlets shall project and terminate sufficiently above the flood rim and basin walls to facilitate complete washing without contact.

Janitor sinks should only be provided in Grade D or CNC spaces. Janitor closets within clean rooms should be for storage and mixing of cleaning materials only. Refer to Section 13.3.4, Common APF Design Elements. Backflow protection for mixing of chemicals is required, and should be located in the accessible service space where possible. Where bleach is utilized as a routine disinfectant, janitor sinks should be acid resistant enameled cast iron.

13.10.6 Emergency Fixtures

Domestic water systems are a known source of contamination in APFs. For this reason, emergency fixtures should only be present in low classification spaces. Within ISO 5/7 rooms, the use of pre-sterilized portable eyewashes are preferred. Where an eyewash and emergency shower must be provided for safety within a clean room space, the safety equipment shall be clean room style and fully sealed and gasketed and constructed of stainless steel or other material compatible with cleaning chemicals. Where piped emergency fixtures are required, potable hot and cold water shall be piped to the fixtures with a point of use mixing valve, and fixture types shall be as addressed in Section 8.2 and Section 8.3. To minimize potential damage where emergency showers are required, utilize 75 LPM (20 GPM) flow restrictors unless otherwise mandated by the application. The dedicated backflow protected water supply requirements of Section 8.3.7, Emergency Fixture Water shall be omitted where fixtures maintain appropriate air gap and do not incorporate hoses.

13.10.7 Liquid Nitrogen (LN_2)

Cryogenic fluid distribution in APFs is typically limited to liquid nitrogen (LN2), the requirements for which are described in Section 12.3. LN2 is vital for maintaining temperature in cryo-freezers and controlled rate freezers. LN2 systems shall have adequate capacity, pressure, flow, temperature stability, and monitoring to maintain operational continuity. LN2 may be supplied from the bulk tank located outdoors, micro-bulk, or from dedicated cryogenic liquid containers (liquid cylinders) located nearby (but outside the clean room). All interconnecting piping between the supply source and freezers shall be made utilizing static vacuum jacketed piping and vacuum jacketed connection hose and fittings. Oxygen monitoring shall be provided in freezer rooms and other rooms where cryogenic fluids are supplied to warn of oxygen depletion. Remote liquid cylinders shall be provided with level monitoring displayed in the freezer rooms as well as other approved and constantly monitored locations. Supply source(s) shall include an emergency supply connection and an integral liquid cylinder reserve with automatic switchover. The stand-by reserve may be waived for liquid systems supplied by exterior bulk systems provided the arrangement incorporates telemetry, separate auxiliary alarm monitoring connected to the liquid level gauge, and provided the freezers and equipment served can maintain satisfactory operation upon unplanned loss of cryogenic fluid service for a duration of not less than 4 days. Automatic switchover arrangements shall maintain constant flow without depleting reserves during normal use, shall include a hot gas bypass to prevent warm gas from entering the system, and (where necessary) shall incorporate circuitry to maintain delivered fluid temperature stability. Where any cryo-fluid may potentially contact product, validation shall include contamination control of all wetted components including but not limited to particles, and such application shall be segregated from other non-critical uses.

13.10.8 Clean Compressed Gases

Compressed gas systems serving APFs may include, but are not limited to Carbon Dioxide (CO_2), Nitrogen (N_2), Argon (AR), Oxygen (O_2), and Pharmaceutical Compressed Air (CA). Primary source equipment (e.g. compressors, filters, reserves, micro-bulks, controls, alarms, and cylinders) as well as distribution piping serving APFs shall be completely independent and fully segregated from laboratory, animal facility, and clinical systems. Critical (product contact) and non-critical system applications shall be fully segregated, as this substantially reduces risks, operational/ validation impact, and potential for disruption. For any case where the use of a shared APF system is permitted between critical and non-critical spaces, approved point of use filtration is required at any outlet whose fluid variability may have an impact on a critical quality attribute (CQA). Refer to Section 12.3 for additional requirements for these systems, including Ultra-High-Purity (UHP) requirements.

The supply source for APFs gasses should be cryogenic/ liquid type wherever possible as this promotes purity and minimizes potential for contamination. This is especially advised for any application with potential impact on a product's CQA. NFPA-99 style liquid cylinder x liquid cylinder automatic supply manifolds as well as high purity liquid cylinder x liquid cylinder automatic switchovers may be used and shall be inclusive of any required vaporizers and economizers to provide reliable gas supply at required pressure and flow, and to minimize fluid losses. Fully automatic liquid-cylinder reserve manifold arrangements are required for system continuity and shall not be shared. Cylinders shall not be located inside classified spaces.

Where facility demands justify large exterior bulk systems, shared use is permitted only with dedicated cryogenic medical gas for human applications (only), and at minimum redundancy of vaporizers is required, as well as redundancy and segregation of pressure control valves and other primary equipment arrangements to ensure completely separate distribution from the bulk tank to the APF points of use.

The supply source shall be fitted with redundant (N+1) particulate filters and shall include a high purity gas purge station arranged to facilitate supply source cylinder and filter change outs to occur without induced contamination. Sintered stainless absolute filter media or sterile gas hydrophobic membrane type PVDF or PTFE is recommended, except that filter media for oxygen applications shall not be constructed of stainless steel. The use of halogenated elastomers (including PTFE and Viton) is unacceptable at any point

(e.g. manifolds) where pressure may exceed 3000 kPa (400 PSIG). Copper, nickel-copper or other appropriate media should be utilized for oxygen applications to minimize combustion risks. Where filtration is applied, the need for pre-filters shall be evaluated.

Where UHP quality gas is required for various analytical instruments (e.g. gas chromatographs), stainless steel point of use purifiers are recommended and shall include purge stations. For applications with direct product contact, provision of an approved point of use sterile gas filter (hydrophobic PTFE or PVDF) is required. Non-disposable filters whose variability may affect a product CQA shall be integrity tested.

As it is typical to experience variability of purity with high pressure gas cylinders (HPGs), the use of HPGs in lieu of a cryogenic source should be limited to small applications where the use of a liquid cylinder would be impractical, the capacity is deemed satisfactory, and the potential variability of gas quality is deemed acceptable for the application. HPG cylinders are frequently shown (upon individual cylinder analysis) to exceed contaminant levels identified in batch quality certifications and (as with all portable liquid and gas supplies) purity certifications do not in themselves represent assurance of particulate levels. The use of liquid cylinders also provides substantially more capacity than high pressure gas containers, thereby minimizing refill frequency and the associated maintenance and potential of contamination.

Gas systems serving critical areas and for any potential product contact within APFs shall be designed and constructed of stainless steel materials and components in conformance with Section 12.3.7, Liquid and Gaseous Lab Nitrogen/Argon Additional Requirements. Systems shall be arranged and constructed of materials to reliably deliver not less than Grade 4.5 fluid purity gasses for CO_2 and for applications in non-critical spaces, and not less than Grade 5.0 fluid purity to critical spaces, within the required particle limits. With regards to filtration, the provisions as indicated above apply in lieu of the filtration portions of Section 12.3.7 or Section 12.3.8.

For non-critical applications with no product contact or potential impact to a CQA, conformance with Section 12.3 via segregated local systems may, at NIH discretion be deemed adequate.

CO_2 is required in APF Cellular Therapy for various equipment located in Tissue Culture and equipment rooms, (such as incubators). The quality of CO_2 gas shall be of high purity similar or higher than USP Medical Grade, Anaerobic and shall be sampled at qualification to prove a required purity of at least 99% and in conformance with the USP monograph. CO_2 shall be supplied by a primary/ secondary automatic supply consisting of at least two liquid cylinders with vaporizer and economizer circuit. Due to potential of evaporation and considering criticality and duration of activities with incubators, the inclusion of an auxiliary short term high pressure gas back-up emergency reserve with gas heater as addressed in Section 12.3 is highly recommended. For extremely small applications, an NFPA-99 type fully automatic gas manifold may be used for CO_2 supply, when sized in conformance with Section 12.3 for local supply systems. A gas heater is required for CO_2 cylinder gas supply sources. For all gas cylinders (including CO_2) Manifolds should switch and alarm before gas drops below 1725 kPa (250 PSIG).

Systems shall be constructed to maintain fluid purity, inclusive of particle limits and shall be validated upon completion as indicated in the Section 13.10.9 for Pharmaceutical Compressed Air Systems. At minimum, the supply and distribution system shall:

1. Maintain the purity of the source gas to the point of use without reduction of quality.
2. Deliver not less than the monographed purity specifications under all conditions.
3. Provide for particle limits, moisture, and hydrocarbon limits that do not exceed those indicated in the following section for Pharmaceutical Compressed Air to Critical Spaces.
4. Fluid applications whose variability may affect a CQA shall also meet an appropriate microbial specification.
5. In the case of CO_2, initial distribution system contamination testing is carried out prior to charging the system with CO_2, by using a high purity surrogate, typically nitrogen or argon.
6. Alert limits shall be sufficient to prevent an excursion from monographed requirements and room/hood classification.

All materials within APFs shall be suitable for use within clean room spaces, inclusive of cleaning protocols and use of hygienic pipe hangers, supports, and penetration seals. The use of hoses (with the exception of cylinder connections) shall be avoided as these are frequently a source of contamination.

A comprehensive installation qualification process shall be provided and shall include, but not be limited to all welding, purge gas, materials, and control of potential contaminants (e.g. contractor purge gas filters) as well as record logs and review of calibration documents performed by competent independent quality assurance personnel.

Outlets shall be located to permit ready access for validation, and shall not be located near a potential water source. The word "Pharmaceutical", "cGMP", or other text as approved by NIH on a site-specific basis shall be provided in piping and equipment identification nomenclature to provide clear identification and minimize potential for cross connections.

Alarms shall be provided to monitor the status of the source supply, reserve, and other aspects including main line valve status as indicated for lab systems in Section 12.3. The alarms shall indicate to the BAS to indicate loss of supply, equipment failures, and alert levels for critical process parameters. In addition to BAS, alert to a secondary monitoring system (typically the scientific monitoring system) is required for critical alarms. Specific details of all alarms shall be recommended by the design team and reviewed and approved by NIH. The appropriate alert levels shall be determined by the A/E and subject to NIH approval. Depending on application, trending may be required.

All systems shall be properly purged, cross-connection tested, and kept under dry nitrogen or argon charge until the final system fill gas purge and validation for use. Prior to use, gas concentration verification shall be conducted to verify proper fluid delivery at use points.

13.10.9 Pharmaceutical Compressed Air

In addition to the provisions of Section 13.10.8, Clean Compressed Gasses, the provisions herein apply to Pharmaceutical Compressed Air.

Compressed air for APFs shall be provided from fully controlled, independent, local systems; in conformance with Section 12.3 for lab air. For fluid services delivered within a critical area or with potential impact on a CQA, the minimum fluid quality shall be determined by site specific risk assessment and approval of NIH but shall not be of lower quality than required for the most demanding room/ hood where an outlet is located. The delivered air through the piping distribution system shall in no case be less stringent than:

1. ISO 8573-1:2010 Class 2:2:1 for ISO Class 7 and dirtier spaces.
2. ISO 8573-1:2010 Class 1:2:1 for ISO 5 spaces/ hoods.
3. Microbial count limits shall be determined by Risk Assessment, however there should be no microbial contaminants detected at ISO Grade 5, and action limits exceeding 5 CFU/M3 are unacceptable for APF areas of ISO Class 7.
4. All compendial requirements for cGMP shall additionally be met for all applications which may contact a product or otherwise affect a CQA.

Air shall be sampled at qualification to verify attainment of required specifications. Piping systems inclusive of the purge gas utilized during construction shall be validated for particulate, moisture, and hydrocarbon contamination (and may require oxygen monitoring). Scientifically validated contaminant test methods utilized by a laboratory accredited in conformance with ISO 17025 by a signatory to the International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Agreement are generally acceptable within the appropriate limits of detection. Wherever possible, test methods should be as recognized by ISO 8573:2010 standards, ISPE, or SEMATECH published documents for high/ ultra-high purity fluids. Unless otherwise required, the following methods should be utilized:

1. **Particles:** Report as per ISO 8573-1:2010. Use laser or laser diode particle counter for systems that may contact a product or affect a product CQA, and for all applications where particle counts of sizes below 1 µM are required. For non-critical applications where no particle count

sizes below 1 µM are required, ISO 8573-4 off-site lab analysis (filter media) may be utilized.

2. **Hydrocarbons:** Report as per ISO 8573-2 and ISO 8573-5 via off-site lab analysis of samples (typically gravimetric, flame ionization detection (FID), and gas chromatography. On-site FID may be used.

3. **Moisture:** Color-reactive detector tubes (Draeger tubes) following ISO 8573-3 from an accredited lab may be used for routine analysis provided the dew point requirement is not below 40°F/C pressure dew point. Use electrolytic cell or aluminum oxide hygrometer for on-site measurements of lower moisture requirements or for critical accuracy applications.

4. **Microbial:** ISO 8573-7 plate methods. Both aerobic and anaerobic testing may be required, as determined by risk assessment.

5. **Gaseous Contaminants:** ISO 8573-6. Field method color-reactive detector tubes may be used only within application sensitivity requirements. Lab analysis of gas samples is typically preferred.

Compressors shall be 100% oil-free, scroll, rotary screw/ rotary tooth, or oil-free reciprocating type. Dryers shall be desiccant type only. Air intakes shall be from the exterior and in conformance with NFPA-99. Continuous automatic type dew point monitoring, carbon monoxide monitors, delivered air pressure monitoring, redundant desiccant dryer and filtration/ purification trains, as well as passivated stainless steel wet and dry receivers are required. Filtration shall be provided prior to entering the cGMP space.

Cylinder tank manifold requirements shall follow those indicated for N_2 and O_2 gas under Section 13.10.8.

13.10.10 Vacuum

Vacuum is generally not required in Cellular Processing facilities. Where required in APFs, general vacuum requirements will follow Section 12.4. Dedicated vacuum systems for each APF are required, except for extremely limited use applications where point of use diaphragm type vacuum pumps with appropriately filtered and piped exhaust is approved after completion of a comprehensive risk assessment.

Piping material within clean rooms shall be compatible with the cleaning regimen, generally 316 Stainless Steel (SS), with orbital weld, VCR, or ISO K-fittings. All materials shall be cleaned and capped for oxygen service. The need for decontamination provisions/ filtration shall be determined on a site-specific application, however, provision of a full air gap is mandatory at the equipment discharge to any drains.

Section 13.11

APF Design Requirements: Fire Protection

Contents:

13.11.0 Introduction

All fire protection systems within the APF area shall be designed in accordance with latest NFPA edition, FM Global, Applicable Building Codes and the Local Fire Marshall. All fire protection system equipment, sprinklers, devices and materials shall be Underwriter's Laboratory (UL) listed and Factory Mutual Global (FM) approved. The use of aspirating smoke detection should be considered for sensitive APF areas and is subject to approval of the DFM. Such systems may be beneficial even where only permitted or utilized as supplemental systems providing a trouble indication (where not approved as primary detection). Where aspirating detection is utilized, maintenance requirements of qualified vendors should be evaluated during the design phase, including experience with cleanroom fire detection. See Chapter 9 for general fire protection and suppression and fire alarm requirements as well as FM Datasheet 1-56.

13.11.1 Automatic Sprinkler Systems

The type of fire suppression system utilized for APF areas shall be evaluated by project with DTR and the DFM. Fires in cleanroom spaces that activate even a single sprinkler can immediately result in substantial financial loss and months of operational impact. For this reason, single interlock cross-zoned preaction systems utilizing nitrogen-charged piping and specialized detectors for cleanroom environments are recommended. Where such preaction arrangement is not acceptable, APF areas shall primarily be protected by a wet-pipe sprinkler system. All new sprinkler piping shall be hydraulically calculated by the sprinkler contractor using up to date properly conducted flow test information. Design shall include not less than a 10% minimum safety factor below the available combined water supply curve.

Sprinkler heads throughout the area shall be of the quick-response type except in areas designated for standard response per the requirements of the DRM. Rooms within clean areas shall have airtight devices.

Where allowed by DFM, sprinkler piping systems shall be initially leak tested with gaseous nitrogen instead of water to mitigate the risk of damage to the APF, see Chapter 9. Sprinkler heads with "gasketed" ceiling cover plates and cleanroom rings over concealed pendant sprinkler head are the industry-preferred type for cleanroom areas but, require the approval of DTR and DFM. Alternative arrangements as described in Chapter 9 (typically for high containment spaces) can be utilized where necessary to meet DFM requirements and FM Data Sheet recommendations.

Section 13.12

APF Design Requirements: Electrical

Contents:

13.12.0 Introduction

The objectives of the electrical design guidelines are to ensure compliance with the applicable standards, establish uniformity of design, achieve the best overall cost-effective installation, and construct an electrical system that is compatible with other building systems. The design of the electrical systems shall meet the program requirements while incorporating NIH's commitment to robustness, resilience, sustainability and energy-efficiency. In addition, the design of electrical systems shall meet all applicable requirements in Chapter 10 and comply with the following additional requirements.

13.12.1 General Requirements

Lighting, power, and communication systems shall meet all current program requirements as well as provide for future growth. These systems must have ample capacity to meet future increased load demand and shall include provisions for the addition of future electrical loads as determined by NIH on a project-by-project basis.

All electrical systems must be designed for safety, long life, efficiency, economy, and maintainability. Appropriate life cycle cost analysis shall be performed to select materials and systems that yield optimum system life. The electrical system shall be designed and built to operate with means for proper maintenance to occur with minimal need for interruption of other services and areas. Electrical equipment within aseptic processing shall be cleanable, ledge and crevice free, non-shedding, and sealed.

A protection and coordination study shall be performed for the portion of the new equipment provided. The results of the study shall be the basis for selection of overcurrent device settings and fuse types for short circuit protection, phase and ground overcurrent protection, system selectivity and coordination.

Arc flash hazard analysis shall be performed during the Construction Administration phase. Associated labels shall be installed prior to the completion of the project. Refer to Section 10.1 for additional requirements.

13.12.2 Normal Power

Provide dedicated normal power distribution for all APF distribution systems and designed to permit segregation of different types of loads to different panels i.e., motor loads shall not be connected to the receptacle panels. Panelboards shall be located in electrical rooms outside the processing or clean areas. Electrical distribution system supplying power to HVAC and motor loads shall be located close to the equipment served.

The distribution switchboard (or power panelboard) shall be provided with a (type-2) Surge Protection Device (SPD-2). The SPD-2 modules shall be integral to or mounted separately next to the equipment served.

All transformers shall be general purpose type specified to have copper windings and have a 115°C (271°F) temperature rise over a 40°C (104°F) ambient and a 220°C (428°F) insulation system. All transformers shall be located in areas where the manufacturer's ventilation requirements and the NEC working clearances are strictly adhered to.

All transformers shall be bonded to the plant/building ground grid and/or building steel with a green copper conductor sized per the NEC, but not less than #4 AWG.

Refer to Section 10.2 for additional requirements.

13.12.3 Emergency Power Systems

The emergency power shall be provided to all life safety loads, legally required standby loads and optional standby loads, including, but not limited to those listed under Section 10.3.1 and:

1. Supply and exhaust fans serving APF
2. EMS systems
3. APF Gas manifolds and air compressors
4. APF High Purity water systems
5. Terminal Units and Critical sensors and pressure monitors serving APF
6. Select electrical outlets in APF

7. Phone system

All new exit and emergency lighting systems shall be fed from the Life Safety distribution, and shall match building standards. Life Safety loads as required by NEC Article 700 shall have battery or UPS system backup.

Uninterruptible Power Supply (UPS) shall be required to serve 208Y/120V for sensitive controls and additional equipment, as indicated by NIH. The UPS power shall be provided from a new adequately sized UPS system; location to be coordinated with NIH. UPS power incoming feed shall include both normal and emergency power and include a manual bypass. Refer to Section 10.3.1.

13.12.4 Wiring Methods

All individual branch circuits shall be provided with a dedicated neutral wire. No shared neutrals shall be permitted. Maximum of two (2) offices' convenience receptacles shall be connected per circuit.

Install all wiring in conduit, and the minimum size of the conduit shall be 21 mm (¾ in.) for power system wiring and 35 mm (1-1/4 in.) for telecommunication systems. Conduit application is as follows:

1. Feeders (Indoors): Feeders up to 103 mm (4 in.) in diameter and concealed within building construction shall be Electric Metallic Tubing (EMT).
2. Damp or wet locations: Hot dipped galvanized rigid steel conduit.
3. Lighting and receptacle branch circuits: Electric Metallic Tubing (EMT).
4. For connection to motors and vibrating equipment such as transformers, provide liquid-tight flexible metal conduit.

Conduits shall be installed concealed in ceiling and wall. Fittings for metallic conduits shall be compression type.

A minimum of one power receptacle shall be provided at each wall surface. Convenience receptacles shall be provided throughout the areas with the distance to a receptacle from any location in the area being served no more than 15.24 m (50 ft.). Special receptacles at 120V, 208V and 480V shall be provided to serve specific equipment requiring more than 20A, 120V circuit as specified by the equipment manufacturer. Dedicated receptacles shall be located as close as possible to the equipment served. Outlets shall be labeled with the panelboard and circuits number of the branch circuit serving the outlet.

To accommodate to flexibility/interchangeability of freezer equipment requiring 20A 120V 1P or 20A 208V 1P circuit, a combination of (1) 208V and (2) 120V receptacles shall be provided next to each other and fed from a 2-pole circuit breaker in the equipment panelboard.

All devices located within clean areas shall be cleanroom type, fully flush, sealed and cleanable, compatible with all required cleaning agents. This includes all horns, strobes, pull stations, and detectors. Covers alone are not considered adequate to make a device cleanable.

Cast device boxes with external hub and gasketed device covers shall be provided in cleanrooms to allow proper cleaning with a spray bottle and hand wipe or mop while in use and easy removal for service. Caulking devices to the wall, floor or ceiling shall not be allowed as a substitute for proper flush gaskets, except where specified by the device manufacturer and where removal is not required for service of the device (e.g. exit sign interface to ceiling or wall).

All devices shall be properly sealed to prevent the migration of air through conduits. Provide 25 mm (1 in.) barrier of silicone caulking around the wire within the device box hub; and provide a continuous bead of silicone caulk around the device cover plate and the adjacent surface.

