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Standard Guide for Biopharmaceutical Facilities Architectural Design Considerations[1]

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1. Scope

1.1 This guide covers architectural design considerations for buildings and facilities used in the biological processing industry to make drugs, chemicals, and other products.

1.2 These designs are intended to meet current good manufacturing practices (cGMP) criteria and guidelines published by the U.S. Food and Drug Administration (FDA) for processes and products manufactured under CFR Title 21.

1.3 While the guidelines described are general in nature, they are not expected to apply to all of the possible biotechnical processes used in the industry today. Accordingly, the user of this guide must exercise good engineering judgment in specific design applications to select the proper guidelines that apply.

1.4 In addition to the cGMP guidelines provided herein, other regulations and guides should be considered that are promulgated by other federal agencies such as the Occupational Safety and Health Administration (OSHA), the U.S. Environmental Protection Agency (EPA), the U.S. Drug Administration (USDA), the National Institute of Health (NIH), and so forth.

1.5 While the buildings will be designed to meet specific functional requirements and comply with local zoning ordinances, building codes, handicapped employee standards, and so forth, these considerations are not included in this guide.

1.6 The values stated in SI units are to be regarded as the standard.

1.7 *This standard does not purport to address all of the safety problems, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *Code of Federal Regulations:*

CFR Title 21, Parts 58, 210, 211, 212, 606, 809, 820[2]

2.2 *Other Document:*

NIH Guidelines, Containment Area Designations[3]

3. Terminology

3.1 *Definition:*

3.1.1 *cGMP*—abbreviation for current good manufacturing practices as defined in CFR Title 21, Parts 210 and 211.

4. Significance and Use

4.1 This guide is intended for use in designing laboratory, pilot plant, commercial production buildings that will use processes involving living organisms to produce products. These products are also manufactured under the FDA and other federal agency regulations.

4.2 These guidelines include the layout of facilities, design of containment areas, ventilation and air quality, personnel areas, special processing hazards, controlled environment areas, and other items.

4.3 This guide is for use by engineers, architects, and owners of biopharmatechnical manufacturing facilities to consider the special factors in laying out the facilities to meet cGMP requirements and other good engineering principles.

4.4 By using these guidelines along with other design criteria required by a variety of regulatory agencies, a validation effort can be achieved more easily to meet agency requirements and obtain operating permits.

4.5 This guide is intended to provide general guidelines for consideration and application in a variety of plant operations and processes in which the designers can make specific decisions concerning the exact architectural design features to use.

5. Summary of Guide

5.1 This guide provides architectural design principles to consider when applying federal regulations to biopharmatechnical plant facilities construction and functions. Check lists for specific plant operation activity areas presented with criteria for their design and layout considerations. Environmental considerations are also included for aseptic and special laminar flow zones of operation. Fermenter area layout and space considerations are presented. When containment and closed

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[2] Available from Standardization Documents Order Desk, Bldg. 4, Section D, 700 Robbins Ave., Philadelphia, PA 19111-5094, Attn: NPODS.

[3] Available from National Institutes of Health, (NIH), 9000 Rockville Pike, Bethesda, MD 20892.

area operations are necessary, the general criteria to be considered by the designer is presented based on NIH Guidelines and good engineering practices.

5.2 Plant layout considerations are included for all normal sections of a biotechnical operating plant.

6. Guidelines

6.1 First, establish which regulations apply to the specific project design. Review 21 CFR, Parts 210, 211, 212, and so forth; NIH Guidelines; and other specific information from federal agencies that applies to the functions intended in these facilities. For example, 21 CFR, Part 606, relates to cGMP for blood and blood components; Part 809 to in-vitro diagnostic products for human use; Part 820 to medical devices; Part 58 to nonclinical laboratories; NIH guidelines to containment requirements, and so forth.

6.2 Adequate laboratory facilities must be provided for the testing of process intermediates and products (see section 21 CFR, Part 211.22). The quality control function of the site requires adequate laboratory space and facilities.

6.3 Manufacturing employees must have education and frequent training (see section 21 CFR, Part 211.25), which requires training space or dedicated rooms for the cGMP training. This space can sometimes be combined with an eating area or conference room.

6.4 Personnel must wear appropriate clothing and protective items (see 21 CFR, part 211.28), which implies storage area lockers for clean and dirty work clothes and change lockers for street clothes. Change rooms, laundry rooms, clothing staging areas, and storage rooms may also apply.