Devices below covers shall also be resistant to cleaning and sanitizing chemical sprays. The A/E shall coordinate with the list of cleaning chemicals for compatibility requirements. Hands-free switches are preferred wherever applicable and should be used throughout. These switches are required for door controls.

Emergency egress buttons for all physically interlocked doors shall be waterproof simulated break-glass type with covers. All interlocked doors shall be equipped with sounders to notify when the egress button has been

used or the door open alert time has been exceeded. Refer to Section 10.5 for additional requirements.

13.12.5 Power Quality

Panelboard serving nonlinear equipment shall be provided with 200% neutral bus to account for harmonic heating. Provide oversized neutral for all branch circuits supplying nonlinear loads and refer to Section 10.6 for additional requirements.

13.12.6 Lighting

Complete lighting system shall be provided for all areas. The lighting system shall primarily consist of energy-efficient fluorescent and/or LED lighting fixtures. The lighting system shall be serviced at 277V for fluorescent/LED fixtures. For egress lighting, dual-voltage (120/277) ballast shall be provided. Lighting level required is shown in Table 13.12.6 and Section 10.7.

Where lighting devices are provided in clean areas, fixtures of all types shall be triple gasketed, smooth, cleanable and compatible with cleaning chemicals. Where lighting is integral with ceiling systems, the light lens and seals shall be provided by the ceiling grid manufacturer. Luminaires (fixtures) should have no areas from which contamination may be released or harbored. Sealed or flush fittings is preferred. Light fixtures should be serviceable and not create glare. Comfort to occupants must be considered as well as photosensitivity to product or materials that will be used.

Since light fixtures can have an impact on the air flow, these factors should be considered when positioning. A diffuser should be used to minimize or negate turbulence.

Lighting controls for open spaces shall be via occupancy sensors with manual step-switched override. Certain fixture circuits shall always remain on to serve as nightlights and as emergency egress fixtures, as required by local and national codes. These fixtures shall be by local and national codes. These fixtures shall be controlled from switch duty rated circuit breakers in the emergency lighting panel and ahead of local switch controls. Circuit breakers controlling fixtures shall be switching duty rated breakers.

13.12.7 Emergency Fixtures

A minimum of one emergency power lighting fixture shall be provided in each space, but additional fixtures could be required based on minimum of 10 lux (1 fc) for emergency egress. Low wattage LED type exit signs

Table 13.12.6 Lighting Uniformity Requirements

Type of Area, Task, or Activity	Lux-level (Em)	Color Temperature (CCT)	Glare rating (UGRL)	Uniformity (Uo)	Color Rendition (Ra)	Cylindrical Illuminance (Ez)	Specific Requirements
General Lighting	300 - 500	≥ 3,500 K	19	0.6	80		Illuminance at floor level
Equipment Rooms	325 - 540	< 6,000 K	19	0.6	80		Illuminance at floor level
Laboratory Support Areas	325 - 430	≤ 6,000 K	19	0.6	80		Illuminance at floor level
Difficult Inspection	1000	≤ 6 - 6,500 K	19	0.7	90	1,200 lx at 1.2 m	Illuminance at benchtop
Exacting Inspection	3 - 10,000	≤ 6 - 6,500 K	19	0.7	90	1,200 lx at 1.2 m	Illuminance at benchtop

shall be installed as required by local and national codes. Exit signs and emergency/night lighting shall be provided by un-switched branch circuits, fed from the life safety/emergency lighting panels(s). Refer to Section 10.7.

Section 13.13

APF Design Requirements: Low-Voltage Systems

Contents:

13.13.0 Introduction

The low voltage systems in APFs require the same high level of attention to detail as do line voltage systems. All back-boxes should be cast metal, and all conductor entries should be via sealed conduits. Cover plates should be gasketed and caulked. Other requirements are as described below.

13.13.1 Telephone and CIT Outlets

Telephone/data outlets/wireless outlets shall be located as required by the users and as described above in the lab surface metal raceway system. In addition, a minimum of one data outlet shall be provided at each wall surface. Each outlet shall include a box with a stainless steel cover plate and not less than a 35 mm (1-¼ in.) conduit to the cable tray. A pull string shall be provided to facilitate the installation of category 6 wiring. In addition to wall outlets, wireless LAN access point shall be provided throughout the space. Provide emergency and UPS power for the telephone/data systems. All boxes serving classified spaces shall be cast metal, sealed into the conduit with 100% silicone, and with a sealed and gasketed cover plate.

Cleanroom telephones should be accessible to minimize movement of personnel into and out of the cleanroom. Windows, speech panels, intercoms, data links and telephones shall be compatible with the cleanroom class and application.

13.13.2 Closed Circuit Television (CCTV)

All cleanrooms shall be equipped with CCTV cameras in wipe-down compatible covers to allow remote monitoring of all rooms. Camera locations shall be such that all portions of the room are visible via this system.

13.13.3 Information Technology

Provide two (2) redundant 208Y/120V 3P 4W panelboards and UPS in the LAN room for all of the communications systems. These panelboards shall be fed from circuit breakers located in the distribution equipment for standby power distribution.

Dedicated, wall-mounted copper ground bus shall be located in electrical and LAN rooms. These ground buses shall be connected to the existing ground bus located in the main electrical room. Refer to Chapter 11.

Section 13.14

APF Design Requirements: Environmental Monitoring System (EMS)

Contents:

13.14.0 Introduction

This section describes the general environmental monitoring system (EMS) considerations, as well as the specific requirements. EMS shall be specified by the A/E in consultation with users and procured and validated under the construction contract. Once the EMS is validated, NIH users typically take ownership of this system. Refer to Section 13.9 for HVAC Controls and BAS Requirements.

13.14.1 General Requirements

Critical HVAC environmental control parameters shall be monitored on an EMS system. EMS shall be complete, functional, tested and ready for IQ, OQ, PQ and Computer System Validation (CSV).

The EMS shall provide validated monitoring and alarming of critical environmental conditions, via dedicated, validated, probes within the compounding / manufacturing environment.

It is recommended that EMS and BAS be fully segregated; however, if approved by DTR, BAS and EMS may share common sensors. In such cases, the qualified portion of the EMS shall be firewalled off from the main BAS, with unique access control, security, change control, audit trail, calibration management, nonvolatile record creation and report generation, and be fully 21 CFR Part 11 compliant with the ability to be qualified and CSV validated.

Where separate EMS and BAS sensors are used, they shall be co-located to ensure the accuracy of the data. Generally, co-location should be interpreted as within 1 m (3 ft.), and at the same elevation, particularly for temperature sensors. Shared sensors must still be under calibration management and the systems isolated by an appropriate signal splitter or communication of the field data to the BAS from the EMS via an appropriate high-speed bus.

All EMS field devices shall be calibrate-able with NIST certified factory calibrations.

The EMS shall provide non-volatile electronic records of monitored conditions over no less than a 2 year period without recourse to archives and 7 years of archive storage.

Room monitoring of classified spaces shall be by the EMS.

This system should be complete, with all components, installation and services outlined herein and as needed to provide a functional system, including:

1. Field devices
2. Signal repeater/isolators
3. Controllers
4. Servers
5. Power supplies
6. Misc. components
7. Wiring
8. Software
9. Configuration
10. Startup/commissioning
11. Testing
12. Documentation

The functionality of this system should include, but not be limited to:

1. Temperature monitoring
2. Humidity monitoring
3. Room differential pressure monitoring
4. Alarming
5. Local and remote notification of alarms
6. Voice dialing notification of alarms

13.14.2 Equipment Monitoring System

Freezers, refrigerators, and incubators shall be monitored by a dedicated, validated equipment monitoring system (similar to REES) that is separate from the BAS system.

The equipment and EMS may be separate or combined system(s). If combined, no element of these requirements shall be compromised in combining the systems.

13.14.3 Program and Graphic of EMS

A. Graphic Display: Display graphic with minimum 20 dynamic points with current data within 10 seconds.

B. Graphic Refresh: Update graphic with minimum 20 dynamic points with current data within 8 seconds.

C. Object Command: Reaction time of less than 2 seconds between operator command of a digital object and device reaction.

D. Object Scan: Transmit change of state and change of analog values to monitoring units or workstation within 6 seconds.

E. Alarm Response Time: Annunciate alarm at workstation and local annunciator within 20 seconds. Multiple workstations must receive alarms within 5 seconds of each other.

F. Program Execution Frequency: Run capability of applications as often as 5 seconds, but selected consistent with mechanical process under control.

G. Performance: Programmable controllers shall execute DDC PID control loops, and scan and update process values and outputs at least once per second.

H. Reporting Accuracy and Stability of Control: Report values and maintain measured variables within tolerances as follows:

1. Space Temperature: +/- 0.5°C (1°F)
2. Relative Humidity: +/- 2 %RH.
3. Air Pressure (Space): +/- 2.5 Pa (0.01 in w.g.)

Fully implemented application and custom software, controllers, network interface and controls devices necessary to accomplish the sequence.

Collect data from connected hardware including panels, processors and sensors at least once per minute, unless approved otherwise by DFOM and DTR.

The system shall keep accurate records of the many data parameters, including analog parameters (like temperature and humidity) and digital parameters (like equipment failure alarms). Data readings are taken at user-defined intervals and stored in a database. This data can be later used in reports for verification of environmental conditions. If a parameter is critical to a facility's operation, the system can notify staff various ways via email or phone notification.

All work, materials and equipment shall comply with the guidelines and regulations, codes and ordinances of the local, state and federal authorities having jurisdiction. As a minimum, the installation shall comply with the current editions of the following codes:

1. 21 CFR Part 11
2. National Electrical Code (NEC)
3. Uniform Building Code (UBC)
4. Uniform Mechanical Code (UMC)

Provide a local analogue readout of analogue sensor values adjacent to or on the surface of all space mounted sensors.

Provide a Human Machine Interface (HMI) touch screen panel for operator interface with all system functions in the clean corridor or gowning space, as directed by the owner.

HMI shall be compatible with cleaning chemicals such as LPH, IPA, peracetic acid or hydrogen peroxide.

Provide a host computer/operator workstation with printer for operator interface, programming, troubleshooting and printing of alarm logs, reports, etc.

The system shall monitor equipment status based upon user designated run-time, starts, and/or calendar date limits, and generate maintenance messages.

Provide graphics for floor plans of the building. This includes each room monitored. Point information on the graphic displays shall dynamically update. Show all input and output points for the system on each graphic.

13.14.4 Local Indicator

Provide local Red/Amber/Green LED indication of monitored parameter status. Solid color, no flashing is required, single multicolor LED or "light stack" are acceptable.

Where mounted in cleanrooms, LED indicators shall be smooth and cleanable, suitable for cleanroom service. They shall also be compatible with cleaning agents, including sodium hypochlorite, hydrogen peroxide, peracetic acid and isopropyl alcohol.

Local annunciation shall be by means of LED indicators. These indicators shall be clearly visible in daylight and at all angles from a distance of 30 m (100 ft).

Room level monitoring and alarming shall be annunciated by local status indicators both within the cGMP manufacturing rooms and within the clean corridor.

13.14.5 Alarm and Voice Access

Provide acknowledgment provisions of alarm conditions, stop the alarm notification process and record name of user taking responsibility for the alarm, and the date/ time of acknowledgement at the System Server.

Allow alarm acknowledgement to expire after a user-defined period ranging from 2 hours to 3 days.

Provide optional provision to require user to complete an alarm checklist prior to alarm acknowledgment. Failure to complete checklist will result in alarm not being acknowledged.

Record and store information about alarm conditions.

Handle alarm and critical conditions by re-notification as values transition to critical.

Provide alarm delays ranging from 0 to 255 minutes to delay the start of alarm notification when current readings are within the alarm range. Ignore alarm delays during critical range.

Provide Clear Alarm delay ranging from 0 to 15 minutes to prevent the premature clearing of an alarm condition.

Provide filtering and signal conditioning to prevent erroneous alarms due to signal noise, floating grounds, faults, voltage spikes and other transient conditions.

Allow a user-defined clean interval ranging from 0 to 240 minutes to prevent report of alarm conditions during standard room cleaning procedures. Allow local activation of clean mode (LP). Log when clean is activated along with the name of the user responsible for activation.

Send alarm start messages to a designated e-mail address via SMTP. Construct a list of users to notify via e-mail from system user list and/or by direct entry of e-mail addresses. Message format to include location date, time, alarm condition and current reading. Acknowledge message format to include the name of the user acknowledging alarm and appropriate notes. Clear message format to indicate the duration of alarm.

Send alarm start message to user on alpha-numeric pager via SMTP.

Voice access and call-out allow the user to hear alarm message from the system server hosted system using a valid PIN.

Voice Access and Callout provide spoken information of alarm conditions via telephone.

Voice Access and Callout allow the user to review current reading associated with alarm conditions.

Repeat alarm messages at a user-defined interval range from 15 minutes to 8 hours.

Send alarm clear and acknowledge messages via all methods provided for alarm messages.

13.14.6 Controller

The controller(s) shall communicate with each other and operator workstations through a high-speed network utilizing ethernet TCP/IP, and to application specific controllers and third-party equipment controllers through a field level network bus.

The controller shall be able to operate at 90% to 110% of nominal voltage rating and below 80% nominal voltage, and shall perform an orderly shutdown. Operation shall be protected against electrical noise of 5 to 120 Hz and from keyed radios up to 5 W at 1 m (3 ft.).

Each controller shall be capable of stand-alone operation and shall continue to provide monitoring functions without being connected to the network for a period of no less than 7 days and shall retain programming in the case of power loss.

Controllers used outdoors and/or in wet ambient conditions shall be mounted within waterproof enclosures and shall be rated for operation at -40°C to 65°C (-40°F to 150°F).

Controllers used in conditioned space shall be mounted in dust-proof enclosures and shall be rated for operation at 0°C to 50°C (32°F to 120°F).

Provide 20% spare capacity. Utilization of spare capacity shall require providing the field device, field wiring, if required, point database definition, and programming. No additional controller boards or point modules shall be required to implement the use of these spare points.

13.14.7 Temperature and Moisture/Humidity Transmitters

Temperature and Moisture/Humidity Transmitters (TT & MT) shall meet the following criteria:

1. Accuracy: Temp 1%, RH 2% of full range
2. Range: 0 to 100% relative humidity
3. Drift: Shall not exceed 1% of full scale per year
4. Output Signal: 4 to 20 mA, linear
5. NIST traceable
6. Room Sensor Cover Construction: Cleanroom style smooth face cover
7. Duct Sensors: Suitable for operations at temperatures of -1°C to 60°C (30°F to 140°F) with element guard and mounting plate.

13.14.8 Room Differential Pressure Transducers

Room Differential Pressure Transducers shall meet the following criteria:

1. Accuracy: +/- 1.25 Pa (0.005 in. w.g.)
2. Range: +/– 62.5 Pa (0.25 in. w.g.)
3. Drift: Shall not exceed 1% of full scale per year
4. Output Signal: 4 to 20 mA, linear
5. NIST traceable

Section 13.15

Construction Phase

Contents:

13.15.0 Introduction

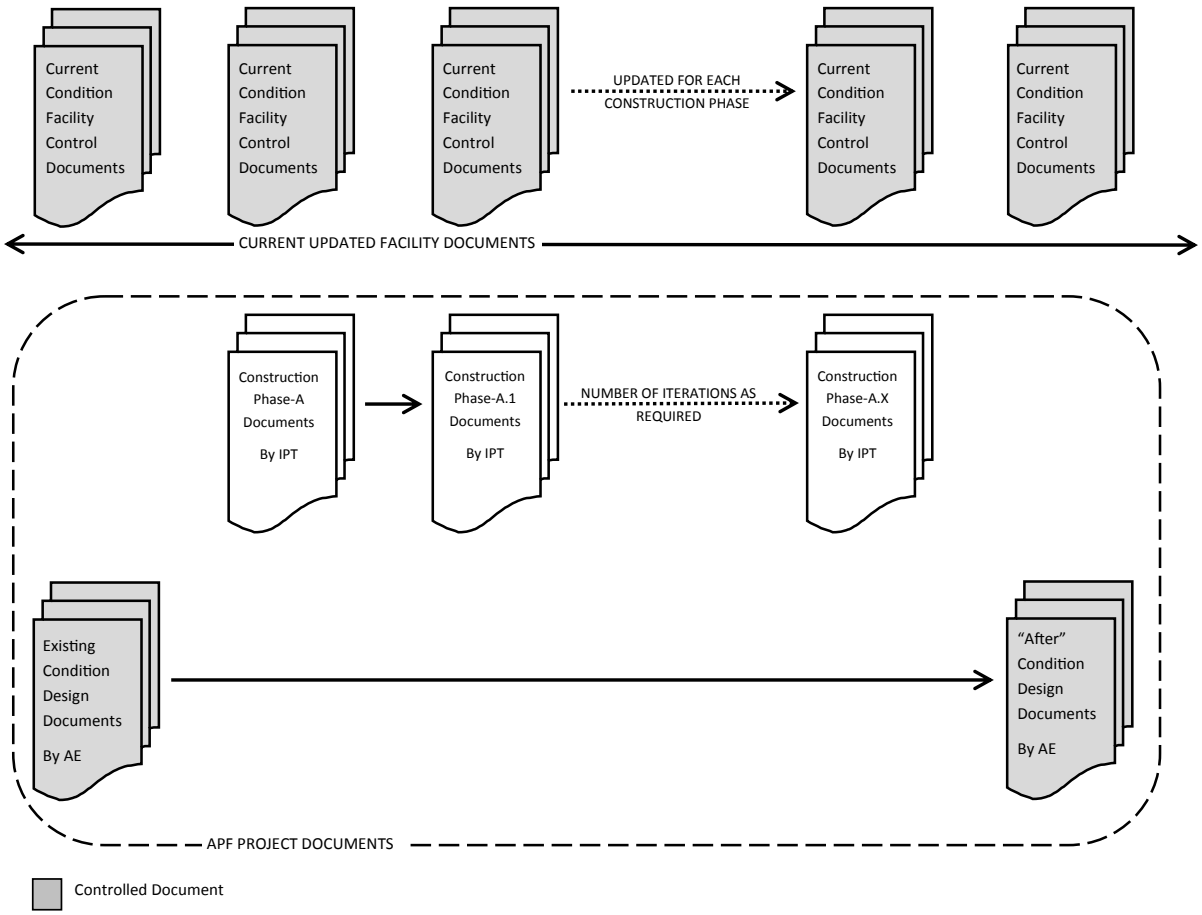
This section describes the additional requirements associated with the transition from Design through the Project Closeout and Facility Handover activities, inclusive of Construction, Commissioning and the execution of the Validation Master Plan (VMP).

At the time of this writing some, but not all NIH APFs have a well-developed set of current condition facility control documents, as defined in Chapter 13. Those which do not should leverage new construction projects to develop documents that meet these new standards.

Figure 13.15.0 shows the ideal construction phase scenario, where the existing facility has such a set of documents in place. Figure 13.15.0 describes the parallel path between Current Condition Facility Control Documents and APF Project Documents. The intent is to emphasize the need to keep the facility control documents current throughout the operation of a facility, even under planned outages and changes. The APF Project's existing condition description should be identical to the conditions described in the current condition facility control documents. The A/E will also describe the "after" condition, which should be identical to the post-construction current condition facility control documents.

In a new facility, or in the case where there is not a fully developed set of current condition facility control documents, the A/E's existing conditions documents should be robust enough to be adopted as this set of documents. During the construction activities the IPT, working with the user group will develop one or more phases (particularly important when working on an active facility). Each iteration of changes, including altered PPE, flows of personnel, equipment, product, temporary barriers, etc., shall be accompanied by a change-controlled update to the current condition facility control documents. See Section 13.2, User Requirement Specification (URS) for a description of the current condition facility control documents. Additional facility documents, such

Figure 13.15.0 Ideal Construction Phase Scenario



as SOPs, etc., may require updating and be kept current on a project-by-project basis, as determined by the User group and DTR/FCIS.

13.15.1 Contracting Officer's Representative (COR) Requirements

This section is not intended to be a construction management manual. APF projects, however, are highly prescriptive; requiring not just the management of the project but also the record keeping associated with the project. Construction management of an APF has additional requirements and responsibilities which are highlighted in this section.

The management of an APF construction project creates a higher burden on the COR, during design, and higher still, during construction, through facility certification. Although extra, these steps are mandatory, to ensure proper GMP facility validation. These responsibilities and restrictions typically include, but are not limited to:

For all APF projects the COR shall:

1. Ensure review and approval of the CQP, developed by the construction contractor, prior to construction start (See Appendix E, and Section 13.15.2).
2. Ensure the construction contractor provides coordinated work plan/drawings for review and approval by DTR/FCIS prior to commencing work.
3. Monitor, report, and document compliance with the CRA, ILSM, and clean build requirements daily.
4. Ensure/Incorporate the review of construction submittals by DTR/FCIS, which is supplemental to the submittal review process by the design A/E. See Section 13.15.5.
5. Monitor for conformance with Clean Build Requirements. See Section 13.15.3, Clean Build Requirements for additional requirements.
6. Monitoring adherence of the construction contractor to their CQP.
7. At a minimum, daily on-site inspections will be required, with additional inspections as dictated by the work being performed.
8. Manage Facility Certification Activities (i.e., Cx, Qx and Vx).Ensure proper training of construction personnel.
9. Witness tests and document results.
10. Manage the heavy documentation requirements by the IPT.
11. Compile Facility Handover Package.

For renovation projects:

1. The Construction Change Request, and associated work plan review and approval process will be in effect.
2. In a typical NIH construction projects, the COR has a level of control over the site, including hours of access, etc.; in APF Renovation projects, the Facility/User has final authority over who enters the facility, the work performed, and the timing of that work.
3. Access to the site may require training on the APF's PPE donning and doffing requirements. The PPE, and therefore retraining is subject to change, at the discretion of the Facility/User.

13.15.2 Construction Quality

A. Construction Quality Plan (CQP): The CQP is a document, created by the construction contractor, which sets out specific quality objectives, practices, resources, and sequences of activities relevant to a particular project.

A standard CQP may be listed as a requirement in the evaluation of construction contractors during acquisition, at the discretion of the COR. The construction contractor shall submit a project-specific CQP that defines the quality performance objectives and how to ensure conformance during the construction phase of a project. The CQP documentation must correlate with

the PVMP and address the following:

1. Quality assurance surveillance
2. Objectives and acceptance criteria of the work
3. Quality standards that apply to the work
4. Quality controlled worklist
5. Work instructions, process steps, and product installation instructions that apply to the work task
6. Required quality inspections and tests
7. Control of nonconformance(s)
8. Location of quality system records and documents
9. Project completion inspections
10. Definition of critical systems/ components and equipment (i.e., will have direct impact)
11. Document management program (i.e., submittals, RFIs, request for substitution, etc.); these documents become part of the validation plan
12. Quality inspections and test plan
13. Nonconformance report
14. Quality and management system for the receipt, inspection, and acceptance of equipment by the construction contractor. This ensures that what was received was per the design specs.
15. Management of installation and inspection of critical facility equipment (i.e., install of AHU, inspection, associated paperwork/ drawings, sign-offs by different trades)
16. Define contractor 'turnover package' of documents that is to be turned over to the government and the IQ/OQ/PQ.
17. Establish the scope and schedule of these activities.

The CQO is executed by the construction contractor from prior to the start of construction on-site through the end of the construction phase. The output from this execution prepares the construction contractor for Cx, IQ and OQ. Output documents may include, but are not limited to the following:

1. Verify installation
2. Verify calibration
3. Verify sequence of operations
4. Perform loop checks
5. Perform facility training
6. Perform HEPA installation
7. Perform BAS alarm checks
8. Perform airflow and pressure tests
9. Perform air change rates
10. Perform system recovery tests

B. Construction Qualification (CQ) Activities: CQ is the execution of the CQP. It is a documented effort by the construction contractor and subcontractors to establish that they have completed their work (including internal setting, testing, and troubleshooting as necessary) and are ready for the third-party observed/led testing and documentation to commence. The intent of CQ is to accelerate startup, by reducing the time required for subsequent IQ and OQ activities.

Following are critical systems that should be inspected during the CQ of an APF project, where applicable:

1. Cleanroom HVAC
2. Purified water (WP) system
3. Water for injection (WFI) system
4. Computerized systems
5. Product contact compressed gases
6. Clean-in-place (CIP) systems
7. Product piping systems
8. Architectural finishes

CQ Documentation may include, but is not limited to:

1. Contractor training
2. Good documentation practices
3. Equipment and component verification
4. Redline drawing control
5. Startup
6. Air duct cleaning and inspection
7. Air duct leakage testing
8. HEPA filter installation
9. Piping system walk down procedures
10. Hydrostatic pressure testing
11. Pneumatic pressure testing
12. Cleaning and passivation
13. Documentation of conformance with clean build protocols
14. Pest management
15. Preliminary FAT/SAT

13.15.3 Clean Build Requirements

The contractor shall fully execute the clean build specifications throughout all construction phase activities. The clean build requirements are site and project specific, above and beyond any site-specific CRA and ILSM requirements and shall include, but not be limited to:

A. Contractor Training and Documentation:

1. Donning/doffing PPE
2. Exclusion of all food and drink (including bottled water) from site
3. Inspection and cleaning of tools and materials as they arrive at the site boundary

B. Clean Construction Requirements (Level-I): This level of clean build requirement correlates with demolition, framing, MEP rough-in, drywall, welding, major cutting and grinding activities, and similar heavy particle-generating work. Activities include:

1. Preparation of the area of work
2. Continuous broom cleaning
3. Continuous trash removal
4. Garmenting requirements (all jackets, hats, scarves and personal items are to remain outside of the construction area)
5. Negative pressurization, where it can be safely generated and maintained
6. Use of HEPA "air scrubbers" throughout work
7. Use of HEPA dust collection during cutting, grinding and similar particle generating activities
8. Frequent changing of sticky mats at all work area construction entrances
9. Floor protection installation and maintenance
10. Frequent wipe down and HEPA vacuuming of horizontal surfaces
11. PPE per OSHA, Contractor liability insurance carrier, general safety practices and as required by the APF to accommodate cleanliness requirements – typically shoe covers at this level.
12. A thorough construction cleaning, starting top to bottom, and from the most remote point back to the construction entrance of the facility is required to transition to Very Clean.

C. Very Clean Requirements (Level-II): These requirements build on the Clean Construction Requirements, listed above. This level of clean build requirement corresponds to the installation of wall and floor coatings, ceiling suspension rods, and grids, MEP terminals and similar work. Additionally:

1. Perform continuous cleaning (mopping, wiping, and HEPA vacuum, in lieu of sweeping).

2. No cardboard, wood, or other packaging materials shall be permitted in the APF.

3. PPE per OSHA, Contractor liability insurance carrier, general safety practices and as required by the APF to accommodate cleanliness requirements – typically shoe covers, hair nets, beard covers, and cleanroom gloves are required at this level.

4. A thorough construction cleaning, starting top to bottom, and from the most remote point back to the construction entrance of the facility, followed by a triple clean is required to transition to Ultra Clean.

D. Ultra-Clean Requirements (Level-III): These requirements build on the Very Clean Requirements, listed above. This level of clean build requirement corresponds to the startup of the air handling equipment and progress towards final pressurization relationships; installation of modular walls; cleanroom ceiling tiles; completion of fire sprinklers; finish MEP work, including HEPA/ULPA installation; and perform IQ/OQ/PQ.

1. Perform continuous cleaning (mopping and wiping with cleanroom mops and chemicals, and HEPA vacuuming).

2. No welding or grinding operations will be permitted, either above the ceiling or within the area of work. Such work, if required will be done elsewhere and cleaned before bringing into the area of work.

3. Clean wall panels prior to, and after installation to remove dust and other foreign materials.

4. All equipment and materials must be unwrapped and wiped down with approved cleaning supplies at the designated material "wipe down" area before they are permitted to enter the area of work.

5. PPE per OSHA, Contractor liability insurance carrier, general safety practices and as required by the APF to accommodate cleanliness requirements – typically shoe covers, hair nets, beard covers, masks, cleanroom coveralls, and gloves are required at this level.

6. A triple clean, starting top to bottom, and from the most remote point back to the construction entrance of the facility is required to transition to operational readiness. After this triple cleaning, the facility is typically allowed to run for some number of days prior to ISO classification testing to further drive-down viable and non-viable particle counts.

Some APFs may require more levels than the three outlined above.

13.15.4 Pest Management

APF shall be maintained pest-free because of the sensitive nature of these facilities; however, pests should be deterred and destroyed (prior to entry to the facility), without the use of chemicals to the extent practicable.

Integrated Pest Management (IPM) is the NIH preferred methodology, but its goal is management in lieu of elimination of pests. In APFs, elimination must be the goal. The approach should be perimeter-based, in lieu of room-by-room.

Effective pest management requires the following:

1. Maintain strict cleaning and sanitation protocols

2. Eliminate harborage

3. Food and drink are strictly prohibited from all APF, even in unopened, sealed containers. This prohibition includes bottled water.

4. Inspections

13.15.5 Construction Submittals

Construction submittal review is part of the IQ process. There are more reviewers, providing a higher level of scrutiny to APF project submittals, particularly submittals of critical systems and components than a typical NIH project (e.g., comparable to a BSL-3, in this regard). During the design phase, the IPT shall identify the critical components of the project. APF project submittals shall be submitted (to the DTR Intake

Center) for review and comment after A/E's review and approval. Review and approval process by DTR does not replace the review and approval process required by the A/E. See Table 13.15.5.

A. Construction Submittal: Typical construction submittals include shop drawings, material data, samples, and product data. Submittals are required primarily for the A/E to verify that the correct products will be installed on the project.

B. Testing Documentation: This is defined by the CxA and includes the range of inspections, adjustments, measurements, and tests that shall be carried out to ensure that each part of the installation complies with the design specifications.

1. **Functional Testing:** A series of tests and measurements that shall be carried out to determine, verify and document that all parts of the installation operate together to achieve required conditions in the "as built" or "at rest" states, per the design specifications.

2. **Operational:** A series of tests and measurements, carried out to determine and verify that the complete installation achieves the required 'operational' performance with the specified process or activity functioning, and with the specified number of personnel present (dynamic) working in the agreed manner.

This testing demonstrates conformance with the requirements for IOQ as well as testing the facility for dynamic conditions. These documents (raw data) may be leveraged by the TAB contractor, CxA, and VxA to develop their reports.

C. Shop Drawing: Shop drawings are a subset of construction submittals; they are a set of drawings produced by the contractor or vendor for the installation and coordination between architectural, structural, mechanical, electrical, plumbing, and fire protection trades during the construction. Shop drawings provide the necessary geometric data to facilitate coordination between trades and schedule.

For APF projects, each construction submittal should provide the following:

1. A unique submittal identification number

2. Identification of the component and description

3. As applicable, provide component identification per the P&ID or other process drawings.

4. Indication of whether it is a, or is part of a critical component

5. Identification of the specification section which addresses the component

6. Attach supporting vendor technical literature with specific models and options selected clearly indicated.

    a. In a "Specified Attribute" column, list the critical attributes of the component as indicated in the applicable specification, such as manufacturer, model number, materials of construction, capacity, etc.

    b. In an "Actual Attribute" column, enter the component information for each of the critical attributes.

    c. In a "Deviation Attribute" column, enter the component information for each of attributes which deviate from specification to enable reviewers to make an informed decision on the acceptability of the component.

    d. In a "Quality Risk Management (QRM)" section, summarize risks and associated impact analysis. On a form, rate the impact of the submission on product quality, safety, and purity, and on the safety of personnel and equipment. Evaluate the proposed (or in-place) mitigation measures to control those risks.

    e. Identify the qualification and validation requirement(s) of the submittal (i.e., IQ/OQ/PQ, etc.)

13.15.6 Testing, Adjusting, and Balancing (TAB)

In APFs, testing, adjusting and balancing (TAB) activities are performed during commissioning of the project. A TAB may be performed at a defined periodicity during operation of the facility, as set forth in the facility SOPs.

The TAB shall be performed per the National Environmental Balancing Bureau (NEEB), Procedural Standards for Certified Testing of Cleanrooms (CPT Procedural Standards), 2009 – latest edition.

During construction, TAB is initiated when the CM informs the TAB contractor that system is ready for startup. The CM then assists the TAB and Cx vendor to complete TAB as part of Cx.

The TAB Acceptance Criteria (a range of acceptable values) is typically +/-10% of the design airflow value. This is commonly measured at the supply and may be calculated as ACH, depending on the design requirements. The exhaust and return air from any space shall be balanced to provide proper pressurization. This requirement shall supersede the engineer's air balance calculations.

13.15.7 Commissioning Activities (Construction)

During the Construction phase of the project, the various quality plans (i.e., PVMP), are executed. There is no universal order or sequence for the execution of the multiple plans that comprise an APF project. Similarly, there are few clear demarcations between plans, and often they are executed concurrently, or nearly so. The governing framework for all facility certification task(s) is the Project Validation Master Plan (PVMP), which defines the testing, sequence of testing and documentation requirements for all of its composite plans, and those executed by others.

A. System Level Impact Assessment (SLIA): The SLIA should be reviewed and approved before the start of construction. See Section 13.16.1.

B. Commissioning Master Plan (CMP): The CMP is executed by the Commissioning Authority (CxA), Execution begins prior to the start of construction on-site. The output from the execution of the CMP is typically leveraged by the VxA to create the execution documents described in the PVMP. See Section 13.16.3.

1. Verify room pressurization mapping
2. Qualify system recovery test
3. Execute the factory acceptance test (FAT) and site acceptance test (SAT). See Section 13.15.8.

13.15.8 Factory Acceptance Test (FAT) & Site Acceptance Test (SAT)

Major system components and all Modular Unit Systems (MUS) shall, at the PO/COR's discretion, be subject to Factory Acceptance Testing (FAT). FAT is intended to assure that all major components are fit for purpose, prior to shipment to NIH. FAT allows for the execution of some commissioning and qualification protocols, prior to delivery. On-site specific tests (i.e. fire alarm testing, etc.) are excluded from FAT, however, performing basic functional and software testing are strongly recommended.

A. Factory Acceptance Test (FAT): The COR and/or designee, authorized by the CO shall witness the execution of the FAT. The end-user, DFOM, DFM, CxA, VxA, and/or others may also attend/observe the FAT, at the discretion of the COR. For large modular facilities, the FAT is a milestone project date, signifying that the manufacturer believes that a component is compliant with the SOW and URS, and ready for shipment to NIH.

The protocols for testing shall be submitted for review and approval by NIH prior to the FAT date. The acceptance criteria shall be clearly articulated in all test protocols. Typical inspections and testing conducted during the FAT include, but are not limited to completeness and quality of construction; compliance with safety regulations; ergonomic requirements; conformity to GxP requirements.

The component, equipment, and systems should be fully pre-tested by the manufacturer/fabricator before

the witnessed FAT. The FAT shall test all equipment and systems as specified in the PEP. The SAT shall re-test all equipment and systems as the FAT as well as any additional tests as specified in the PEP, which may also include components installed on-site and/or other tests which are impractical or moot to conduct as FAT.

During the FAT, the manufacturer shall compile a document that reflects the PEP, URS, and PVMP documents. The executed FAT shall fully document the tests performed, including all certifications, reports, etc. Any corrective actions required will be fully documented and retested after mitigation.

Typical equipment receiving FAT include, but are not limited to:

1. Air handling units (AHU)
2. Compendial and RO/DI water systems
3. Prefabricated modular cleanroom systems
4. Decontamination systems
5. Autoclaves
6. Washers
7. Boilers
8. Electrical gears
9. Emergency generators
10. UPS
11. BAS
12. EMS
13. CCTV
14. Intercom
15. Door interlocks and red/green indicator lamp systems
16. Waste disposal systems
17. Chillers
18. Pumps
19. Cooling towers
20. Heat exchangers
21. Exhaust fans
22. Energy recovery
23. Bottled gas systems
24. Vacuum systems
25. Liquid gas systems

A punch list shall be initiated at the FAT, and corrective actions identified. This list shall be maintained current.

Division of Fire Marshal (DFM) requirements for FAT:

1. NIH DFM must review and approve fire protection shop drawings before any system installation begins.
2. Prior to the FAT the contractor must hire a licensed third-party Fire Protection Engineer (FPE) to inspect the sprinkler and fire alarms systems prior to ceiling close-in at the factory.
3. Fire alarm installation must be inspected at rough-in for compliance with NFPA 72 and NIH DFM approved shop drawings.
4. Sprinkler installation & hydrostatic test must be certified using the NFPA 13 test certificate for the factory-installed portion tested.
5. Photos must be taken of all areas before close-in and submitted to NIH DFM for record. Label photos to delineate areas shown.
6. FAT must include pre-delivery inspection by the licensed third-party FPE.

B. Site Acceptance Test (SAT): Shipping to the site typically requires breaking-down the component from its FAT state, shipping it to the site, moving it into place, and connecting it to site utilities. This transit process subjects the component to unusual stresses. Site Acceptance Testing (SAT) is required to demonstrate that the component has been readied for use, and any required corrective actions have been satisfactorily completed. Include repeating many/all FAT tests to ensure damage did not occur during transit and that the site installation has been successfully accomplished.

During the SAT, the manufacturer shall update their FAT-phase document that reflects the PEP, URS, and PVMP. The executed SAT shall fully document the tests

performed, including all certifications, reports, etc. Any corrective actions required will be fully documented, and retested after mitigation. Additional scrutiny should be given to FAT corrective actions during the retest. A SAT punch list will be developed and executed prior to acceptance.

At the completion of the SAT, the Owner's validation shall be initiated, including IQ, OQ, and PQ. The FAT punch shall be maintained as current. Any new corrective actions identified during SAT shall be added to the punch list until the PO/COR has accepted all items as corrected.

All pre-manufactured systems shall be subjected to SAT. Site acceptance tests are intended to assure fitness for purpose prior to acceptance of equipment or systems. SAT includes execution of commissioning and qualification requirements and other tests as outlined in the system or equipment specification.

Typical inspections and testing conducted during the SAT include repeating many/all of the FAT tests to ensure damage did not occur during transit and that the on-site installation has been successfully accomplished.

Division of Fire Marshal (DFM) requirements for SAT:

1. The SAT must be used for all other fire protection systems and remaining portions of factory-installed systems.
2. The responsibilities for the tie-ins between factory and site-installed systems must be clearly delineated and documented in the PEP.
3. The SAT must include performing:
    a. A complete fire alarm test witnessed by DFM. Contractor to provide NFPA 72 Completion Certificate.
    b. A full hydro test of sprinkler systems. NIH is aware of the risk of full hydro testing on-site, including factory installed portions already closed in. This is, however, the NIH DFM approved method to test the tie-in. The contractor must certify using the NFPA 13 test certificate for the remaining portion tested.
4. Site-installed portions and any tie-ins must remain visible on-site until all inspections, including hydro testing, are done.

At project turnover, all nonconformities must be satisfactorily resolved, either through corrective action or acceptance via change control and recorded in the URS and other documents.

Table 13.15.5 APF Document Review and Approval (Construction)

Document	Signed	Controlled	PO/COR	Per DRM Section 1.5.3.3	FCIS	ORSC	DFOM	NIH Program (User)	User QA	External Regulatory Agencies
Project Execution Plan (PEP)*	•		IRS		R	R		RS	R	
User Requirement Specifications (URS) *	•	•	R	R	RS	RS		IRS	RS	R
Basis Of Design (BOD) *	•	•	IRS	R	RS	RS		RS	RS	R
Quality Risk Management (QRM) Report, as needed	•		R		RS	RS		IRS	RS	R
VE and Sustainable Design Analysis, as needed			IRS	R	RS	R		RS	R	R
Piping and Instrumentation Diagrams (P&ID)			IRS	R	R	R		R	R	
Final Design Contract Documents (Dwgs., specs., etc.,) *	•	•	IRS	R	RS	R	R	RS	RS	
FDA meeting document package(s), if applicable	•		R	R	R	R		IRS	R	R
Project Validation Masterplan (PVMP) *	•	•	IRS	R	RS	R	R	RS	RS	
Commissioning Masterplan (CMP) *	•	•	IRS	R	RS	R	R	RS	RS	
Test Protocols as applicable per DRM Section 13.17. X	•	•	IRS	R	RS	R	R	RS	RS	
SAT/FAT Protocols, where applicable *	•	•	IRS	R	RS	R	R	RS	RS	
SOPs for Construction Phase *	•	•	IRS	R	RS	R		RS	RS	
Construction Quality Plan (CQP)	•	•	IRS	R	RS	R		R	R	
Construction Submittals			IRS	R	R	R		R	R	
DFOM Training Plan	•	•			RS		IRS			
Facility SOPs (for existing/operating facilities)	•	•		R	RS		IRS	R	R	
SOW for Construction, CxA, VxA, etc.	•		IRS		R		R			

* *Updated as Needed*
I *Initiated By*
R *Reviewer*
S *Signatory*

Note: Unless indicated otherwise, PO/COR is responsible for the management of the above document(s).

Section 13.16

Facility Commissioning, Qualification, and Validation Phase

Contents:

13.16.0 Introduction

This section describes the roles and responsibilities in Commissioning (Cx), Qualification (Qx) and Validation (Vx) related activities of operational APFs. The purpose of Cx and Qx is to provide assurance (by proving and documenting) that the facility, its systems and equipment have been properly designed, installed and tested for conformance with pre-determined acceptance criteria to meet the design requirements for the APF.

The purpose of Vx is to provide documented assurance that the methodology and execution of commissioning and qualification meet the GDP requirements for the facility; that the facility meets the predetermined acceptance criteria; and that the performance of the facility conforms to the GxP requirements for the product being produced.

13.16.1 Validation Master Plan (VMP)

The VMP is a user initiated, high-level document which establishes an overarching validation for the entire project, to be used as guidance for resource and technical planning. The VMP addresses both facility and other activities, such as gowning, cleaning, production materials, process validation, etc.

The VMP establishes the philosophy and principals involved in qualifying a facility by defining the areas and systems to be validated and provides the written program for achieving and maintaining a qualified facility. The VMP is used to develop the PVMP.

13.16.2 Project Validation Master Plan (PVMP)

The PVMP is a prescriptive set of documents, compiled and executed by the Validation Authority (VxA) that define the rationale and strategies associated with the facility quality assurance requirements of an APF project. All APF projects shall have a PVMP, developed during the design phase and progressively updated during design and maintained throughout the life cycle of the project.

The PVMP is developed during the design phase and becomes a signed, change controlled document upon acceptance of the final design-phase submission of the PVMP (parallel with the final design submission of the construction documents). The PVMP is executed during the construction phase of the project and completed by the end of the project closeout and facility handover phase.

The PVMP shall:

1. Define direct, indirect and no-impact systems
2. Describe the following with precise technical language and illustrations, as required:
    a. Qualification philosophy and testing rationale
    b. Quality Assurance/Quality Control procedures
    c. Test procedures
    d. Acceptance criteria
    e. Areas and systems to be validated
    f. Testing plan
    g. Deliverables
    h. Provide a written program for achieving and maintaining a qualified facility

If the methodologies and rationale of the PVMP differ from the DRM requirements, the rationale behind the alternate approach shall be documented appropriately and submitted as a variance to DTR for review and approval.

All facility validation associated activities shall be planned, executed, and documented in accordance with the PVMP. The PVMP is comprised of a number of component activities, and documents, chief among these is the Commissioning Master Plan (CMP).

The PVMP is updated during design up to the point of execution, which begins in the construction phase. The validation authority (VxA) should have the introduction, scope, and facility description well underway by this stage, if not approaching the final draft level. See

Section 13.16.1 and below:

1. Validate execution of IQ
2. Validate execution of OQ
3. Validate execution of FAT/SAT
4. Validate calibration
5. Validate loop checks
6. Validate completion of SOWs
7. Validate completion of facility training
8. Validate HEPA installation and integrity tests
9. Validate BAS alarm checks
10. Validate airflow and pressure tests
11. Validate air change rates
12. Validate qualification of ISO classifications
13. Validate system recovery tests

The PVMP is comprised of many component plans, and shall generally be organized into a final report as follows:

A. Introduction: The introduction should include the name, location, division and sector served. All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration. A quality risk management approach shall be used for qualification and validation activities. Provide a short overview of the project and a cross-reference to the relevant quality assurance policy.