6.5 Personnel sanitation and health activities require adequate wash rooms, showers, toilets, and storage areas for supplies, according to Part 211.28.

6.6 Building design and construction features in Part 211.42 require adequate space for the manufacturing, processing, packing, or holding of a drug product. These areas include the following:

6.6.1 Receipt and identification of raw materials,

6.6.2 Storage offtest and ontest raw materials,

6.6.3 Sample preparation and testing,

6.6.4 *In-process Materials*—Ontest and offtest,

6.6.5 Manufacturing equipment,

6.6.6 Equipment holding, cleaning, and staging,

6.6.7 Packaging and labeling,

6.6.8 Quarantine storage of finished products,

6.6.9 *Utilities*—Inert gases, steam generators, water for injection (WFI), treated water, air (utility, clean, instrument, and sterile), and so forth,

6.6.10 *Sterilization Systems*—Clean-in-place and sterilize-in-place,

6.6.11 Waste treatment,

6.6.12 Offices, personnel change rooms, and containment access areas, and

6.6.13 Control room, quality assurance and quality control areas, and so forth.

6.7 The controlled environment area must be environmentally controlled, with special air quality, lighting, and construction (see 21 CFR, part 212.3) to minimize contamination from air-borne particulates, including microorganisms. Personnel entering the controlled environment area must use appropriate non-linting garments inside it that are not to be used outside it, including in the changing area. This means that the design of facilities will include a gowning area and garment storage areas adjacent to the controlled environment area.

6.7.1 *Gowning Area Design Considerations*:

6.7.1.1 Sole means of personnel entry and exit, except for emergency exit.

6.7.1.2 Located immediately adjacent to work areas.

6.7.1.3 Equipped with containers for the disposal of used clothing and protective equipment.

6.7.1.4 Clean air supplied to the gowning area will have a negative air pressure relative to the contained work area and positive air pressure relative to the adjacent non-controlled areas. Differential pressures may be 1.3 to 3.8 mm water gage.

6.7.1.5 Provide hand washing facilities and warm-air drying equipment within the gowning area similar to surgical room washing facilities operated by foot or knee.

6.7.1.6 The gowning room should have a higher pressure than the wash room and have loading changers to insert personnel clothing items into the room. Air showers and air locks should be considered.

6.7.1.7 Finishes within the gowning room should be of the same quality as those in the controlled environment work area.

6.7.1.8 The use of HEPA filters and ultraviolet lights should be considered for garment lockers.

6.7.1.9 Doors should remain closed when not in use; consider using automatic door closure and interlocks.

6.7.2 The air quality for controlled environment areas is described in 21 CFR, Parts 212.221 to 222. Consider the following:

6.7.2.1 *Temperature Range*—22 ± 3°C.

6.7.2.2 *Humidity Range*—30 to 50 % relative humidity.

6.7.2.3 *Pressure Differential*—0.05 in. (1.27 mm) of water, minimum, with all doors closed relative to the adjacent less clean area.

6.7.2.4 *Sterility, HEPA Filtration*—Not to exceed a particle count (0.5 µm size) of 100 000/ft^3 when measured with automatic counters, or 700 particles of 5.0 µm size using a manual microscopic method. For sterile air over filling lines, a 100 count is maximum for 0.5 µm particles at the point of use.

6.7.2.5 *Air Change Rate*—20/h, minimum.

6.7.3 Construction considerations must be designed to prevent the physical facilities from becoming a source of particulate contamination:

6.7.3.1 Coating on all surfaces must resist deterioration and flaking.

6.7.3.2 Surfaces should be able to be cleaned effectively and easily.

6.7.3.3 Smooth, hard surfaces clean best; use coatings such as epoxy, cove bases flush with wall, covered corners, sealed joints, flush fitting doors and windows, wall protection, and corner guards.

6.7.3.4 Conceal all ducts, conduits, piping, etc. above ceilings and behind walls. Exposed pipe and conduits for equipment connections should be installed vertically.

6.7.3.5 Install insect control units and screens on vents and openings, as appropriate.

6.7.3.6 Separate underslab piping from the controlled environment areas.

6.8 *Containment Area Designations from NIH*:

6.8.1 Containment safety levels are given in Table 1 for recombinant DNA research or production facilities based on the maximum quantity of culture designed to be handled. Since these levels of containment differ in process complexity, it is important to specify the requirements on an individual case basis.