B. Objective: The objective defines the focus of the validation effort in clear, concise, declarative language

C. Scope: The scope defines the boundaries of the qualification/validation effort covered by the PVMP. Provide a brief description of the installation, whether single- or multi-product, and a breakdown of installed equipment as new or existing.

D. Facility Description: The facility description includes the facility characteristics such as the number of floors; the inter-connectivity of process and utility systems; isolation means; the design product and Process Flow Diagrams (PFDs) depicting the anticipated personnel, raw material, process, and waste material flow used to minimize cross-contamination; cleanroom ISO classification levels; specialty surfaces and details integral to achieving the required product quality.

E. Facility and Utilities Qualifications: These describe the qualifications seeking to be obtained/maintained in the facility following the current validation effort.

F. Key Acceptance Criteria: These describe the conditions that the validation effort must satisfy to be accepted as fit for purpose by the user; these criteria may be at or above the minimum regulatory requirements determined during GxP harmonization.

G. System Level Impact Assessment (SLIA): The System Level Impact Assessment intends to identify those systems that have the highest risk to product quality and provide the appropriate level of attention by SMEs and other appropriate stakeholders. Based on the listing of equipment, controls, and systems, a SLIA shall be performed. The classification of systems (e.g., as "Direct Impact" or "Indirect Impact" systems) should be clearly outlined, supported by explicit rationale and be reviewed and approved by:

1. ORSC (Review Only)
2. DTR/FCIS (Review Only)
3. User Group
4. User Group Quality Assurance

H. Commissioning Master Plan (CMP): See Section 13.16.3 Commissioning Master Plan (CMP). Alternately, if the project utilizes a combined commissioning and validation methodology, see Section 13.16.5, Integrated CQV Services.

I. Qualifications: Per Sections 13.16.4, Qualification Plan, and below:

1. Design Qualification (DQ), if required
2. Installation Qualification (IQ)
3. Operational Qualification (OQ)
4. Performance Qualification (PQ), if required

J. List of Required Protocols & Procedures: All testing shall be performed per an approved protocol and testing

results and documented. ISO 14644 protocols for testing shall include but are not limited to, the following:

1. Cx testing protocols (See Section 13.16)
2. HEPA filter testing protocol
3. AVS protocol
4. Qualification (IQ/OQ/PQ) protocol
5. Airborne particle test protocol
6. Room temp uniformity protocol
7. Lighting illuminance uniformity test protocol
8. Viable/non-viable particle count test protocol
9. Cleaning integrity test protocol

K. List of Relevant SOPs: All Standard operating procedures (SOPs) developed for the APF testing, O&M.

13.16.3 Commissioning Master Plan (CMP)

The CMP is a component of the PVMP. Commissioning is a well-planned, documented, managed, quality-oriented engineering approach to the startup and turnover of facilities, systems and equipment to NIH that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

The CxA shall develop the CMP during the design phase and coordinated with the PVMP. The CMP describes the engineering approaches and practices involved in activating/energizing, testing, and tuning the systems to be commissioned at the APF. The CMP also describes the test schedule, protocols, and organizes the data collected to assure that the construction conforms to the design drawings and specifications. The CxA executes the CMP during the construction phase of the project.

Refer to Section 1.10, Commissioning for additional requirements. For APF projects, the VxA may leverage data collected in the execution of the CMP for the execution of the PVMP. For APF projects, the Project Closeout and Facility Handover Project Closeout and Facility Handover Phase do not conclude with the execution of commissioning, rather it continues through NIH's review and acceptance of the executed PVMP.

The following are generally required components of the Cx process, but may vary depending on the project:

1. Develop Commissioning Master Plan (CMP) in coordination with the Project Validation Master Plan (PVMP)
2. Verifying (through documentation) that material used for construction meets the specifications
3. Conduct checks to installed systems prior to energizing
4. Verify that systems perform to meet the design specifications for:
    a. Sequence of operations
    b. As-balanced airflow diagram
    c. Room integrity test
    d. Classification of rooms
    e. General airflow patterns
    f. Temperature mapping
    g. Room pressurization mapping
    h. Alarms, warnings, and recorders
    i. Interlocks
    j. Operation under failure scenarios
    k. System recovery
5. Lead loop tuning effort to optimize the performance of commissioned systems

The CMP is the document which sets forth the Cx execution plan. The CMP addresses the entire commissioning team. The following are generally required components and content descriptions of the CMP, but these may vary depending on the project:

1. **Roles and Responsibilities:**
    a. Defines the Cx team members, roles and responsibilities

b. Sets Cx procedures and methodologies

c. Establishes communication and management tools relating to Cx

d. Defines Cx deliverables and schedule

2. **Risk Assessments:**

   a. For the construction of APF projects, in a healthcare, laboratory, or mixed use building, the performance of each system may affect the performance of other systems, many of which are critical support systems for other patient care or research activities. A comprehensive understanding of the potential impact of commissioning activities is essential, including back-out planning.

3. **Extent of Commissioning:** Cx shall include acceptance criteria for each system to be commissioned, coordinated with the URS.

   a. Architectural/Structural: Accessibility and operational safety; doors and hardware; specialty/high-performance coatings

   b. Mechanical: HVAC systems; HVAC control systems (BAS); environmental monitoring systems (EMS)

   c. Plumbing systems: water systems; DWV systems; compressed gas systems; vacuum systems

   d. Electrical systems: low voltage (below 750 V) distribution systems; standby and uninterruptible power, battery systems; lighting controls, equipment and distribution systems; lightning protection systems

   e. Low voltage systems: voice communications and audio/video systems; electronic data and communications information systems; intrusion detection and access control systems

   f. Life safety systems: fire suppression and fire protection systems; fire exit emergency signage; emergency power, emergency lighting.

4. **Fully Executed Documents in the final Cx Report:**

   a. CMP summary report

   b. Cx schedule

   c. Cx specifications

   d. System readiness plan, checklist and report

   e. A/E's pre-startup inspection report

   f. Contractor's startup report

   g. Functional test plan (FTP) and reports

   h. Controls programming, loop tuning, sequence of operation, calibration review and comments

   i. Integrated performance test (IPT) plan and report

   j. TAB contractor's report

   k. Product information (PI) report forms

   l. Performance verification report

   m. Outstanding commissioning issues and action log

   n. System test summary reports

   o. Calibration certificates of instruments used

5. **Review Comments:** Review comments including the CxA review comments and back-checks for the following at each official review stage:

   a. URS

   b. BOD

   c. Design drawings

   d. Design specifications

   e. Construction submittal review comments

   f. Record drawings

   g. Record specifications

6. **Standard Operating Procedures (SOP) Manual:** This shall include a description of each system together with a description of all operating modes. It will be produced by the A/E during the design phase and revised/updated through the end of the Cx execution.

7. **Operating and Maintenance (O&M) Manual:** Produced by the construction contractor during the construction phase. This document should be 90% complete prior to startup testing and inspections. During the Cx execution, all missing/remaining data will be added. This manual shall be organized so that keeping it up-to-date will require minimum time and resources (After the project, this document will be "owned" and maintained by ORF/DFOM, for the life cycle of the facility).

8. **Factory Acceptance Test Report (FAT):** Performance verification tests and inspections conducted at the factory. These shall be witnessed and certified by the CxA and shall include the fully executed Pre-Delivery Inspection Plan.

9. **Site Acceptance Test Report (SAT):** Performance verification tests and inspections conducted at the factory shall be witnessed and certified by the CxA.

10. **Warranties:** The Contractor shall provide a complete inventory to the designer who will review before submission to the CxA for additional review.

11. **Service Contracts:** Although service contracts are not part of commissioning, the A/E will assist the CxA in developing a complete description of all items included in the service contract(s).

12. **Facility Training Plan:** This will be developed during the design phase by the A/E, contractor, and led by the CxA, to meet project-specific requirements. The training plan will detail the following:

    a. Training Schedule: Number, duration and frequency of training sessions

    b. Identify Instructors and Trainers: This may include the A/E, construction contractor, factory-trained and certified equipment suppliers and manufacturers, factory-trained and certified maintenance specialist personnel and/or service contractors holding service contracts.

    c. Standards of Training: Demonstration of content mastery requirements, and recommended frequency of refresher training, etc.

    d. Training Materials: This includes specifications for training resources and collateral (handouts, etc.)

    e. Demonstration Requirements: Whether, and to what extent the equipment being trained can/should/must be trained with hands-on, by the instructor hands-on, or by recorded document.

    f. Manufacturers' Video-based Training: Standards for review, inclusion, and maximum periodicity of refreshment.

    g. Video Recording of Training: Hands-on and classroom training sessions will be videotaped for future reference and retraining. Recordings shall be produced only after all systems have been fully commissioned. Production should be professional quality (well lit, clear audio overdubbing, post-production editing, and graphics, etc.). The video shall be organized into several short modules to permit the incorporation of changes during operation.

13. **Inventory of Spare Parts, Special Tools, and Maintenance Materials:** Critical inventory will be identified during the design stage by the A/E with input from the construction contractor, CxA, and DFOM. It will be based on consideration of the complexity of the project and criticality of immediate availability as specified by the A/E.

14. **Cx Activities During Warranty Period:** All planned commissioning activities must be completed before the issuance of the final qualification/validation report. It is typical for certain commissioning activities to be planned for execution during the warranty period,

including:

a. Fine tuning of environmental control systems

b. Seasonal recommissioning

c. Continuous commissioning

15. **Commissioning Deliverables:** The Cx shall provide the required documents per the project-specific CMP. Generally, the schedule of Cx deliverables includes:

    a. **Schematic Design Phase:** Preliminary CMP; initial review comments of the URS, BOD, design drawings and specifications.

    b. **Design Development Phase:** Updated CMP; Updated review comments of the URS, BOD, design drawings and specifications; preliminary SOP manual; preliminary FAT/SAT plan; preliminary training plan; preliminary warranty phase Cx activity plan.

    c. **Construction Document Phase:** Updated CMP; updated review comments of the URS, BOD, design drawings and specifications; updated SOP manual; updated FAT/SAT plan; updated training plan; preliminary inventory of spare parts report; updated warranty phase Cx activity plan.

    d. **Construction Phase:** Updated CMP; final review comments of the URS, BOD, design drawings and specifications; updated SOP manual; final FAT/SAT plan; updated training plan; preliminary TAB report; updated inventory of spare parts report; updated warranty phase Cx activity plan.

    e. **Project Closeout and Facility Handover Phase:** Fully executed CMP; final review comments of the construction submittals; final TAB report; final warranty report; final service contract report; final inventory of spare parts report; final SOP manual; final training plan; updated warranty phase Cx activity plan.

    f. **Operations and Maintenance:** Warranty phase Cx report; updated URS.

13.16.4 Qualification Plan (QP)

This section describes the qualification of an APF project at NIH. Qualification is a quality-oriented process for verifying and documenting that the design, installation, testing, operation and performance of the facility conforms to the acceptance criteria as specified in the URS, BOD, drawings and specifications. Qualification planning is a sub-part of the PVMP. The following are generally required components of the Qualification Plan, but may vary depending on the project:

1. **Qualification Rationale:** Provides an outline of the approach to be taken in assessing the qualification efforts; determining the extent and boundary limits of the qualification effort; and executing and assigning responsibility for the projects qualification activities.

2. **Selection Criteria:** The first step is determining what equipment and utility systems will undergo qualification. This includes considerations such as product-contacting surfaces, critical/non-critical instrumentation, direct and indirect impact systems, reviewing policies, regulatory references, and published guidelines. In general, all "direct impact" systems are subject to qualifications. "Direct impact" systems are those systems that are expected to have an impact on product quality, such as, temperature, humidity, differential pressure, HEPA filters, etc. Direct impact systems may also be referred to as "qualified" systems.

3. **Listing of Equipment, Controls and Systems:** The listing of the equipment, controls, and systems shall serve as the basis from which resource requirements can be assessed.

4. **Sequence of Testing:** Once the equipment list and the system level impact assessment are completed, a detailed schedule shall be established. An analysis to determine the optimum sequence of testing from a system-to-system perspective shall be completed, and interdependencies between systems and their support utilities determined. The sequence of testing in APF should integrate qualification activity with the overall construction, commissioning, controls and startup schedule, so that maximum leverage can be accrued to minimize duplication of

effort and time.

A. Qualification Protocol (QP): The Qualification Protocol (QP) is an individual detailed document that describes each system under consideration, testing plans and protocols, acceptance criteria and the test results that ensure that a system is installed and operated in accordance with predetermined specifications. Much of this material will usually be developed for commissioning. The Qualification Protocol should include those activities that are critical in nature and can affect the operation, equipment and operator safety, processing parameters, and quality attributes of the product. A "direct impact" system requires a Qualification Protocol.

Execute the construction phase activities of the Qualification Protocol. See Section 13.16.4.

Some of the items that a protocol may include are:

1. **System Description:** This is a general description of the system, describing its components, its designed unit operation functional capabilities, critical functions, and the boundaries of the system(s) covered under the protocol.

2. **Documentation Deliverables:** This is a list of the supporting documentation that should be received as part of the completed qualification package. It may include drawings (e.g., P&ID, record drawings, wiring diagrams, etc.), manuals, preventative maintenance procedures, reports, calibration records, turnover documents, supplier test packages, etc.

3. **Testing Requirements:** This is a description of the testing requirements and challenges, testing sequence, and testing methodology. This may include items such as records and verification of the installation process, verification of installation and operational function procedures and records, instrument testing and calibration records, pre-requisite commissioning requirements, etc.

4. **Forms for Documenting Results:** The protocol should contain the format in which to collect and record pertinent data. Raw data may be captured within the protocol itself, or verification can be made within the protocol that relevant testing has been completed, results documented, analyzed and accepted outside of the immediate protocol as meeting specified requirements. The format for collection or verification of testing data should allow for space to provide identification and execution date of the responsible party at inspection verification points throughout the protocol.

5. **Deviations:** Pertinent deviations that occurred during the qualification phase of a project should be addressed in the protocols, with corrective actions and results described. A deviation/exceptions handling procedure should be established.

6. **Acceptance Criteria:** The expected result for each of the specified tests should be described. This should include enough detail information so an evaluation of pass or fail can be conducted.

B. Design Qualification (DQ): Is the process of reviewing and documenting approval of the design for compliance with GxP (i.e., USP, GMP, etc.) regulations. This process may be integrated into the design review process, at the approval of NIH.

C. Installation Qualification (IQ): Ensures that the critical system or equipment and its components are installed as designed, specified and to the original manufacturer's recommendations and requirements. Calibration of sensors, equipment, and/or utilities shall be performed during the execution of the IQ protocol. IQ protocols are site and project specific, and may include, but are not limited to the verification of:

1. Components installed in the correct location and that location affords all of the safety and maintenance clearances as required

2. Utility connections

3. Environmental and operating conditions

4. Unpacking and checking for damage

5. Materials of construction

6. Installer qualifications (e.g. welding)

7. Tools, supplies, and methods associated with installation (e.g. purge gas purity, fabrication locations)

8. Equipment and instrument calibration documentation
9. Chain-of custody documentation
10. Cross-checking contents against the packing list
11. Documentation of instrumentation
12. Installation ancillary instruments and options
13. Function of room alarms, indicator lamps, and interlocks
14. Function of communication
15. Calibration of sensors, equipment, and/or utilities
16. P&ID loop verification
17. BAS and EMS parameters (alert and alarm set points)
18. Verifying HEPA filters installation
19. Door gaskets and seals in classified spaces
20. Architectural finishes in classified spaces
21. Sealing in classified spaces
22. Installation
23. Calibration
24. Sequence of operations
25. Loop checks
26. Interlock functions, overrides and red/green indicator lamps

Additional IQ tasks include:

1. Tagging with IQ stickers
2. Recording calibration and validation dates of equipment used for IQ
3. Gathering all manuals
4. Verifying spare parts list and inventory
5. Site acceptance tests (SATs)
6. CO_2, compressed gas, and LN_2 systems
7. High purity water systems if applicable

By the end of construction phase activities, the IQ should be complete. See Section 13.16.4.

1. Verify installation
2. Verify calibration
3. Verify sequence of operations
4. Verify loop checks
5. Verify function of interlocks, overrides and red/green indicator lamps

D. Operational Qualification (OQ): Tests are performed on critical systems, equipment components and "Direct Impact" systems to ensure they are capable of operating within established limits and tolerances, such as temperature, pressure, flow, etc. All test data and measurements shall be documented as a system baseline. The main purpose of OQ is to identify and inspect features of the equipment and plumbing that can influence final product quality, such as:

1. Testing HVAC system operation against specified functional requirements
    a. Critical operating parameters defined on the URS
    b. Equipment operates correctly through all anticipated operating ranges
    c. Sequence testing
    d. Power failure testing
    e. Challenge functions while under load comparable to routine production
    f. Pressure differential controls and fluctuations
    g. Temperature uniformity and control
    h. Relative humidity uniformity and control
    i. CO_2, compressed gas, and LN_2 controlling systems
    j. High purity water and clean steam systems if applicable
    k. Humidity and temperature measuring

l. Fan and fan-speed controllers

m. Emergency power and emergency power testing/transfer ride-through and/or recovery

n. Measurements of contamination control system recovery

o. HEPA filter integrity tests

2. Airflow visualization
3. Illumination levels
4. Sound pressure levels
5. Door interlocks, delays, and alarms
6. SOPs

By the end of construction phase activities, the OQ should be underway.

1. Verify completion of facility training
2. Document HEPA installation and integrity tests
3. Verify completion of as-balanced airflow diagram
4. Qualify BAS alarms, warnings, and recorders
5. Qualify airflow and pressure tests
6. Qualify air change rates
7. Verify qualification of ISO classifications (room integrity test)
8. Verify documentation of general airflow patterns (AVS)
9. Verify facility temperature uniformity mapping

E. Performance Qualification (PQ): PQ is conducted to demonstrate and document that the systems and equipment produce product or materials conforming to all predetermined specifications and Critical Quality Attributes (CQAs) while operating within normal expected ranges.

By the end of construction phase activities, the facility PQ activities (if any) should be written, reviewed and approved.

PQ typically involves sampling plans and collection of sample data over a defined period. PQ protocols will describe the necessary steps to test the performance characteristics of the equipment and/or system to ensure conformance with the appropriate user requirements, monographs, or quality standards that are required to assure conformance to product quality attributes and critical process parameters. PQ elements are typically specific to a type of equipment or system. A PQ typically tests the output from a piece of equipment or system as a whole, with respect to specifications, requirements, and/or monographs. PQ testing will follow specific procedures, as applicable.

1. **Cleaning Validation (CV):** Cleaning Validation documents evidence that a cleaning and disinfection process consistently and effectively reduces potential product and/or cleaning agent residues to pre-determined acceptable limits.
2. **EMS Computer System Validation:** This section addresses the Programmable Logic Controller (PLC) or a Distributed Control System (DCS) and Computer Validation criteria including secure audit trails, authority checks, etc. The COR should consider ICH-Q7, 5.4 as a basis for this activity.
3. **List of Required Protocols and Procedures:** This includes all the equipment and utility systems, and the required protocols and procedures associated with each. This list defines the validation requirements for the project.
4. **List of Required Standard Operating Procedures (SOPs)**: The list of SOPs should include the installed equipment and utility systems and the required SOP associated with each. This will help identify the level of SOP generation necessary to complete qualification/validation activities. These will generally take the form of Operation, Maintenance, and Cleaning SOPs.
5. **Equipment and Utility System Descriptions:** These descriptions provide an overview of each system aligned with the basis of design documentation. A listing of proposed qualification tests (IQ/OQ/PQ) should be identified with a brief description of the procedure and how the associated acceptance criteria will be

determined.

6. **Equipment and System Qualification:** Each piece of equipment or systems must be qualified to operate within the facility. The goal of qualification is to produce consistent, conforming products without compromise. A qualification plan should be drafted and executed by qualified personnel to satisfy the guidelines. The qualification plan generally consists of IQ and OQ sections. Major equipment changes after the initial qualification will result in the need for subsequent requalification.

F. Documentation: The PVMP provides the documentation requirements for the project including relevant SOPs, calibration records and procedure, qualification and validation protocols (IQ/OQ/PQ, automation, cleaning, analytical methods, process, etc.), Vendor/ contract engineering support documents, training and certification records, and change control.

13.16.5 Integrated Commissioning, Qualification and Validation (CQV) Services

Integrated CQV is an option for the delivery of Cx and Vx services from a unified contract. If the project intends to pursue a CQV strategy, it must be reflected in the PEP. Individuals or firms that provide CQV services shall meet the requirements of both a CxA and VxA, as outlined in Section 13.16.

The CQV effort will be led by the CQV Project Manager (PM). The CQV PM will be a part of the IPT from conceptual design through the validation phase of the project to effectively communicate the CQV requirements throughout all phases of the project to ensure success. The CQV PM will focus on integrating all CQV activities and deliverables into each phase to minimize redundant activities, as specified in their SOW. Roles and responsibilities assigned to the CQV may include, but are not limited to:

1. Provide input into the engineering, construction, and CQV scope of work documents
2. Gain an understanding the manufacturing and the GxP basis of the project to incorporate the applicable regulatory requirements, and critical aspects of the process into the overall CQV strategy
3. Participate in the GMP design reviews
4. Develop the roles and responsibilities for the CQV activities and deliverables
5. Review and provide input into the development of the URS
6. Define system boundaries
7. Performing quality risk assessments, and system level impact assessments
8. Provide direction, review, and input into the development of the commissioning and validation master plans
9. Work with the IPT to set up the project document control and management process to ensure an efficient and effective turnover of critical documents
10. Work with the project scheduler to ensure CQV activities are integrated throughout the schedule by setting up proper tasks, durations, predecessors, successors, and resources
11. Facilitate the component criticality assessments on Direct Impact Systems
12. Review and provide input into the equipment specifications, vendor document requirements, construction quality plan, design qualification, change management, construction startup integration plan, and the develop of factory acceptance testing where applicable
13. Provide direction, review, and input into the development of the CQV protocols
14. Conduct good documentation practice (GDP) Training to all contractors involved with the CQV process
15. Audit the Construction QA/QC inspection process
16. Review FAT and SAT documentation for

pre- and post-approval.

17. Audit the "as-built" development process and engineering drawing QA process to ensure latest revisions are used for creating the "as-built"
18. Audit the project document control and Management process
19. Review and provide input into the development and execution of; commissioning test plans, installation/operation qualification protocols, and performance qualification protocols
20. Provide input into exceptions and deviations throughout the CQV process.
21. Audits document turnover process
22. Verify all project turnover documents have been received and located in a secure storage location

The roles and responsibilities, listed above, are not intended to be materially different from the un-integrated performance of a CxA and VxA.

Section 13.17

APF Facility Certification Requirements

Contents:

13.17.0 Introduction

The intent of APF facility certification is to ensure protection of patients, products, and workers. Failure of the modes and systems certified under this section could directly lead to the adulteration of product, placing patients at risk for injury or death. Likewise, failure of the modes and systems certified under this section could directly lead to unintended worker contact with potentially hazardous materials. The following subsections describe general guidelines for APF certification requirements, however the type, number, periodicity, and other details are highly subject to the regulatory environment, products and processes at each individual APF.

All SOP/Protocols covered in this section shall be submitted to NIH for review and approval prior to performance. Each APF should develop and maintain a Project Validation Master Plan (PVMP), which would cover the following plus additional site-specific certifications and tests. See Section 13.16.1 for guidance on PVMP.

All instruments used in certification shall have valid calibration certificates based on frequency and method of calibration per ISO 21501-4.

Validated cleanrooms shall be validated to a required class of cleanliness, defined in ISO1464-1. Acceptable methods for evaluation and measurements for Certification are specified in ISO14644-3, which specifies the following required and optional tests, as listed in Table 13.17.0, which are required of NIH APFs.

Once certified to a particular class the cleanroom factors, APF cleanrooms shall be monitored to ensure that parameters have not drifted, or changed, and that the environment is under control.

13.17.1 Airborne Particle Test (APT)

APFs shall be tested for airborne particle counts as an indication that work processes, cleaning and HVAC are working as intended. An APT captures a snapshot of the cleanliness of the air in a particular moment. As a snapshot, values under this test may be anticipated to have considerable fluctuations, yet should remain below specified threshold values.

These particles are measured using a discrete particle counter (different from a photometer that is used to test installed filter leaks) that is used to count number and size of particles.

An APT should be performed:

1. An APT is required when bringing a new facility online.
2. At a frequency sufficient to produce meaningful and actionable trends, and the soonest of:
    a. The time interval as specified in ISO 14644-2
    b. In APF areas ISO 5 or cleaner, the maximum periodicity for re-qualification shall be not more than 6 months.
    c. In APF areas less ISO 6 or less clean, the maximum periodicity for re-qualification shall be not more than 12 months.
    d. As determined by the APF QA to adequately demonstrate the facility is operating in a state of control
3. The APF User QA shall develop an APT plan to establish minimum sampling criteria, including number of sampling locations, volumes and periodicity of sampling. A formal risk assessment is a requirement for a compliant APT plan.
    a. The APT plan shall be based on statistical criteria proscribed in ISO 14644. Each APF may choose to establish maximum concentration limits that are more restrictive than these minima for a given particle size (i.e. 0.1 µm - 5.0 µm).
    b. Sampling should be toward likely problem spots, such as near entrances and workstations.
    c. The APT plan shall specify static, dynamic or both conditions to be sampled.
    d. Periodicity of monitoring may be continuous, sequential, or periodic.

Table 13.17.0 NIH APF Cleanroom and Associated Controlled Environments Test Methods

ISO 14644 Required	NIH APF Required		Test	Reference in ISO 14644-3			Referenced In
	Biologics Facilities	Pharmacy Facilities		Principle	Procedure	Apparatus	
•	•	•	Airborne Particle Count for Classification and Test Measurement of Cleanrooms and Clean Air Devices	4.2.1	B.1	C.1	ISO 14644-1, ISO 14644-2, and DRM Section 13.17.1
♦	♦	♦	Airborne Particle Count for Ultrafine Particles Test	4.2.1	B.2	C.2	ISO 14644-1 and DRM Section 13.17.1
♦	♦	♦	Airborne Particle Count for Macro-Particles Test	4.2.1	B.3	C.3	ISO 14644-1 and DRM Section 13.17.1
•	•	•	Airflow Tests	4.2.2	B.4	C.4	ISO 14644-1, ISO 14644-2, and DRM Section 13.17.2
•	•	•	Air Pressure Differential Test	4.2.3	B.5	C.5	ISO 14644-1, ISO 14644-2
♦	•	•	Installed Filter System Leakage Test	4.2.4	B.6	C.6	ISO 14644-2 and DRM Section 13.17.3
♦	•	•	Airflow Direction Test and Visualization	4.2.5	B.7	C.7	ISO 14644-2 and DRM Section 13.17.2
♦	♦	•	Temperature Test	4.2.6	B.8	C.8	ISO 7726 and DRM Section 13.17.4
♦	♦	♦	Humidity Test	4.2.6	B.9	C.9	ISO 7726
♦		♦	Electrostatic and Ion Generator Tests	4.2.7	B.10	C.10	
♦	♦	♦	Particle Deposition Test	4.2.8	B.11	C.11	
♦	•	•	Recovery Test	4.2.9	B.12	C.12	ISO 14644-2
♦	♦	•	Containment Leak Test	4.2.10	B.13	C.13	ISO 14644-1 and ISO 14644-2
	•	•	Lighting Uniformity Test (LUT)				DRM Section 13.17.5
	•	•	Cleaning Integrity Test (CIT)				DRM Section 13.17.6
	♦	♦	Sound Pressure Test (SPT)				DRM Section 13.17.7
•	•	•	EMPQ				DRM Section 13.17.11

- • *Required Test*
- ♦ *Optional Test*

The tests listed may not be all-inclusive, nor may these be all of the tests required for a given APF certification. Tests and methods should be selected in a manner agreed to by the User QA group, and the IPT, with the QA having final approval. Selected tests may be repeated with a scheduled periodicity as part of a routine facility monitoring program per ISO 14644-2. Specific test protocols should be developed for each facility, including test sequence per ISO 14644-3 Annex A.

e. Meet or exceed the requirements of ISO 14644-3.4.1.

f. Define instrument calibration (per ISO21501-4) and technician training requirements.

4. Shall define acceptance criteria.

5. Specify adverse result actions.

References:

1. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments, and Annex-A

2. ISO21501-4: Determination of particle size distribution -- Single particle light interaction methods -- Part 4: Light scattering airborne particle counter for clean spaces

13.17.2 **Airflow Visualization Study (AVS)**

Airflow Visualization Studies (AVS, sometimes referred to as "smoke studies") are a critical activity in the qualification, operation, and monitoring of APFs. AVS are conducted to confirm unidirectional airflow by providing visual documentation of conformance to regulatory requirements and intent. An AVS should be performed:

1. A full AVS is required when bringing a new facility online.

2. A localized (i.e., suite or room level) AVS shall be performed when large equipment is relocated, any time a PEC, or supply/return/exhaust device is added, removed, or significantly altered.

3. A targeted (or full) AVS should be performed when supply, exhaust, differential pressure set points are changed. All spaces that are impacted by the pressure cascade should be re-tested (i.e., targeted).

4. A full AVS should be re-performed at a periodicity, typically not more than every 2 years, set forth in an AVS SOP.

AVS SOPs/Protocols shall:

1. Proscribe the specific methods, techniques and materials acceptable for AVS, including the use of a cleanroom; the time to open, hold, close and recover at doors; etc.

   a. Acceptable: WFI grade water or Food Grade Propylene Glycol

   b. Less Acceptable: CO_2 and N_2

   c. Unacceptable: Glycerin Bubbles, Smoke Candles, ($ZnCl_2$ or Zn Stearate), or Titanium Smoke

2. Describe the performance of static and dynamic conditions, as applicable.

3. Describe the airflow characteristics throughout the APF.

4. Specify AVS test acceptance criteria. These criteria should include site-specific criteria and the following general requirements:

   a. Airflow shall move toward potential sources of contamination and away from areas of higher product risk.

   b. Airflow shall flow smoothly in one direction with no turbulence or eddies, in a downward sweeping pattern, without stagnation.

   c. Airflow, when disrupted, shall recover quickly and reestablish unidirectional flow.

   d. Define acceptance criteria.

   e. Airflow pattern analyses shall evaluate both static and dynamic conditions to determine that personnel activities do not negatively affect airflow patterns in critical areas (e.g., ISO 5 PECs, air movement and cascade in transitions between differing ISO classified areas, etc.).

5. Describe AVS report criteria.

6. Discuss photography and videography issues, such as reflections, lighting, shadows, white balance and other techniques that have a direct impact on the quality and utility of the

end-product.

7. Address video post-production requirements, including superimposed text, voiceovers, and related issues.
8. Include specifications on documentation standards, including sections for written results, discussion, and conclusion.

References:

1. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments
2. IEST-RP-CC002.3: Unidirectional-Flow, Clean-Air Devices
3. IEST-RP-CC006.3: Testing Cleanrooms

13.17.3 HEPA Filter Integrity Test (FIT)

The cleanliness of the air, and the ability of the primary and secondary engineering controls to resist adulteration of the product, and to mitigate patient and worker risk are highly reliant on HEPA filtration. Regular maintenance and operation of the APF reflects the need to have a high confidence of the acceptable status of these filters and their seals. A FIT should be performed:

1. Whenever HEPA filters are decontaminated, qualified, or requalified.
2. At the discretion of NIH.
3. At a periodicity, typically not more than every 1 year, set forth in the SOP.

FIT SOPs/Protocols shall:

1. Integrity test 100% of filters
2. Validate filters as an assembly (integrity test certified) for efficiency and leak integrity by the manufacturer and shall be validated again in situ.
3. Require forwarded certification of tests and procedures to DOHS and ORF for approval.
4. Document the values for integrity testing/validation in the SOPs, and as approved by DOHS.
5. Define the testing agent and procedures.
6. Define allowable repair materials and methods.
7. Define acceptance criteria.

References:

1. IEST RP-CC001 HEPA and ULPA Filters
2. IEST RP-CC034.2 HEPA and ULPA Filter Leak Test
3. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments
4. Section 8.6.12.1, HEPA Filters/In-line Filters

13.17.4 Temperature Uniformity Test (TUT)

Temperature poses a risk to product quality during production and storage of products and raw materials. A TUT may be performed within a single piece of equipment or within the whole space. This section only refers to the room/facility. A TUT should be performed:

1. At a frequency sufficient to demonstrate the facility is under control as established in the SOP.
2. Frequently enough to produce meaningful and actionable trends.
3. When heat-generating equipment is added or removed, or any large equipment is moved within the space.

TUT SOP/Protocol shall:

1. Describe the specific monitoring plan for TUT at the APF.
2. Map all sensor locations, for BAS, EMS and temperature mapping.
    a. A TUT test deploys multiple, independent, calibrated sensors arrayed about a space to create a 3-dimensional temperature map of

a given space

b. The validated EMS system probes should be the reference point for all TUT studies for regulatory compliance purposes.

3. Specify acceptable ranges.
4. Identify areas at risk, and sampling should skew toward likely problem spots, such as near entrances and workstations.
5. Define TUT test duration and periodicity of retesting.
6. Define calibration requirements.

References:

1. USP Chapter 1079 Monitoring Devices – Good Storage and Shipping Practices
2. USP Chapter 1118 Monitoring Devices – Time, Temperature, and Humidity
3. 21 CFR Part 211 cGMP for Finished Pharmaceuticals
4. FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations (2006)
5. FDA Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach (2004)
6. ISO/IEC 17025:2005 General Requirements for the Competence of Testing and Calibration Laboratories
7. ISO 10012:2003 Measurement Management Systems

13.17.5 Lighting Uniformity Test (LUT)

Lighting properties are an essential component of the visual inspection process. The visually demanding tasks at the laboratory bench require illumination and must be provided at adequate and uniform levels from low-glare; ceiling reflection, and shadow-free lighting systems. These factors combine to impact productivity and accuracy, based on expectations, motivation, and cost.

A LUT should be performed:

1. At facility validation
2. At a periodicity, typically not more than every 2 years, set forth in an LUT SOP to account for output fall-off of LEDs and other lamp-types.

A LUT SOP/Protocol shall:

1. Define the illumination intensity required for the various areas within the APF, per IESNA and EN12464-1.
2. Require certification of tests and procedures shall be forwarded to DOHS and ORF for approval.
3. Document the values for integrity testing/validation in the SOPs, and as approved by DOHS.
4. Define the testing procedures.
5. Define acceptance criteria.

References:

1. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments
2. Illuminating Engineering Society Handbook
3. RP-29 Lighting for Hospitals and Health Care Facilities

13.17.6 Cleaning Integrity Test (CIT)

Cleaning integrity testing is the initial and ongoing qualification of the cleaning materials and methods to achieve the desired efficacy of the cleaning program as required and the risks associated with the product(s) being produced at the APF. The cleaning program must reduce the bioburden present in the facility and achieve the necessary level of microbial reduction. This is achieved through the application of appropriate chemical agents, for a requisite length of time, then neutralized or removed, with sufficient residual antimicrobial action to suppress growth until the next scheduled

cleaning, without degradation of the finishes.

The efficacy of this program must be regularly surveilled and tested, informing the process of whether changes such as longer/shorter contact time, a change in rotation of agents, or lapses in application technique need to be addressed.

The final description and implementation of the CIT is the responsibility of the individual APF, however a general awareness of the program and the preparation of representative coupons, as described, below, falls to the design and construction team.

A. Disinfection vs Sanitization: The key difference between these terms is whether the agent will "reduce" or "Kill" the microbial growth it is applied to. In different areas of the APF, the goal may be one or the other. Successive application of agents may have the goal to sanitize, and on the successive application of material, to disinfect.

The surface test described below cannot fully demonstrate the effect of environmental factors like temperature, pH, detergent residues, mechanical stress, and attachment in the facility. For these reasons, a disinfectant which appears effective for the coupon test can have significant variability when applied more broadly in the APF. Field trials (or in situ studies) are an important part of the qualification of the Cleaning Integrity Test (CIT). These trials determine if cleaning materials and methods are suitable or require modification.

B. Addressing Sanitization/Disinfection Effectiveness: Effectiveness of sanitization/disinfection is assessed through environmental monitoring (EM). Viable monitoring of surfaces is the most relevant approach for assessing the effectiveness of surface sanitization, although air sampling is also performed. To demonstrate the efficacy of a sanitization/disinfectant protocol (material and method) within the APF environment, the following tests should be performed:

1. **Use-Dilution Test:** Use-Dilution Testing assesses disinfectants for efficacy at various concentrations and contact times against a wide range of standard test organisms.

2. **Surface Challenge Test:** Representative manufacturing surface samples (coupons) are inoculated with a selection of microbial challenge organisms (organisms of concern, and typical local isolates). A disinfectant is applied to the inoculated surfaces and exposed for a predetermined contact time after which surviving organisms are recovered using a qualified disinfectant-neutralizing broth and test method (surface rinse, contact plate, or swab). The number of challenge organisms recovered from the test samples (exposed to a disinfectant) is compared to the number of challenge organisms recovered from the corresponding control sample (not exposed to a disinfectant) to determine the ability of the disinfectant to reduce the microbial bioburden. Successful completion of the validation qualifies the disinfectant evaluated for use. The disinfectant efficacy validation shall document that the disinfectant demonstrated bactericidal, fungicidal, and/or sporicidal activity sufficient to control microbial contamination in the facility.

3. **Marker & Token Test:** A test where the APF quality assurance personnel strategically place marks with a permanent marker and leave small, loose, numbered, stainless steel markers about the facility which are to be collected by the cleaning crew and returned to the QA to assess whether all locations have been cleaned as required.

4. **Visual Assessment Test:** A visual assessment test is conducted by the APF quality assurance personnel, immediately subsequent to the performance of a cleaning to look for visual evidence of the insufficiency of a particular cleaning effort (i.e., dust, streaks, films, etc.)

A CIT SOP/Protocol shall:

1. APF Startup Tests should include Use-dilution Test, Surface Challenge tests, and Environmental Monitoring.

2. APF In-Operation Tests should include: Environmental Monitoring; Marker & Token Test; Visual Inspection Test.

3. Create an APF-specific environmental sampling program per GxP. Each APF may choose to exceed these minima.

4. Define the testing locations, periodicity and related procedures.

5. Specify the incubation procedures.
6. Define equipment calibration and technician training requirements
7. Refer to the acceptance criteria as defined in the EM Plan.
8. Specify adverse result actions
9. In USP <797> facilities, if any CFUs are detected on a test plate from an ISO 8 or better area, then regulation requires that the colonies growing on that plate be identified to at least the genus level, even if the number of colonies is below the recommended action level. See Table 13.17.11. In all other (i.e. non-USP <797>) areas, the facility QA shall define the action limits.

A CIT shall be performed when:

1. Coupon tests are recommended, during design.
2. Mockup and/or coupon tests shall be performed during construction.
3. At any change in cleaning products or methodology and not to exceed 2 years.
4. May be required upon a surface excursion beyond 15 CFU recovered from a single ISO 5 sample, at the discretion of the APF QA

References:

1. Vina, P., Rubio, S. and Sandle, T. (2011): 'Selection and Validation of Disinfectants', in Saghee, M.R., Sandle, T. and Tidswell, E.C. (Eds.) (2011): Microbiology and Sterility Assurance in Pharmaceuticals and Medical Devices, New Delhi: Business Horizons, pp 219-236

13.17.7 Sound Pressure Test (SPT)

Sound pressure level testing should be considered for both occupant comfort and safety. Typical A-weighted sound pressure level range for cleanroom is between 55-65 dBA. NIOSH recommends limiting the 8 hour exposure to less than 85 dBA, which is more conservative than the OSHA exposure limit, and consistent with Section 6.5.5. The design target for APFs shall be not more than 60 dBA, due to the scarcity of acoustical treatments available in these environments.

An SPT shall be performed:

1. During commissioning
2. After major HVAC changes during O&M

An SPT SOP/Protocol shall:

1. Define the testing locations, periodicity and related procedures
2. Define equipment calibration and technician training requirements
3. Define acceptance criteria
4. Specify adverse result actions

References:

1. ISO 3746:2010 Acoustics – Determination of sound power levels and sound energy levels of noise sources using sound pressure – Survey method using an enveloping measurement surface over a reflecting plane
2. ANSI Standard S12.12-1992 (R2012), Engineering Method for the Determination of Sound Power Levels of Noise Sources Using Sound Intensity, 2012
3. Air Conditioning, Heating & Refrigeration Institute (AHRI) Sound Intensity Testing Procedures for Determining Sound Power of HVAC Equipment, 2013

13.17.8 Airflow Test (AFT)

APFs shall be tested for airflow as an indication that airflow supply airflow volume, velocity distribution, and uniformity meet the design intent and conform to applicable regulations. An AFT captures data from multiple occupancy states and is generally indicative of the ability of the system to provide uniform airflow.

An AFT should be performed:

1. During qualification
2. After major HVAC changes during O&M
3. At a frequency sufficient to demonstrate the facility is under control
4. Frequently enough to produce meaningful and actionable trends
5. The maximum periodicity for re-qualification shall be not more than 12 months, or as determined by User QA

AFT SOPs/Protocols shall:

1. Describe the specific monitoring plan for the APF, either downstream of the final filters, or in the supply air ducts, as prescribed in ISO 14644.
2. Specify operational (dynamic) conditions, and at-rest (static) and be sampled in the monitoring plan.
3. Define equipment calibration and technician training requirements
4. Define acceptance criteria.
5. Specify adverse result actions.
6. Meet or exceed the requirements of ISO 14644-3.B.4.

References:

1. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments, and Annex-A

be performed:

1. During qualification
2. After major HVAC changes during O&M
3. At a frequency sufficient to demonstrate the facility is under control
4. Frequently enough to produce meaningful and actionable trends
5. The maximum periodicity for re-qualification shall be not more than 12 months, or as determined by user QA

APD SOPs/Protocols shall:

1. Describe the specific monitoring plan for the APF, either downstream of the final filters, or in the supply air ducts, as prescribed in ISO 14644.
2. Specify operational (dynamic) conditions, and at-rest (static) and be sampled in the monitoring plan.
3. Define equipment calibration and technician training requirements.
4. Define acceptance criteria.
5. Specify adverse result actions.
6. Meet or exceed the requirements of ISO 14644-3.B.5.

References:

1. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments, and Annex-A

13.17.9 Airflow Pressure Differential Test (APD)

APFs shall be tested to verify the capability of the facility to maintain specified pressure differentials, both internally, and to the surrounding environment. An APD captures data from multiple occupancy states and is generally indicative of the ability of the system to provide the designed pressure differentials. An APD should

13.17.10 Environmental Monitoring (EM)

Environmental Monitoring (EM) is the overall program for the monitoring of the levels and sources or potential contamination within an APF. The EM program is a risk-based, ongoing assessment of the conditions measured/surveyed/sampled within the APF, and the efficacy of local controls, both process and engineering,

to deter microbial ingress, microbial proliferation, and the overall presence of particles (both non-viable and viable). The EM program is a function of the user's QA. The EM program is inclusive of raw materials, product, process, equipment, and facility, but for the purposes of this section, the focus will be on the latter.