6.8.2 Physical containment requirements for large-scale production facilities with recombinant DNA operations are given in Table 2.

6.9 *Plant Layout and Equipment Arrangement*:

6.9.1 Based on cGMP and good engineering practices, the overall facility layout can be categorized as follows:

6.9.1.1 Warehousing and storage of raw materials,

6.9.1.2 Product preparation,

6.9.1.3 In-process and off-test materials storage,

6.9.1.4 Product finishing,

6.9.1.5 Packaging,

6.9.1.6 Finished product storage and warehousing,

6.9.1.7 Waste treatment,

6.9.1.8 Utilities, and

6.9.1.9 Support and administration facilities.

6.9.1.10 Design considerations for these facilities are described in the following categories.

6.9.2 *Warehousing and Storage of Raw Materials*:

6.9.2.1 Provide sufficient space for the storage and movement of raw materials from the receiving dock to the quarantine area, where these materials are sampled, approved or rejected, and then sent to the appropriate storage area, which could be a hot room, cold room, or ambient warehouse storage section. Sufficient aisle space should be considered for one-way motorized handling equipment movement in order to avoid congestion and accidents.

6.9.2.2 Space should be provided for segregation of the classes of raw materials based on hazard and container style. For example, for safety purposes, flammable solvents may be stored in outside covered storage away from the warehouse. Quantity-distance tables may be developed for different classes of materials based on company safety procedures.

6.9.2.3 Plan sufficient layout and space in the storage areas for identifiable material flow paths for quality control released materials, held materials, and rejected materials.

6.9.2.4 Separate the storage and warehouse areas from the main manufacturing areas.

TABLE 1 Containment Safety Levels

Facility	Litres of Culture	Bio Safety Level	
		Current	Formerly
Laboratory	<10	BSL1	P1
		BSL2	P2
		BSL3	P3
		BSL4	P4
R/D, production	>10	BSL1-LS	P1-LS
		BSL2-LS	P2-LS
		BSL3-LS	P3-LS

TABLE 2 Physical Containment Requirements

	BSL1-LS	BSL2-LS	BSL3-LS
Emergency plans for handling large losses	X	X	X
Must use a closed system	X	X	X
Add materials, sampling in a closed system	X	X	X
Inactivate cultures using a validated procedure before removal from contained area	X	X	X
Use a HEPA filter on exhaust air, gas stream, and vent	X	X	X
Monitor integrity of containment area using instruments		X	X
Use special pump seals to prevent leakage to environment		X	X
Challenge containment area with host organism to qualify the containment system		X	X
Identify closed system for use in all records		X	X
Identify closed system boundary with universal biohazard signs		X	X
Minimize the pressure above the cultures in the closed system			X
Closed systems within a controlled area must have:			
Separate entry area (air lock)			X
Easily cleaned wall, floor, and ceiling surfaces			X
Seal all penetrations			X
Protect all piping and wiring from contamination			X
Provide hand washing and showers			X
Containment facilities for spills			X
Use negative pressure ventilation			X

6.9.2.5 Provide facilities to keep the storage area clean and free of insects and vermin.

6.9.2.6 Provide adequate office space for record keeping. Also, provide space for parking and conducting preventive maintenance on material handling equipment.

6.9.3 *Product Preparation and Manufacturing*:

6.9.3.1 *Aseptic Processing*:

(1) Use airlocks to separate aseptic areas from non-aseptic areas. Use a higher air pressure in aseptic areas than in adjacent areas. When containment is also required, the adjacent areas should be surrounded by areas of higher pressure.

(2) Install piping, electrical conduit, and structural members behind walls or above ceilings.

(3) Avoid horizontal shelves or other particle traps.

(4) Provide space to avoid the particulate contamination of aseptic products by moving equipment or traffic that could fluidize solids into the air.

(5) Arrange the equipment to minimize disturbance to laminar air flow designs and avoid cross contamination.

(6) Provide sufficient space for the maintenance and cleaning of aseptic facilities.

(7) Locate idle and non-aseptic equipment in adjacent areas if they are not involved directly in aseptic operations. Consider locating clean-in-place (CIP) and sterilize-in-place (SIP) equipment outside the aseptic area and pipe the cleaning or sterilizing medium to the aseptic equipment.