The EM Plan shall define:

1. The Risk Management Team, headed by QA, to include APF manufacturing, CC/DLM, DFOM, and FCIS, and/or others based on APF-specific requirements. Team must be cross-functional.
    a. Define scope of activity
    b. Determine risk management tools to be used
        i. Hazard Analysis and Critical Control Point (HACCP)
        ii. Failure Mode and Effect Analysis (FMEA)
        iii. Failure Mode and Effect and Criticality Analysis (FMECA)
        iv. Risk Management of Contamination (RMC)
    c. Determine evaluation protocol (Prioritization)
    d. Define communication plan
    e. Define periodicity of assessment/re-assessment of controls, risks, etc.
    f. Define controls requirements, both engineering and administrative
    g. Evaluation of regulatory and internal audit findings
2. The acceptance criteria for non-viable and viable particles (Alert and Alarm levels) for facilities as-built, at-rest/static, and operational/dynamic:
    a. **Non-Viable Particles:** ISO 14644-1, USP <1116> and the European Commission Annex-I all address the limits for total (specifically inclusive of non-viable particles) somewhat differently. A non-viable particle (such as a dust mote, etc.) is a particle that does not contain or have adsorbed to it, a living microorganism, rather it acts as transportation for viable particles. These types of particles are frequently produced by construction and maintenance activities. Non-viable particles are monitored using particle counters that do not distinguish between viable and non-viable, reading out only total particles per cubic meter. Supporting data can be leveraged from the APT.
    b. **Viable Particles:** ISO 14698 establishes a forma system for monitoring and applying control measures against the risks of biocontamination (i.e. viable particles). Any required harmonization must be performed by the APF QA and well documented. A viable particle contains a living microorganism (bacteria, mold, spore, fungi, yeast, etc.). Viable particles typically enter APFs on personnel, materials and tools, but also may enter through leakage, HVAC/Control system failures which lead to undesirable pressure conditions, etc. Early detection and mitigation is crucial for the prevention of product contamination. Viable particles may be detected by some counters, such as those using Laser Induced Fluorescence, but such counters are not in common use at NIH. In lieu, various agar plates are collected, using swab, touch, and impacted air methods, then incubated. This allows for colony forming unit (CFU) counts and speciation of any observed growth, which can help identify potential sources of contamination/growth in the facility. These viable/non-viable particle counts and the incubation and speciation of viable particles are managed by the APF staff, and adverse results are shared with ORF to assist in planning and executing corrective actions when required.
3.

References:

1. Vina, P., Rubio, S. and Sandle, T. (2011):

'Selection and Validation of Disinfectants', in Saghee, M.R., Sandle, T. and Tidswell, E.C. (Eds.) (2011): Microbiology and Sterility Assurance in Pharmaceuticals and Medical Devices, New Delhi: Business Horizons, pp 219-236

2. United States Pharmacopeia Convention. <797> Pharmaceutical Compounding – Sterile Preparations. Revision Bulletin
3. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments, and Annex-A
4. ISO 14698-1:2003: Cleanrooms and associated controlled environments -- Biocontamination control -- Part 1: General principles and methods
5. United States Pharmacopeia Convention. <1116> Microbiological Evaluation of Cleanrooms and Other Controlled Environments. National Formulary
6. ISO21501-4: Determination of particle size distribution -- Single particle light interaction methods -- Part 4: Light scattering airborne particle counter for clean spaces
7. PHSS Technical Monograph #20 "Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas"

13.17.11 Environmental Monitoring Performance Qualification (EMPQ)

Environmental Monitoring Performance Qualification is a user QA-managed Performance Qualification (PQ) that demonstrates control of non-viable and viable particles in critical areas, including, but not limited to the monitoring of the air, surfaces and personnel for contamination. The EMPQ is a subset of the EM Plan, which establishes the facility requirements for type, periodicity, location and methodology of the routine testing of the APF environment.

The EMPQ plan shall define the following:

1. Graphically, supported by calculation/chart, as appropriate under GxP, define the number of sample point locations for air and surface monitoring.
    a. Locations should be risk-biased, including those in close proximity to exposed product, product contact surfaces, areas for donning/doffing of PPE, high traffic areas, etc.
    b. Locations should include some walls and floors.
    c. The number of sampling locations per room should be risk based, rather than simply ISO-based, while avoiding over/under sampling to the extent practicable.
2. Provide risk-based rationale for sample locations and periodicity.
3. Develop and execute protocols:

    For viable testing, define:

    a. Testing and media type (active air sampling, contact plates, swabs, etc.)
    b. Incubation temperatures and durations
    c. Microbial Identification:
        i. Which samples need to be identified
        ii. Monitoring including classical and Rapid Micro Methods (RMM), and whether genotypic, biochemical, or phenotypic techniques are required (may be case specific)

    For non-viable and total particle testing follow harmonized GxP requirements.
4. Describe the specific evaluation of the data, including:
    a. Trend analysis of data to confirm whether the facility is under adequate control. Monitoring results alone (historical data), shall be considered insufficient if it does not support and inform a clear and approved

plan.

b. Positive characterization of organisms of concern.

c. Ongoing assessment of overall cleaning program efficacy and tuning of plan to address changes in facility condition.

5. Define adverse result action:

a. If any CFU's are detected on a test plate from an ISO 8 or better area, then USP <797> requires that the colonies growing on that plate be identified to at least the genus level, even if the number of colonies is below the recommended action level. See Table 13.17.11.

b. If excursion exceeds USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments, Table 3 for aseptic environments.

c. If excursion exceeds USP <1115> Bioburden Control of Nonsterile Drug Substances and Products limits for non-aseptic environments.

d. Provide guidance for undertaking investigations and initiating/informing Corrective And Preventative Actions (CAPAs), associated with a detected excursion.

Table 13.17.11 Air Quality Monitoring Acceptance Derived from FDA Requirements

ISO Class	≥ 0.5 µm Nonviable Particles / m^3	Viable Airborne (CFU / m^3)	Viable Surface (CFU / contact plate)
5	3,520	> 1	> 3
7	352,000	> 10	> 5
8	3,520,000	> 100	> 100

References:

1. Vina, P., Rubio, S. and Sandle, T. (2011): 'Selection and Validation of Disinfectants', in Saghee, M.R., Sandle, T. and Tidswell, E.C. (Eds.) (2011): Microbiology and Sterility Assurance in Pharmaceuticals and Medical Devices, New Delhi: Business Horizons, pp 219-236

2. United States Pharmacopeia Convention. <797> Pharmaceutical Compounding – Sterile Preparations. Revision Bulletin

3. ISO 14644 – Parts 1-6: Cleanrooms and Associated Controlled Environments, and Annex-A

4. ISO 14698-1:2003: Cleanrooms and associated controlled environments -- Biocontamination control -- Part 1: General principles and methods

5. United States Pharmacopeia Convention. <1116> Microbiological Evaluation of Cleanrooms and Other Controlled Environments. National Formulary

6. ISO21501-4: Determination of particle size distribution -- Single particle light interaction methods -- Part 4: Light scattering airborne particle counter for clean spaces

7. PHSS Technical Monograph #20 "Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas"

Section 13.18

Project Closeout and Facility Handover Phase

Contents:

13.18.0 Introduction

The activities of the project closeout and facility handover phase begin subsequent to the acceptance of the fully executed PVMP, which documents conformity to the project design documents as well as the requirements of the harmonized GxP environment, regulating the facility. These activities include the finalization of all project activities and the receipt of all project documents in final, reviewed and accepted form.

The purpose of a formalized project closeout process is to ensure that all documentation has been completed, with the required documents under document control, and all documents have been delivered to and accepted by the appropriate parties, per the PEP.

There is no "Substantial Completion" in APF projects. The "Handover" date is the point at which the construction contractor's work is deemed complete, including:

1. Completion of all punch list items
2. The CMP has been fully executed
3. The IQ/OQ have been completed (PQ may still be underway)
4. All construction-related documentation has been reviewed and accepted (closeout)

This section does not address the administrative or contract closure requirements. These are managed by the CO and COR per the requirements of the individual contracts and options exercised under this project.

The project closeout includes documents which end at the point of acceptance; documents which persist, to be updated/maintained as current throughout the life cycle of the facility; and documents which are derived in a post-project examination process. See Table 13.18.0.

Documents which terminate at the acceptance of the APF project:

1. Project Design Documents:
    a. As-Designed Record Drawings: Record of everything the A/E designed for the project, the original construction documents with all addenda, A/E's supplemental instructions, change orders, construction change directives and minor changes in the work – shall include a full set of bound, editable CAD files and PDF files of each sheet, and may include project BIMs, as defined in the SOW.
    b. As-Constructed Record Drawings: Record of the project as constructed based on information the contractor provided to the Government under the contract for construction – typically a color scan of the contractor's field set with all markups. May include a full set of bound, editable CAD files and PDF files of each sheet, and may include project BIMs, updated per the revisions noted on the contractor's field set, per the SOW.
2. Fully executed PEP
3. Type-C meeting package(s)
4. BOD
5. Construction submittals
6. Fully executed FAT
7. Fully executed SAT
8. Fully executed CQP
9. Fully executed PVMP
    a. Design Qualification (DQ)
    b. System Level Impact Assessment (SLIA)
    c. Commissioning Master Plan (CMP)
    d. Qualification Plan/Protocol (QP)
    e. Installation Qualification (IQ)
    f. Operational Qualification (OQ)
    g. Performance Qualification (PQ), if any apply to facilities
10. Facility SOPs

The following documents shall be furnished to NIH and are to be maintained as current after the acceptance of the APF project:

1. Project Documents:

a. Documents shall include Record of the Work As Constructed drawings. Record of the Project as constructed based on information the contractor provides to the owner Government under the contract for construction coupled with re-survey by the Architect and Engineer(s) – typically a full set of editable CAD files and PDF files of each sheet.

b. Record of the Work As Constructed specifications

c. Record of the Work As Constructed BOD

d. URS

e. PVMP

f. TAB

g. O&M manuals

Documents which derive from after-action analysis of the APF project:

1. Post-Project Assessment by IPT:

   a. Conformance to schedule/WBS

   b. Conformance to budget

   c. Assessment of project methodology/ approach

   d. Assessment of project communications

   e. Lessons Learned

   f. Lessons Learned by Project Team; NIH-Internal Stakeholders (Users, ORSC, DTR/ FCIS, CCOFM, HEFS, DFOM, etc.)

   g. Project organization

   h. Risk management

   i. Recommended changes to approach to improve subsequent projects

13.18.1 Certificate of Use

APFs, upon completion, testing and acceptance shall receive a certificate of use, issued by DTR/FCIS. This certificate designates that the facility has been inspected, documents received, and the facility is ready to begin operation. The certificate of use is re-issued annually, in conjunction with a facility re-inspection and maintenance of the facility. See Exhibit 13.3, APF Certificate of Use Checklist. The certificate of use shall be based on the PEP document and shall be used to determine issuance of the certificate of use.

13.18.2 Dashboards

A dashboard for the APF is a central component for the operation and communication of advanced, resilient and regulatory compliant facility.

The dashboard shall be developed, implemented and maintained by ORF, for the entire APF portfolio. The dashboards are intended for internal use and are meant to be informative, facilitate quick inspection and preliminary inquiry only. Dashboards are not intended to replace detailed engineering analysis, or impinge on the primacy of the validated EMS for regulatory compliance purposes.

The dashboard for each facility shall report and configure BAS sensor data through a secure webpage. The dashboard shall display the floorplan (with room names and numbers) of the facility along with critical parameters of the APF as follows:

1. Design Directional Airflow
2. ISO classification of the facility rooms (i.e., NC, CNC, ISO 8, ISO 7, etc.)
3. Room Differential Pressure (dynamic image)
4. Room Temperature (dynamic image)
5. Room Humidity (dynamic image)
6. Room Air Changes Per Hour (dynamic image)
7. Indicate on a room-by-room basis the conformance/out of specification (OOS) of each room, individually, via a red/green indicator.
8. Display the current alarms and warnings.
9. Display the alerts over the past 24 hours.

Table 13.18.0 APF Document Review and Approval (Commissioning and Validation Phase)

Document	Signed	Controlled	PO/COR	Per DRM Section 1.5.3.3	FCIS	ORSC	DFOM	NIH Program (User)	User QA	External Regulatory Agencies
Project Execution Plan (PEP) *	•		IRS		R	R		RS	R	
Final Design Contract Documents (Dwgs., specs., etc.,) *	•	•	IRS	R	RS	R	R	RS	RS	
User Requirement Specifications (URS)*	•	•	IRS	R	RS	RS		RS	RS	R
Basis Of Design (BOD) *	•	•	IRS	R	RS	RS		RS	RS	R
Project Validation Master Plan (PVMP) *			IRS	R	RS	R	R	RS	RS	
Test Protocols as applicable per DRM Section 13.17	•	•	IRS	R	RS	R	R	RS	RS	
Fully Executed Cx with Report(s)	•	•	IRS		RS	R	R	RS	RS	
Fully Executed PVMP with Report(s)	•	•	IRS		RS	R	R	RS	RS	
SAT/FAT, where applicable, fully executed with report	•	•	IRS		RS	R	R	RS	RS	
Facility and Program SOPs	•	•			IRS	R	IRS	IRS	RS	
Facility Training Plan	•	•			RS	R	IRS	R	R	

* *Updated, if required, due to unforeseen conditions*
I *Initiated By*
R *Reviewer*
S *Signatory*

Note: Unless indicated otherwise, PO/COR is responsible for the management of the above document(s).

Section 13.19

Cleaning and Sanitation

Contents:

13.19.0 **Introduction**

One of the features which distinguish APFs from other laboratories and healthcare spaces is the development and maintenance of a robust and verified, effective cleaning procedure. These procedures must be documented, performed by trained personnel, using approved materials and methods, on both a regularly scheduled and an as-needed basis. The cleaning protocols shall be developed using scientific and technical considerations. The purpose of cleaning is to remove bioburden and to make sanitizing and disinfecting chemicals more effective. The purpose of sanitizing is to kill/inert >99.9% of bio-active particles remaining on the surface after pre-cleaning. The purpose of disinfecting is to kill/inert 100% bio-active particles on the surface (may require pre-cleaning), including 100% of vegetative bacteria, target viruses and target fungi. The purpose of sterilizing is to kill/inert 100% of the bio-active particles, including all microorganisms and spores, on the surface after pre-cleaning.

Facility cleaning is above and beyond the facility user's daily cleaning. Facility cleaning is largely a manual process and is subject to variation in effectiveness due to applicator technique, materials and adherence to the facility's cleaning SOP. These SOPs detail the requirements for the cleaning and maintaining of scientific equipment, which may employ some combination of automated Clean-In-Place (CIP) cleaning procedure and manual processes. Manual cleaning procedures must follow a written, validated, SOP which details the overall strategy and approach.

Because of the aggressiveness of the chemical agents, the kinetic energy imparted and frequency of their application, the impacts of the cleaning SOP is a significant design requirement.

Ongoing assessment of the efficacy of the cleaning materials and methods will be done through periodic cleaning efficacy tests (See Section 13.17.6, Cleaning Integrity Test) and regular viable/non-viable particle testing.

13.19.1 Finish Selection for Cleanability

All surface finishes and interface details shall be selected to be compatible with the materials (agents, as well as pads, wipes, etc.) and methods used for cleaning, disinfection or sterilization, without damage or degradation, including discoloration. Materials selected shall have a proven, tested record of performance with the chemical agents listed below, as well as all agents and methods identified by the program that will be used in the facility. Testing shall be performed for each agent individually, and again in sequence, as described in the protocol. If a record of performance with the materials and methods per the protocol is not available, then a mock-up test shall be conducted, documented and passed prior to selection.

Surface finishes shall not be selected based on first-cost, but on a life-cycle cost basis for the facility. Systems shall be impact resistant and shall have smooth, sealed joints and transitions, eased outside corners and coved inside corners.

All materials shall resist damage due to exposure to heat and humidity as anticipated to be encountered in the life cycle of the project to, at, or above highest temperature without degradation below minimum service level for the application.

All finish material selections shall exhibit mold and mildew resistance properties. Products shall be installed over cellulose-free (inorganic-faced) substrates only.

The rotation of disinfectants shall generally consist of two agents, used alternately, with a third agent held in reserve in case of a spike in environmental monitoring, or physical upset at the facility, such as an air-reversal.

Selection of the chemical cleaning agents, in application order, how long, and in what order will they be applied to the surfaces should influence the selection of architectural and MEP design finish selections.

13.19.2 **Facility Cleaning SOP**

The following are key facility considerations when developing the facility cleaning SOP requirements:

1. Select the chemical cleaning agents to be used, in application order.
2. Determine how long and in what order they will be applied to the surfaces. The materials and methods shall be robust enough to ensure adequate kill is achieved, overcoming the inherent variability in the manual cleaning process.
3. The methodology should be developed to minimize inherent variability in the manual cleaning process.
4. The cleaning technicians should be adequately trained in the performance of the specific manual cleaning procedures of the APF they are working on.
5. The manual cleaning procedures of a specific APF should harmonize with a standard/typical SOP for the APF program, and only differ where required to meet specific needs of the APF program.
6. The cleaning technicians should be trained on the inspection acceptance criteria of their work, including mark-removal, tokens, visual inspection, etc.
7. Cleaning procedures should generally specify top-to-bottom, and from cleanest-to-dirtiest areas.
8. The cleaning SOP shall include a section on sink and trap maintenance.
9. Through their APF-specific training, the cleaning technicians should be made aware that varying from the SOP can result in an insufficiently clean facility, endangering patients and research, or can result in severe damage to the facility.
10. Cleaning equipment (mops, handles, buckets, etc.) used in one APF should be dedicated to that facility, and not used across multiple facilities to mitigate cross-contamination risks.
11. The SOP shall clearly specify the following:
    a. The type of detergents and disinfectants to be used (The agents must be compatible)
    b. The order and frequency of rotation of disinfectants
    c. A list of suitable cleaning materials (lint-free wipes, mop heads, etc.)
    d. Chemical shelf-life
    e. Chemical concentration and means of assurance
    f. Cleaning techniques
    g. Contact times
    h. Rinsing
    i. Frequency of cleaning and disinfection
    j. Procedure for the transfer of cleaning agents and disinfectants into and out of clean areas
    k. Procedure for sterilization of disinfectants (when utilizing field diluted agents, i.e., non-pre-packaged and ready-to-use – which is preferred)
    l. Holding times for detergents and disinfectants
    m. Training requirements
    n. Documentation requirements
12. Disposal and primary treatment of traps is an essential part of the trap maintenance SOP, but no agents may be placed into the drains unless pre-approved by the Division of Environmental Protection (DEP), ORF. This includes bleach solutions.

13.19.3 Cleaning, Sanitizing, and Disinfecting Chemicals

The program shall make the final determination of the agents, sequence, and dwell time requirements of the SOP. The SOP must take into consideration the robustness of the finishes of the facility to avoid pitting of stainless steel, de-bonding epoxies and other degradation.

Provide space for mixing of cleaning solutions at the APF. Programmatically, the trend has been towards the use of premixed chemicals. However, the intent is to preserve the capability to revert to site-mixed/diluted if the program or regulatory needs or requirements change.

Packaged water of the appropriate level may be brought into the APF to mix with the concentrated solutions. Alternatively, a reverse osmosis/deionized (RO/DI), or higher, if required, water outlet may be provided.

A. Cleaning Chemicals: These include detergents and surfactants for removing gross surface contamination and bio-burden from the surfaces. Water, the most common cleaning agent, is a polar solvent, often enhanced with detergents or surfactants to make it more effective at removing surface contamination. Some common chemicals in this class include:

1. Detergents
2. Ammonia
3. Calcium hypochlorite (bleach)
4. Sodium hypochlorite (bleach)
5. Citric acid
6. Acetic acid (vinegar)

B. Sanitizing and Disinfecting Chemicals: Disinfectants kill vegetative micro-organisms but do not necessarily kill bacterial spores. Disinfectants vary in their modes of action, spectrum of activity, and efficacy. Some are bacteriostatic in which the ability of the bacterial population to grow is halted. Once the disinfectant is removed from contact with bacteria cells, the surviving bacterial population could potentially resume growth. Some common chemicals in this class include:

1. **Non-Oxidizing Disinfectants:** This group includes alcohols, aldehydes, amphoterics, phenolics, and quaternary ammonium compounds (QACs or "quats." Phenolics are bactericidal and antifungal, but are not effective against spores).
2. **Oxidizing Disinfectants:** This group includes oxygen-releasing compounds like peracetic acid and hydrogen peroxide.

13.19.4 Cleaning Air Systems

The supply air (SA), exhaust air (EA), and recirculating air (RA) systems shall be designed, constructed, located, and configuration to facilitate cleaning, maintenance and proper operation.

For APF rooms subject to CFR Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart C-Buildings and Facilities, Section 211.42.C.10.v, "aseptic processing areas shall be provided with a system for cleaning and disinfecting the room and equipment to provide aseptic conditions".

This is not interpreted by NIH to generally require a fixed gaseous decontamination system. In lieu, the design of the HVAC systems across all NIH APFs shall accommodate physical decontamination to the extent practicable and configuration of the air handling system per Section 13.8, APF Design Requirements: HVAC and shall accommodate appropriate isolation and compartmentalization to deploy gaseous decontamination on an as-needed basis, safely.

13.19.5 Cleaning Protocols

The APF-specific protocols shall include, but not be limited to written procedures that address:

1. Require the use of suitable rodenticides, insecticides, fungicides, fumigation agents and cleaning and sanitation agents to prevent contamination, pre-approved by the facility QA.
2. Prior to installing filters and after room-side, construction-level cleaning has been completed, all ducts walls, ceilings, floors and installed fittings should be cleaned to remove contamination which could affect the testing for classification of the cleanroom. Only after cleaning should the final filters be fitted and commissioned.
3. Equipment used to clean a particular ISO level should not be used to clean other ISO levels, and shall not be used to clean a more restrictive class than it has already been used to clean (i.e., A mop used to clean an ISO 7 ceiling may, but is not recommended, be used to clean an

ISO 8 ceiling, but cannot then be returned to the ISO 7 area for the next cleaning – one way migration).

4. Disposable equipment, such as lint-free wipes should be rated to the ISO class they are cleaning, or better.

5. Vacuum-cleaning equipment either portable or built-in should be provided to ensure that particulate contamination can be removed during periodic cleanings.

6. Plan for contamination generated by any operation that cannot reasonably be conducted outside the APF. See requirements for permanent vacuum in ISO 14644-4 D.1.4.2.

7. Portable vacuums should be fitted with exhaust filter of at least the same efficiency as the HEPA supply in that room (i.e., ISO 7)

8. Protocols shall specify that cleaning occur, from the ceiling-down of the most remote part of the facility, working back towards the entrance to the facility.

9. Protocols should define minimum training requirements, and periodicity/conditions requiring training recertification.

13.19.6 Cleaner Qualifications

The cleaning technician, whether contracted, or provided by NIH staff, shall have the same minimum qualifications. The APF-specific SOPs shall define the specific requirements, but the qualifications shall generally include, but not be limited to:

1. Safe use and handling of the cleaning, sanitizing, and disinfecting chemicals

2. The donning and doffing of approved PPE for the APF

3. Proficiency training in APF-specific materials and methods

4. Cleaning validation

5. Cleaning qualification on specific equipment and APF conditions

6. APF cleaning planning and types of cleaning approved for the specific APF

7. Other training, as deemed appropriate for the APF by the facility QA

Section 13.20

Operations & Maintenance

Contents:

13.20.0 Introduction

The maintenance of the cGMP facilities is essential to keeping the facility in a validated state, while in operation. Thus, the maintenance of the APFs plays a critical role in achieving this effort. At NIH, APFs are managed, operated and maintained by the Division of Facilities O&M (DFOM) within the Office of Research Facilities (ORF). In addition to ensuring safety and health of personnel, DFOM maintains facility equipment and systems that support critical process parameters including temperature, relative humidity, pressurization, and environmental conditions in the APF as well as the utilities (i.e., CO_2, LN_2, etc.) that serve equipment within the APF. However, laboratory equipment such as refrigerators, incubators, biological safety cabinets, environmental monitoring systems (EMS) are excluded. Bottled lab gases may be excluded from DFOM's responsibility based on user agreements.

APF Operation and Maintenance (O&M) program includes, but is not limited to the following:

1. A Quality Management System (QMS)
2. SOPs
3. Work order plan/order review and approval
4. Corrective maintenance and PM
5. Spare parts management
6. Documentation system
7. Detecting and investigating and correcting maintenance deviations
8. Change control
9. Training
10. Calibration program

DFOM's responsibilities include:

1. Appropriate controls over facility management computer controls and systems (i.e., HVAC, BAS, etc.) to limit changes to critical process parameters.
2. Training of all maintenance personnel (including contractors), on SOPs as well job-specific tasks.
3. Proper labeling/identification of critical and associated equipment is executed
4. Scheduled maintenance activities are tracked and coordinated.
5. Work orders are prepared with sufficient details for review and approval by technical and facility user(s), as well as QA of user group, as needed.
6. Preventive and corrective maintenance plans are developed and executed per SOP
7. RCAs & CAPA are prepared per SOP
8. Reviewed and coordinated contractor's work plans
9. Corrective maintenance procedures, and all associated activities are executed per approved plan
10. CAPAs are executed
11. Approved change control is executed
12. Calibration plans are executed
13. Alerts and alarms are properly responded to
14. Record keeping of all maintenance is executed per SOP
15. Late preventive maintenance is reported per SOP
16. Record keeping of all work orders is executed per SOP
17. Record keeping of all alarms for traceability is executed per SOP
18. Maintenance records are reviewed to identify trends

Facilities Compliance and Inspection Section (DTR/FCIS), Division Technical Resources (DTR), ORF provides independent quality assurance and oversight of DFOM O&M functions in support of the APF owners.

DTR/FCIS responsibilities include:

1. Provide quality assurance for facility regulatory compliance, including certifications, calibration

records, deviations/discrepancy reports, change controls, RCA, CAPA, SOPs, training records, facility audits, etc.

2. Review and approve work orders and conductions inspections of work plan to ensure installations are performed in accordance with plans and that testing is conducted within performance specifications.
3. Regularly review of maintenance records to review trends.
4. Identify O&M improvement.
5. Provide oversight of DFOM CMMS system.
6. Maintains the ORF facility control documents, per Section 13.20.6.
7. Dashboard monitoring and reporting.
8. Conducting periodic internal audits.

13.20.1 Standard Operating Procedures (SOP)

All NIH APFs shall have approved, signed SOPs for its operations and maintenance; this includes O&M of facility equipment and systems that support critical process systems and associated pieces of equipment. These critical process SOPs shall be followed to prevent any potential negative impact on the final product, manufactured at the facility. The SOPs shall establish and address approved practices and procedures/protocols that describe all aspects of (routine, preventive and corrective) maintenance being performed and administrative controls. SOPs should address both routine, preventive and corrective maintenance.

Training is required for new or amended SOPs and retraining, on a regular schedule not to exceed one year.

13.20.2 Maintenance Program

The maintenance program of the APF shall address both routine, preventive, predictive and corrective maintenance; this includes routine calibrations to inspections, to assure proper performance of facility equipment and the maintenance program(s). Maintenance activities may impact systems that support critical process parameters, and environmental conditions in the APF. SOP(s) shall address involve planned or unplanned facility, system or equipment shutdown. Routine maintenance may not require facility shut down but must be scheduled in advance. Maintenance may also require entry into the GMP facility by maintenance staff.

When any new critical equipment or a component is added or removed from the facility maintenance program, it must be documented via change control. Whether the maintenance is planned or emergency there must be an SOP in place that addresses:

1. Roles and responsibilities
2. Clear handover between each activity or shutdown phase
3. Necessary cleaning and sanitization
4. Control over facility access, contractors and changes to facility, process and equipment

A. Preventative Maintenance (PM): A Preventative Maintenance Program (PMP) must not only comply with regulatory requirements but be balanced to prevent over-and-under maintaining instruments and equipment. A PMP must be established for any critical piece of equipment affecting the APF and to ensure that mechanical parts that are subject to wear are included in programs for replacement, cleaning and lubrication.

Risk assessments should be conducted for some PM but are not necessary for all PM, based on the criticality and the classification of the equipment.

Major maintenance might require shutdown so must be scheduled and coordinated with the users to provide an opportunity for production to be adjusted accordingly. Post maintenance and/or shutdown may require cleaning and sanitization as follow up to prevent contamination of product when a facility is returned to operation.

B. Corrective Maintenance: Corrective maintenance is performed after failure detection. Its purpose is to restore the equipment, machine or an asset to its established limits/specifications.

C. Predictive Maintenance (PdM): Predictive

maintenance (PdM) techniques are designed to help determine the actual condition of in-service equipment in order to detect the onset of system degradation or, predict when maintenance should be performed. The data produced via PdM should be indicative of current and future functional capability.

PdM differs from preventive maintenance by basing maintenance need on the actual condition of the machine rather than on a preset schedule.

13.20.3 Root Cause Analysis (RCA), and Corrective and Preventative Action (CAPA)

Root cause identification is an expectation of the FDA and is the most frequently cited problems during regulatory inspections. A through Root Cause Analysis (RCA) Investigation and Corrective and Preventative Action (CAPA) ensures that problems are accurately identified and that the repair is effectively designed, targeting the root cause or error.

Lack of effective corrective action management can lead to repeated System Discrepancy (SD)/deviation. The RCA may be triggered by an alarm from any one of the critical process parameters (such as differential pressure, temperature and humidity) that may affect the quality of the product.

The user can initiate the RCA investigation to address SD/deviation for ORF to conduct the investigation. It is, however, the user's responsibility (and not the ORF) to determine if there is any impact to the product based on the CAPA. Although not all alarms initiate RCA and investigation, as some may be due to false indications (such as someone leaving the door open for a prolonged period), all alarms must be noted and recorded for traceability.

DFOM also conducts internal RCAs and investigations on systems that may indirectly impact the product now but can have a direct impact on the product in the future (predictive). Such deviations shall follow a similar procedure as a direct impact deviation, except user approval may not be required.

Executing a Corrective Action (CA), to prevent recurrence is always immediately required, however, executing a Preventative Action (PA) is NOT always immediately required. This is different from a SD that may or may not require a RCA.

13.20.4 Calibration

All APF equipment and instrumentation with direct or indirect product impact, must be routinely calibrated traceable to NIST standards, and documented. Written protocols and SOPs shall be established, followed, and documented to ensure these devices are maintained in a calibrated state. Schedules for equipment and instrument calibration must be at appropriate intervals.

The record and results of the calibration and calibration data shall be reviewed and stored with DTR/FCIS, as part of the quality assurance program. See FDA Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry ICH-Q7: 5.3 for additional recommendations which shall be treated as requirements for the purposes of the NIH APF program.

13.20.5 Change Control

Change control supports quality, consistency, and protects the integrity of all aspects of the APF that require regulatory control by the FDA. By definition, that includes changes to any direct impact system and may also apply to some indirect impact systems. A change control process/SOP shall be established that solicits the input, review and approval by the user, DFOM, DTR/FCIS and the Change Control Board prior to instituting the change when one or more of the following conditions occur (other similar conditions may also compel this requirement):

1. The change alters the Impact Assessment (i.e., it causes an "Indirect Impact'' system to become a "Direct Impact" system, or vice-versa)
2. There is a fundamental change in the design concept
3. The change results in a deviation from the

original User Requirement Specification (URS) for the system in question

4. Where "Like for like" equivalency is not readily achievable

5. When there's a change to direct impact systems and critical parameters: (i.e., BAS systems, terminal units, alarms, equipment cleaning, calibrations)

A quality change control process system may contain the following attributes:

1. Record the name of the originator and date.

2. Describe the change, the affected system or area, and intended purpose.

3. Provide a justification for the change. Such a justification may include, but is not limited to:

    a. This change required to close a deviation or CAPA.

    b. This change required to address a current GMP requirement condition.

    c. This change required to respond to an Inspection Observation? (FDA, Health Authority, Internal Audit, etc.)

    d. This change required to respond to a non-compliant NIH APF requirement.

    e. This change required to address a product safety issue.

    f. This change improves the quality performance of the process, equipment, computer system, facilities, utilities, quality system, or testing.

    g. This change improves the operational performance of a process or piece of equipment? (Increased volume, reduced lead time, improved productivity, etc.)

    h. This change addresses/resolves an equipment breakdown or malfunction.

    i. This change improve the capacity of a piece of equipment, the facility, or the building.

4. Assess the potential impact of the change on:

    a. System scope, design, or performance requirements (including safety, operability, reliability), construction, commissioning, operations and maintenance.

    b. Other systems.

    c. Engineering documentation.

    d. Qualification documents (including the System Level Impact Assessment).

5. Determine if additional testing is required.

6. Describe the type of testing that is necessary. If additional testing is not required, provide rationale.

7. Those who need to know of the proposed change shall be notified per SOP.

8. Record the approval or denial of proposed changes.

9. Track through to completion.

Note: Any corrective or non-routine maintenance that can be understood as a change to a validated system or piece of validated equipment, especially parts changes, must be processed through change control before being performed.

Documentation of the installation shall contain:

1. Description of install

2. Function

3. Final and approved test data

4. Conditions at time of install/testing

5. Parts and equipment and spare parts list/source

13.20.6 Documentation & Storage

Good documentation is essential to NIH APF program's facility quality assurance system and ensures traceability of all O&M activities. The process of documentation and storage, like other APF processes, must be unambiguous and controlled. Documents must be

regularly reviewed, updated, and systematically distributed, tracked, stored and retained, archived or destroyed according to SOPs. Critical records must be stored at a secure location, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc. See also Section 13.3.10 on controlled documents.

A determination must be made as to which records which are critical to regulatory compliance or to support essential business activities. These critical records must be duplicated on paper, electronically, or other appropriate means, and stored in a separate, secure location from the originals.

DTR/FCIS is the designated holder of these documents; however DFOM has the responsibility of storing log books, work orders, work plans, and similar.

Documents held by DTR/FCIS may include, but are not limited to:

1. Engineering studies
2. BOD documents
3. Drawings
4. Specifications
5. Vendor equipment
6. URS
7. Design reviews and reports
8. Deviation reports/CAPA/Change requests
9. Distribution records (for notifications of new or revised documents)
10. Environmental control records (temperature, humidity, pressurization, ACH)/Dashboard reports
11. Vendor testing documents (i.e., TAB, etc.)
12. ISO Certifications/Tests
13. Commissioning, qualification and validation plans
14. Commissioning, qualification and validation protocols and summary reports
15. SOPs
16. Calibration/Certification records
17. Training records
18. Contractor qualifications
19. Other engineering and compliance deliverables
20. Internal audit reports

If documentation is handled by electronic document management system, only authorized persons should be able to enter or modify data in the computer; access must be restricted by passwords or other means; and entry of critical data must be independently checked.

13.20.7 Spare Parts and "Like for Like" Replacements

A listing of critical Spare parts and consumables shall be maintained and controlled by DFOM to ensure availability of correct replacement parts and consumables when needed.

Availability and storage of quality spare parts is critical to a strong PM/PdM program. A Computerized Maintenance Management System (CMMS) system is used at NIH to track the availability of spare parts for the APF. All PMs must be recorded in CMMS.

The preferred spare part is an identical replacement with the same manufacturer, part number, material of construction and version. Since obtaining an identical part may not be possible, procedure and documentation is required to support a determination of its functional equivalency. Functional equivalency parts are subject to review and approval prior to its use. Where functional equivalency is not easily achievable, additional evaluation or change control is required.

Note: "Like-for-like" terminology is used to describe a piece of equipment that is functionally equivalent.

13.20.8 Training and Education

Per CFR 211.25, the FDA requires training for personnel engaged in the manufacture, processing, packing or holding of a drug product to have appropriate education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. The O&M of the facilities where the products are manufactured or compounded, shall institute a quality control system to ensure that staff is adequately trained in the O&M of these facilities. Additionally, training for O&M must also comply with the "ANSI/ IACET 1-2013 Standard for Continuing Education and Training".

The program includes training, retraining and testing scheduled at regular intervals for cGMP implementation related to maintenance functions such as work practices, environmental monitoring (temperature, humidity and differential pressure control), hygiene, verification procedures, corrective action processes, root cause analysis, calibration, preventive action process, recordkeeping and review, and sanitation practices.

13.20.9 Auditing

APF audits are a thorough inspection of the facility condition, practices, and documentation against the requirements of the URS, SOPs, Key Performance Indicators (KPIs), GDP, GxP, and cGMP. Audits may be external, conducted by regulatory bodies, internal, conducted by NIH staff, or contract SMEs, to assure readiness for external audits. Audits may be routine, announced and planned, or they may be unplanned and unannounced. They may be for cause, or may be for other purposes, unrelated to a for-cause report or event.

Facility audits typically look at:

1. Facility Condition
    a. Base building O&M program
    b. APF cleaning and O&M programs
2. Documentation Available and Current
    a. URS
    b. Record of work as constructed documents
    c. Diagrams with airflow patterns, differential pressures, and classification of production areas indicated
    d. Diagrams with personnel, equipment, supplies, materials, and waste flows indicated
    e. Facility's SOPs
    f. CMMS system
3. Facility personnel
    a. Key Personnel for maintenance, engineering (DFOM) and quality assurance (DTR and FCIS)
    b. Training records
4. APF Key Performance Indicator (KPI's) Records

Internal Audits: The internal audit process for NIH APF quality system is a systematic and independent examination that takes place on a regular schedule, as defined by the APF's SOPs. The goal of an internal audit is to help ensure that proper controls, governance and risk management processes are in place and whether the evaluated activities were conducted, documented, analyzed, and accurately reported on, in conformance with the written SOPs and the GxP and cGMP requirement(s). The auditor shall present objective findings and make recommendations for corrective measures to facilities and processes to the user group, FCIS and DFOM.

Exhibit 13.1

APF Questionnaire

The purpose of this questionnaire template is to obtain information necessary to produce the Program of Requirements (POR) for APFs. This questionnaire is a template with additional data fields than the one found in the DRM, Exhibit 2.1. Any data depicted on this template are for illustrative purposes only and are not intended to convey APF requirements.

1.0 General Parameters

1.1 List all of the institutes/centers to be accommodated in this space.

1.2 Define the research/clinical trial that's proposed by the research program, Clinical Trial Phase level, description of processes that will be performed by the program, the required process environments, types of procedures, and equipment to be used and the resulting product(s).

1.3 Identify project stakeholders and responsibilities.

1.4 Identify project deliverables and responsibilities.

2.0 Program Parameters

2.1 Describe the product(s) that's being made, its requirements, limitations.

2.2 Describe the product path of travel from building level to floor, to suite, to room, to the end user/patient.

2.3 Describe the functions that are to be accommodated within the space.

2.4 Identify functions that are to be fully segregated

2.5 Describe required adjacencies between the functions.

2.6 Describe personnel path of travel from building level, to floor, to suite, to room.

2.7 Describe the material path of travel from building level, to floor, to suite, to room.

2.8 Describe the cleaning regimen to address material storage, cleaning function, personnel, frequency, etc.

2.9 Describe program and functions (to include equipment used) that are to be accommodated in the space.

2.10 Define quarantine, storage, and decontamination locations and equipment.

2.11 Define critical adjacencies.

2.12 Define requirements and rationale for compartmentalization of different areas within the facility or any special considerations of note in describing the design intent.

2.13 Identify and conduct risk assessments.

2.14 Define the User, ORSC facility management roles and responsibilities (i.e. Facility Chief, Compliance Officer, etc.).

3.0 Regulatory Parameters

3.1 Identify the regulatory environment (may consist of one or more regulatory platforms).

3.2 Verify that a risk assessment has been completed and identifies provisions of the assessment that may affect facilities, SOPs, and engineering controls.

3.3 Identify the GxP regulatory parameters that need to be satisfied.

3.4 Perform harmonization analyses, as needed.

3.5 Identify the regulatory environment (may consist of one or more regulatory platforms).

4.0 Standard Operating Procedures (SOP)

4.1 Define the SOPs that are applicable to the facility Operation & Management.

4.2 Define the Training that are applicable to the facility Operation & Management.

5.0 Design Parameters

5.1 Airlocks:

5.1.1 Describe when and where are they required.

5.1.2 Are combined personnel and material airlocks acceptable?

5.1.3 Are combined entry/exit airlocks acceptable?

5.2 Is the flow of personnel from less clean to cleaner areas, with increased gowning requirements acceptable?

5.3 Define the initial state of control requirements.

5.4 Define the function, associated equipment and space requirements.

5.5 Describe relationships between functions.

5.6 Describe segregation requirements (spatial and temporal).

5.7 Describe required ISO levels.

5.8 Define facility Critical Process Parameters (CPP) and Critical Quality Attributes (CQA), temperature and humidity to the extent known.

5.9 Define critical adjacencies.

5.10 Define areas of adequate size and separation and/or other such control systems for the planned operations as necessary to prevent contamination or mix-ups during production (for example airlocks).

5.11 Define activities that occur within the processing areas and equipment needs.

5.12 Equipment Schedule - to include dimensions, clearances, utilities, emergency power, equipment monitoring.

5.13 Room Data Sheets - Use template and develop for each room type.

5.14 If drug product, ensure separate and defined areas for: receipt, identification, storage, and withholding from use of components, drug product containers, closures, labeling, etc.

5.15 Design provisions for handling any potent narcotic, or high particle-generating materials.

5.16 Define any specific requirements for finishes, above and beyond standard APF requirements.

5.17 Design provisions for handling any potent narcotic, or high particle-generating materials.

5.18 Define boundary conditions of classified and non-classified spaces.

5.19 Determine whether conceptual design meets requirements defined in the URS.

5.20 Determine cost effectiveness of proposed design.

5.21 Define cleaning and sanitizing materials and methods as required to produce aseptic conditions, including agents, sequence and dwell times.

6.0 Material & Personnel Flow Parameters

6.1 Identify and define the logistical flows to be accommodated at the facility to mitigate the risk of cross-contamination, mix-ups, and other risks.

6.2 Material Flows:

6.2.1 Describe how material enters the facility.

6.2.2 How materials flow through the facility?

6.2.3 How materials exit the facility?

6.3 Personnel Flows:

6.3.1 Personnel - How many and function?

6.3.2 How personnel enter the facility?

6.3.3 How personnel flow through the facility?

6.3.4 How personnel exit the facility?

6.4 Define levels of PPE donning, PPE doffing, Lines of Demarcation (LOD) and other required features.

6.5 Identify need for personnel lockers and level of change, based on PPE donning requirement.

7.0 Security System Parameters

7.1 Define access control requirements for the facility, and special security zones within the facility.

7.2 Define forced-entry protection requirements.

7.3 Define closed-circuit video monitoring requirements.

7.4 Define required biometric security requirements.

7.5 Define secure storage requirements.

7.6 Define data and communications security requirements.

7.7 Define facility hardening and critical utility requirements.

8.0 Mechanical System Parameters

8.1 Define the specific HVAC parameters for adequate control appropriate for the manufacture, processing, packing, or holding of a drug or biologic.

8.1.1 Temperature

8.1.2 Relative Humidity

8.1.3 ISO Classification

8.1.4 Air Changes Per Hour

8.1.5 Differential Pressure and Airflow Directionality

8.2 Define the necessary parameters for adequate control over air supply, including filtration; whether flow is unidirectional and non-turbulent.

8.3 Define Supply Air (SA) requirements, including single pass and recirculating/re-filtered air.

8.4 Define consideration for system reliability and robustness.

8.5 Define utility requirements and feasibility.

8.6 Design spatial requirements for locating mechanical equipment and terminal units and devices.

8.7 Define a BAS and EMS validated system for monitoring environmental conditions.

8.8 Define zoning requirements to enable partial shutdowns of the facility (defined areas within the facility).

8.9 Define mechanical space, including interstitial access (should be from outside the APF).

9.0 Plumbing System Parameters

9.1 Define specific compressed gases and liquid such as C0₂, CA, LN₂, etc. for adequate control appropriate for manufacture and processing and holding of a drug or biologic.

9.2 Define specific vacuum appropriate for manufacture of drug or biologic.

9.3 Define specific pure water for adequate control appropriate for manufacture and processing of a drug or biologic.

9.4 Identify if any sinks are required and associated emergency eye washes or showers.

10.0 Electrical System Parameters

10.1 Define emergency and stand-by power requirements for the facility.

10.2 Define program lighting requirements, including level (in Lux or foot-candles), uniformity, temperature and color rendering index (if different from 3,500°K (6,300°F) and 80 CRI).

10.3 Identify any higher densities of 120V receptacles than normally provided.

10.4 Identify receptacles other than standard 120V receptacles, other specialty electrical wiring

devices or other utilization requirements.