6.9.3.2 *Non-Aseptic Manufacturing Areas*:

(1) Provide space to move, stage, and charge raw materials into the processing equipment. Design traffic flow to avoid cross-contamination.

(2) Arrange the equipment to enhance the sequential flow of materials.

(3) Provide adequate office space for supervisory, document preparation, and observation of the area (windows).

6.9.3.3 *Weighing and Media Preparation Area*:

(1) Locate these facilities separate but adjacent to the manufacturing area.

(2) Provide space for cleaning, dust control, and sterilization as appropriate.

(3) Lay out equipment to avoid cross contamination and provide for lot integrity.

(4) Provide an area for documentation.

6.9.3.4 *Fermentation*:

(1) Depending on the aseptic or non-aseptic nature of the fermentation process, the above considerations may apply.

(2) May need to provide a separate containment area for biosafety if recombinant organisms are involved.

(3) Provide spill containment facilities for recovery, treatment, and recycle or disposal.

(4) Provide an inactivation or kill processing area for active organisms.

(5) Provide a fermenter vent treatment system, which may be chemical deactivation, incineration, and so forth.

6.9.4 *In-Process and Off-Test Materials Storage*:

6.9.4.1 Provide an area adequate to store the sealed containers of in-process chemical intermediates, off-test products and raw materials, and other work-in-progress materials. Depending on the product and process, these chemicals may have to be quarantined, or at least segregated by lot, for proper care and custody until disposition is resolved by approved standing operating procedures (SOP).

6.9.4.2 Provisions may be necessary for processing or deactivating the off-test products separately.

6.9.4.3 Sufficient warehouse space will be necessary for staging and returning off-test raw materials to the supplier.

6.9.5 *Product Finishing*:

6.9.5.1 Final product finishing operations should be segregated and possibly contained or closed in order to meet sterility requirements and FDA standards for drugs such as parenterals.

6.9.5.2 Similar considerations apply as discussed in 6.9.3, especially for aseptic design considerations.

6.9.6 *Packaging*:

6.9.6.1 All containers and packaging components for aseptic fill materials must have space available for storage of the packaging units before and after sterilizing. Adequate space is necessary for the filling line, including idle equipment staging area, when specific loading system equipment is not in use during a fill operation.

6.9.6.2 Separate cleaning and sterilizing equipment space must be provided for equipment such as container washers and drying and steam sterilizers. CIP and SIP systems can be located remotely, with the cleaning and sterilizing materials being transferred to the aseptic filling area.

6.9.6.3 Provide adequate space for inspecting the final packaged product.

6.9.7 *Finished Product Storage and Warehousing*:

6.9.7.1 An adequate quarantined storage area is necessary for the finished packaged product until testing and QC release is complete. Lot integrity is necessary. Special environmental conditions may be required for storage and proper shelf life.

6.9.7.2 A final, approved product storage area is necessary in the secure warehouse facilities. Since the products may be controlled substances or of high value, a special security area may be necessary for storing these products until shipment.

6.9.7.3 Adequate space is necessary for transportation systems used to load and deliver these products. These truck, rail, etc. staging areas may be shared with incoming raw material deliveries, or they may be separate areas.

6.9.8 *Waste Treatment and Disposal*:

6.9.8.1 Space is to be provided for waste stream catch basins, holding basins, kill tanks, final neutralization, and holding basins, as required, for the type of biopharm operations authorized for the plant design.

6.9.8.2 Space will be required for other process waste and sanitary waste streams prior to sending to public-owned treatment works (POTW).

6.9.9 *Utilities Sections*:

6.9.9.1 Provide adequate space for the utilities and their buildings within reasonable distance from planned consuming sources.

6.9.9.2 Segregate the clean/sterile utilities systems from the conventional systems. These clean utilities would include SFI, deionized water (DI), sterile stream, etc. This guideline is considered good engineering practice.

6.9.10 *Support and Administration Facilities*:

6.9.10.1 Personnel changing areas and lockers must be provided for proper dressing and gowning, as discussed before.

6.9.10.2 Administrative offices should be considered for appropriate personnel such as plant management, quality assurance and quality control, engineering, chemists, clerical, documentation, and so forth.

6.9.10.3 A plant in-process control laboratory for all process testing should be provided with adequate space, usually near the source of the materials to be tested. Central laboratory facilities is also an option, depending on the situation.

7. Keywords

7.1 architectural; biopharmaceutical; cGMP; containment; controlled environment; facilities; layout