10.5 Identify any laboratory equipment requiring emergency power.

10.6 Identify any special grounding requirements.

10.7 Identify any scientific equipment monitoring or unique power or UPS requirements.

11.0 Facility Operations & Maintenance Parameters

11.1 Define maintenance/calibration requirements for equipment.

11.2 Define elements of the HVAC and other systems that may require decontamination and preferred method of decontamination.

11.3 Identify standard operating procedures for facility shutdown and maintenance of the facility during shutdown.

11.4 Define failure modes on critical equipment/systems.

11.5 Define backup, recovery, and restoration of critical equipment/systems.

Exhibit 13.2

APF Room Data Sheet

The purpose of this room data sheet template is to obtain information necessary to produce the Basis Of Design (BOD) for APFs. This exhibit is a template and includes additional data fields compared to the one found in the DRM, Appendix F, Room Data Sheets. Any information depicted on this template is for illustrative purposes only and is not intended to convey APF requirements.

Lab Type: **APF Cleanroom**

Project:

WR Number:

Date:

Room Name:

Room Number:

1. Room Data		Other Special Requirements
a. Size/Dimensions	(1) module, 11' width	Anteroom required for gowning with bench, PPE storage, waste bins
b. BSL	BSL-3	
c. Ceiling height	2,896 mm (9'-6") minimum	
d. Door size	1,200 mm (4'-0")	Active leaf 900 mm (3'-0"); inactive leaf 300 mm (1'-0")
e. Door type	Aluminum-Framed Cleanroom Swing Door, Full Lite	Card key access control
f. Access Control	Red-Light/Green-Light Indicator	
g. Windows	Aluminum-Framed Cleanroom Window	
h. Normal occupancy	4	
i. Special requirements	Confirm with program	All surfaces cleanable; sticky mats at entrance; all penetrations sealed
2. Finishes		**Other Special Requirements**
a. Floor	Seamless sheet vinyl, Welded	
b. Base	6" vinyl, integral with floor	Reinforced, factory formed coved corners
c. Wall type	High Performance Composite Wall System	Bubble-tight stainless steel access panel, where required
d. Wall Protection	Stainless steel, Low Carbon (304L or 316L)	Full-height cornerguards, and fully adhered scuff plates, gapped 1/2"
e. Ceiling type	High Performance Composite Ceiling System	Bubble-tight stainless steel access panel, where required
3. Furnishings and Fittings		**Other Special Requirements**
a. Casework	Stainless steel, Low Carbon (304L or 316L)	Minimize casework to promote cleanliness; use tables and carts where possible
b. Bench top	Stainless steel, Low Carbon (304L or 316L)	
c. Sink(s)	No	
d. Piped services	No	
e. Flammable storage cabinet	Yes	
f. Vented corrosive storage cabinet	No	
g. Other	Minimize horizontal surfaces	
4. Equipment – See Equipment List for Additional Items		**Other Special Requirements**
a. Biological safety cabinets	(1) 6', class II, type A2	Vacuum in BSC
b. Laminar flow hood (LFH)	No	
c. Compounding aseptic isolator (CAI)	No	
d. Containment isolator (CACI)	No	
e. Compounding safety enclosure (CSE)	No	
f. Restricted access barrier system (RABS)	No	

g. Controlled rate freezer (CRF)	No					
h. -20/-30/-80 Laboratory freezer	No					
i. Incubator	No		Water jacketed, CO_2, N_2, and air			
j. Microscope	Yes		Phase contrast, photo port			
k. Other						
5. HVAC Requirements	**Min Regulatory Value**	**Min Alarm Setpoint**	**Setpoint**	**Max Alarm Setpoint**	**Max Regulatory Value**	**Alarm Delay**
a. Temperature	25°C (59°F)	16°C (60.8°F)	20°C (68°F)	21°C (69.8°F)	22.2°C (72°F)	2-Min)
b. Relative humidity	N/A	N/A	40% RH	42% RH	50% RH	2-Min
c. Differential pressure	0.020 IWC	0.025 IWC	0.033 IWC	0.035 IWC	N/A	2-Min
6. HVAC System Description	**Notes**					
a. Iso class	ISO 7					
b. Airflow type	Unidirectional					
c. Supply air	472 LPS (1,000 CFM) Ceiling HEPA diffusers					
d. Exhaust air	377.6 LPS (800 CFM) low sidewall grille, 47.2 LPS (100 CFM) door undercut					
e. Recirculation air	472 LPS (1,000 CFM) Ceiling HEPA diffusers					
f. Relative pressure	12.5 Pa (0.05 " WC) positive to anteroom					
g. BAS Sensors	TEMP, RH, dP, and Door Position Red/Green Light					
h. EMS Sensors	TEMP, RH, and dP					

7. Piping/Plumbing	**CHW**	**CW**	**PW**	**HW**	**OTHER**	**CO_2**	**AIR**	**VAC**	**LN2**	**WASTE**	**STEAM**	**FD**
a. Utility	No	No	No	No	No Condensate	Yes	No	Yes	No	No	No	No
b. Other	Piping services as determined by program											

8. Electrical		**Other Special Requirements**
a. Power receptacles	Yes	General purpose NEMA 5-20R receptacles, cast boxes and conduits sealed
b. Lighting	Recessed cleanroom LED luminaire	Lighting lensed, sealed, gasketed, wet location listed, with overlapping door
c. Telephone/Communication	Yes	
d. Data/Computer	Yes	
e. Emergency power	Yes	Emergency power for equipment per equipment list
f. Standby power	No	
g. Task lighting	Yes	
h. Other		

Exhibit 13.3

APF Certificate of Use Checklist

The purpose of this checklist is to clarify and consolidate the requirements for obtaining a DTR/FCIS Certificate of Use for an APF. This depicts a typical, generic flow and may not represent an inclusive, or specific listing for a particular APF project or facility.

1.0 Document Handover

1.1 User Requirements Specification (URS)

1.2 Basis of Design (BOD)

1.3 Calculations

1.4 Record Drawings

1.5 Record Specifications

1.6 Record Submittals

1.7 Commissioning Report (Cx Report)

1.8 Installation Qualification (IQ)

1.9 Operation Qualification (OQ)

1.10 Performance Qualification (PQ)

1.11 URS Traceability Matrix

1.12 Training Documents

1.13 SOPs

1.14 ISO Clean Room Certification Report

1.15 Air Visualization Studies (AVS)

1.16 Testing and Balancing Report

1.17 HEPA and BSC/LAFW/CACI/CAI Certs

1.18 Calibration Reports

1.19 Use and Occupancy Permits

2.0 Facility Demonstration

2.1 Adequate HEPA filtered airflow supplied and proper airflow velocities

2.2 Unidirectional airflow in cleanroom spaces and that air flows from cleaner to less clean areas

2.3 Adequate differential pressure and displacement airflow between rooms of different cleanliness purpose and classification

2.4 Demonstrated HEPA filters are adequately leak-free

2.5 Adequate particle counts during static and dynamic conditions

2.6 Adequately holding uniform temperature

2.7 Adequately holding relative humidity

2.8 Adequately providing uniform illuminance

2.9 Adequately providing less than the allowable noise and vibration

2.10 BSC/CAI/CACI/LAFW have been adequately tested and certified

2.11 Material seams and transitions have been adequately detailed and implemented

2.12 Finishes are appropriate and have been adequately detailed and implemented

2.13 DFOM and User have been adequately trained to operate and maintain the facility

2.14 BAS and EMS have been adequately designed/coordinated, implemented and functioning

2.15 Door interlocks and administrative controls adequately control airflow

2.16 Adequate recovery of differential pressure in rooms after door cycles

2.17 Compressed gases, LN_2 and pure water are adequately tested and certified

Exhibit 13.4

Aseptic Project Execution Plan (PEP) Checklist

The purpose of this checklist is to illustrate a generic Project Execution Plan outline for an APF project or facility. This depicts typical/generic content and may not represent an inclusive, or specific listing for any particular APF project or facility.

1.0 Project Overview

1.2 Change Log

1.3 Contract and MOU Basis

1.4 Project Objective

1.5 Execution Strategy

2.0 Design Management

2.1 User Requirements Specification (URS)

2.2 Basis of Design (BOD)

2.3 Construction Drawings and Specs

2.4 Calculations

2.5 Commissioning Plan (CP)

2.6 Construction Quality Plan (QQP)

2.7 Qualification and Validation Plan (QVP)

2.8 Design Qualification

3.0 Construction Management

3.1 Construction Submittals

3.2 Field Engineering

3.3 Permits and Inspections

4.0 Construction Quality Management

4.1 Quality Audit Plan

4.2 Quality Reports

4.3 Corrective Action Program

4.4 Testing and Evaluation

4.5 Commissioning Report (Cx Report)

4.6 Installation Qualification (IQ)

4.7 Operation Qualification (OQ)

4.8 Performance Qualification (PQ)

4.9 URS Traceability Matrix

5.0 Construction Close-Out

5.1 Close Out Documents

5.2 Transition to Operations Plan

6.0 Operations and Maintenance

6.1 DFOM SOPs

6.2 Training Documents

6.3 Audit Logs

6.4 Activity Logs

6.5 Current Status Documents (Record Documents)

Exhibit 13.5

APF Tests Roles and Responsibilities

The intent of APF facility certification is to ensure protection of patients, products, and workers. Refer to Section 13.17 for detailed information on specific APF facility certification requirements. The specific types and periodicity of re-testing is established in APF-specific SOPs.

SR	Tasks	Construc-tion Con-tract	Commis-sioning Contract	Qualifi-cation / Validation Contract	NIH (ORF/ ORS)	NIH (USER/ ORSC)
1	Testing and Balancing	P	W	R	M/R	M
2	BSC Certification	W	W	R	P	R
3	Pressurization, Temperature and Humidity Verification	W	P/R	P/R	M/R	M/R
4	Four Season Performance	W	P	R	M/R	M
5	BAS vs EMS Coordination	R	W	P	M/R	M/R
6	Air Flow Test (Include Velocity and Air Flow Rate)	R	R	P	M/R	M/R
7	Air Visualization Testing (Smoke Studies)		R	P	M/R	M/R
8	HEPA Filter Integrity Testing (Leakage Testing)	P/R	W	P	P/R	M/R
9	Airborne Particle Count Cleanliness Classification Test		R	P	M/R	M/R
10	HVAC, Gases, LN2, Pure Water IOPQ	R	P	P	M/R	M/R
11	Pressurization Testing	R	R	P	M/R	M/R
12	Room Temperature and Humidity Uniformity Test	R	R	P	M/R	M/R
13	Lighting Illuminance Test	M	P	R	M/R	M/R
14	Room Recovery Testing	M	R	P	M/R	M/R
15	Room Integrity (Leak) Testing	M	R	P	M/R	M/R
16	EMPQ	N/A	R	R	R	P
17	User Equipment IO/PQ	N/A	R	R	R	P
18	EMS IO/PQ	M	W	W	R	P

P *Perform*
W *Witness*
R *Review*
M *Monitor*
N/A *Not Applicable*

Note: The RACI Test Matrix is typical, but can be adjusted based on the project requirements, size of the project, available contracts in place, capabilities of the various teams involved in the project as long as the prime or their subcontractors meet the required qualifications to perform the work.

Exhibit 13.6

APF Sealant Table

All material interfaces and penetrations into and through partitions, floors, and ceilings shall be sealed to enhance sanitation, facilitate gas and vapor decontamination, and resist air infiltration. The table found here is specifically for use in selecting and detailing sealants for use within the APF suite. This table is based on the Sealant Table found in DRM Appendix L. Refer to that table for use outside the classified spaces and for General Sealant Notes. Sealants shall be applied in a uniform, smooth, and continuous manner, resulting in a finish free of voids, pinholes, sharp edges, or excess sealant. Sealant must be compatible with all material that it is in contact with, including other sealant. Sealant must have chemical resistance, flexibility, durability, adherence, and other characteristics appropriate for its use.

Key:

JS Joint Sealant

N/S No Sealant

N/A Not applicable

* Refer to Comments

Sealant Types:

JS-3 Siliconized Acrylic Latex ASTM C834 (Note: Latex plus silicone is not an acceptable product)

JS-4 Non-Halogenated Latex-Based Elastomeric Sealant ASTM C920

JS-5 Mildew Resistant, 100% Silicone ASTM C920

Group	Description	USP <795>	USP <797>	USP <800>	USP <823>	21CFR211 cGMP	Comments
Doors	Seal all penetrations in doors	JS-5	JS-5	JS-5	JS-5	JS-5	Cleanroom doors should have minimal penetrations
	Seal all door hinge plates (not at pin)	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal door frame and wall interface	JS-5	JS-5	JS-5	JS-5	JS-5	Some systems may not have a joint here
	Seal lite frames (around glass whether or not gasketed)	JS-5	JS-5	JS-5	JS-5	JS-5	Interior and exterior sides
	Seal around lock sets	JS-5	JS-5	JS-5	JS-5	JS-5	Seal between escutcheon plates and door
	Seal around all sides of latch boxes installed within frames	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal door thresholds to the floor and around the threshold	N/A	N/A	N/A	N/A	N/A	Thresholds should be avoided in APFs. Some regulatory environments preclude caulking to floor (i.e. USP <797>) even where thresholds are required.
	Seal door protection plates and tapered door guards to doors	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal gaps around door magnet latch at head of door and frame	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal gaps around door door closer at head of door and frame	JS-5	JS-5	JS-5	JS-5	JS-5	Do not caulk closer cover in place (needs to be removable for service)
Cabinetry/ Shelving	Seal openings in the base of tables where the support feet mount to the table	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal openings in table legs where the support feet mount to the floor	JS-5	N/A	N/A	JS-5	JS-5	
	Seal all cabinets where they contact dissimilar materials and where they contact one another	JS-5	JS-5	JS-5	JS-5	JS-5	Cabinets need to be closed boxes. Seal all voids and joints in cabinet construction. Seal all removable panels. Provide stainless steel closure panels as required to fill large or multiple holes, fully adhered and sealed.
	Seal all counter tops where they contact with dissimilar material	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal around all shelf support brackets where they contact the shelves and are mounted to the walls	JS-5	JS-5	JS-5	JS-5	JS-5	This is for specialty shelving used in laboratories. Provide stainless steel closure panels as required to fill large or multiple holes, fully adhered and sealed.
	Seal tops and bottoms of all wall mounted shelving brackets	JS-5	JS-5	JS-5	JS-5	JS-5	Provide a pre-manufactured plug and seal
	Seal all gaps and openings in racks	JS-5	JS-5	JS-5	JS-5	JS-5	Provide stainless steel closure panels as required to fill large or multiple holes, fully adhered and sealed.

Group	Description	USP <795>	USP <797>	USP <800>	USP <823>	21CFR211 cGMP	Comments
Cabinetry/ Shelving	Seal covers between shelf standards	JS-5	JS-5	JS-5	JS-5	JS-5	Provide a pre-manufactured cover and seal
	Seal peninsula shelving support at countertop and at ceiling	JS-5	JS-5	JS-5	JS-5	JS-5	
Walls/ Floors/ Ceilings	Seal around all wall guards, bumpers, and rails	JS-5	JS-5	JS-5	JS-5	JS-5	Brackets/fasteners shall be installed tight to wall.
	Seal all penetrations on the top and bottom of slab	JS-5 over JS-4	JS-5 over JS-4	JS-5 over JS-4	JS-5 over JS-4	JS-5 over JS-4	To include but not limited to HVAC, plumbing, and electrical penetrations, and like penetrations through interstitial space. Install JS-4 to within 1/8" of surface, cure, then install JS-5 above and finish.
	Seal around all corner guards	JS-5	JS-5	JS-5	JS-5	JS-5	Stainless steel corner guards shall be installed tight to wall, fully adhered, and full height.
	Seal around all door bumpers and scuff plates	JS-5	JS-5	JS-5	JS-5	JS-5	Scuff plates shall be installed fully adhered to wall and sealed. Guard brackets/fasteners shall be installed tight to wall, then sealed.
	Seal top of trim strip and sheet flooring at wall	JS-5	JS-5	JS-5	JS-5	JS-5	A cleanroom termination detail is required.
	Seal top of cove base	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal bottom of cove base	JS-5	JS-5	JS-5	JS-5	JS-5	Integral base required in BSL-3, ABSL-3 and ABSL-2
	Seal all ceiling access panels (whether or not 100% gasketed)	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal the perimeter of all cleanroom ceiling grid to the wall	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal the perimeter of all cleanroom ceiling tiles to grid (whether or not 100% gasketed)	Optional	JS-5	JS-5	JS-5	Optional	
	Seal all interior window frames	JS-5	JS-5	JS-5	JS-5	JS-5	Seal all joints, including stops, juncture to glass and screw heads
	Seal around wall and ceiling, surface-mounted cover and mounting plates	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal all around floor surface mounting plates	N/A	N/A	N/A	N/A	N/A	Floor surface mounting plates shall be avoided in APFs.
	Seal all around floor surface-mounted cover plates	N/A	N/A	N/A	N/A	N/A	Floor surface cover plates shall be avoided in APFs.
	Seal and cap the tops of all CMU walls	N/A	N/A	N/A	N/A	N/A	CMU walls are prohibited in APFs.
	Seal control joints in walls	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal control joints in ceilings	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal control joints in floors	N/A	N/A	N/A	N/A	N/A	Not visible to room – beneath floor. Use sealants recommended by flooring manufacturer under resinous floors
	Seal joints between walls of dissimilar materials	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal space in wall penetrations, including inside sleeves, collars, and surrounding construction	JS-5	JS-5	JS-5	JS-5	JS-5	Provide stainless steel closure panels as required to fill large or multiple holes, fully adhered and sealed.
HVAC	Seal all duct work that penetrates the wall envelope	JS-5	JS-5	JS-5	JS-5	JS-5	Use of JS-3 outside of controled spaces per Appendix L is acceptable.
	Seal all diffusers/grill joints and room-side HEPA housings in hard ceilings	JS-5	JS-5	JS-5	JS-5	JS-5	

Group	Description	USP <795>	USP <797>	USP <800>	USP <823>	21CFR211 cGMP	Comments
Plumbing	Hot water line insulation shall be wrapped in aluminum and the seams and ends of the insulation sealed	N/A	N/A	N/A	N/A	N/A	
	Seal at vacuum pass through	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal all cracks in foam rubber water line insulation	N/A	N/A	N/A	N/A	N/A	
	All flat escutcheon plates and support standoff brackets for animal water systems shall be sealed all around	N/A	N/A	N/A	N/A	N/A	
	Seal plumbing to surface	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal all plumbing escutcheon and cover plates at the wall and pipe junctions	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal around sprinkler collars	JS-5	JS-5	JS-5	JS-5	JS-5	Seal inside and outside of collar. Confirm that sealant does not interfere with sprinkler operation.
	Seal all piping that penetrates the wall envelope	JS-5	JS-5	JS-5	JS-5	JS-5	
Electrical	Conduit and raceway shall be sealed tight to wall or ceiling surfaces	JS-5	JS-5	JS-5	JS-5	JS-5	Sealant is required on both sides of surface mounted conduit and raceway.
	Seal the perimeter of all electrical panels	N/A	N/A	N/A	N/A	N/A	Panelboards are precluded from installation in APF controled spaces.
	Seal joints between ceiling and light fixtures in hard ceilings	JS-5	JS-5	JS-5	JS-5	JS-5	Surface and recessed mounted lighting fixtures shall have sealant applied between fixture enclosure and ceiling surface. Recessed mounted fixtures shall have manufacturer's gasketing applied between fixture lens trim cover and adjacent ceiling surfaces.
	Seal perimeter of device boxes to adjacent drywall/CMU. Wire within conduit shall be sealed also.	JS-5	JS-5	JS-5	JS-5	JS-5	Applicable for ALL power, communications, signal and control applications within APF facilities: All device boxes shall be cast type with external hub. Where device boxes and conduits are recessed mounted, the box to the adjacent wall, ceiling or floor surface shall be sealed. Gasketed device cover plates shall be shall be used, with an additional continuous bead of sealant between the device box cover plate and the adjacent surface. Where device boxes and conduits are surface mounted, and where the device box meets the wall, ceiling, or floor surface, a continuous bead of sealant shall be provided. Once wiring is installed, the wiring shall be surrounded by a one inch barrier of caulking around the conductors within the device box hub.
Equipment	Seal all fixed equipment that is within 38 mm or less from a ceiling	JS-5	JS-5	JS-5	JS-5	JS-5	
	All sinks shall be sealed, including mounting and support brackets	JS-5	JS-5	JS-5	JS-5	JS-5	

Group	Description	USP <795>	USP <797>	USP <800>	USP <823>	21CFR211 cGMP	Comments
Equipment	Large gaps, behind the back splash shall be completely covered and sealed.	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal all gaps and openings in secured/fixed equipment	JS-5	JS-5	JS-5	JS-5	JS-5	May hinder function of equipment – Review on a case-by-case basis.
Equipment	Seal gaps that exist between stainless steel sheet metal in all cage washers	N/A	N/A	N/A	N/A	N/A	Not permitted in APFs.
	Seal gaps that exist between stainless steel sheet metal in all tunnel washers	N/A	N/A	N/A	N/A	N/A	Not permitted in APFs.
	Seal gaps that exist between stainless steel sheet metal in all rack wash equipment	N/A	N/A	N/A	N/A	N/A	Not permitted in APFs.
	Seal around frames and holes inside of fire extinguisher boxes	JS-5	JS-5	JS-5	JS-5	JS-5	Some doors have hollow channel in access doors. Seal access door frame channels and glass cover where no clips are present.
	Seal around the metal rod hangers used to hold the exhaust hoods where they penetrate the drop ceiling	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal wall-mounted heating/air conditioner unit casework and utility penetrations	N/A	N/A	N/A	N/A	N/A	Not permitted in APFs.
	Seal floor mounted equipment supports, legs and standoff supports	N/A	N/A	N/A	N/A	N/A	Floor surface mounting shall be avoided in APFs.
Fixtures	Seal stainless steel equipment at all joints and gaps	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal toilet mounted to surface	N/A	N/A	N/A	N/A	N/A	Not permitted in APFs.
	Seal sink faucet mounted to surface	JS-5	JS-5	JS-5	JS-5	JS-5	
	Seal wall hung equipment at surface attachment	JS-5	JS-5	JS-5	JS-5	JS-5	