

Chapter 2

Facilities

Objectives

This chapter provides an overview of biomanufacturing facilities. After completing this chapter the student will be able to:

- Describe the regulatory framework around which biomanufacturing facilities are designed and operated.
- Identify the layout of the functional areas in a biomanufacturing facility.
- Describe how personnel, equipment, materials, product, and waste flow within a biomanufacturing facility.
- Define the various room classifications within a biomanufacturing facility.
- Explain the controls required within a biomanufacturing facility, such as security (facility design, badges).
- Define the equipment, instrumentation, and control systems used in biomanufacturing.
- Describe the role and purpose of utility and support systems within a biomanufacturing facility.
- Describe the elements needed to sustain a biomanufacturing facility, such as preventive maintenance, cleaning, and housekeeping.
- Identify standard documents used to describe a biomanufacturing facility.

Terms

Clean room: a room or interconnected rooms maintained and controlled to prevent particle and microbiological contamination of drug products. They are assigned and reproducibly meet an appropriate air cleanliness classification

Distributed Control System (DCS): a series of computer-based devices that operate by interacting with each other on a variety of applications. These are usually widely separated throughout the system being controlled.

Heating, Ventilation, and Air Conditioning (HVAC): a critical utility used to distribute, recirculate, and exhaust, while meeting required air temperature, relative humidity, supply, differential pressure, and cleanliness requirements.

Piping & Instrumentation Diagram (P&ID): engineering drawings that specify all piping in a facility, including the sequence of branches, valves, equipment, instruments, and control interlocks. **Process Flow Diagram (PFD):** a basic, standard drawing that depicts the flow of a product through a process.

Standard Operating Procedure (SOP): a written and approved procedure that is revision controlled and used consistently for current Good Manufacturing Practices (cGMPs)-related testing or operations.

Work Instruction (WI): WIs are similar to SOPs and are also the more commonly accepted terminology in ISO 9001 certified sites. Typically SOPs are more general in nature than WIs.

Water For Injection (WFI): high-quality water made by filtering and distilling potable water. This purification process results in a significantly lower microbial activity level than tap water

Introduction to Facilities

Biomanufacturing processes require a physical building or set of buildings to house them; the building is referred to as a facility or site. Biomanufacturing facilities are similar in many ways to other types of manufacturing facilities. Raw materials are brought in to the facility, processed using various types of equipment and tools, then packaged and distributed. A biomanufacturing facility can include many of the features found in a typical manufacturing site, such as:

- manufacturing space (Figure 2-1), which can be divided into sections known as functional areas or units, based on process requirements
- warehouse/storage
- shipping/receiving
- control rooms/areas
- maintenance shop/custodial
- Heating/Ventilation/Air Conditioning (HVAC) system
- utilities (air, gases, water, electricity)
- computing/Information Technology (IT) rooms
- security
- office space, break rooms, locker rooms



Figure 2-1. Scientist in an upstream processing area in a facility

Biomanufacturing facilities have various features that are unique to the industry and its processes and products. They are designed and constructed to protect these processes and products from contamination. This design is based upon regulations established by government agencies such as the United States Food and Drug Administration (FDA). The FDA can also regulate and inspect foreign facilities that fall under its jurisdiction.

Facility design and regulatory framework

A key component of process control is facility design and operation. How do organizations decide upon the design of biomanufacturing facilities? Are there any guidelines that the manufacturers can follow? What if an organization manufactures several different products in a single facility?

To answer these and other facility design questions, one must first understand and examine the primary element of the design of facilities that will manufacture biopharmaceutical products which is to protect the product (and process) from adulteration, such as contamination from microorganisms, airborne contaminants, etc.

Since a wide variety of biomanufacturing processes and associated products exists, there is not a single design that fits the numerous variations. However, as a general guide the following factors are considered when companies design and operate a biomanufacturing facility:

- process and product characteristics
- process complexity
- single product or multiple products

To assist organizations in the design and operation of biomanufacturing facilities, the FDA has provided general guidelines. These guidelines state that buildings and facilities used in the manufacture of intermediates and Active Pharmaceutical Ingredients (APIs) should be located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. The FDA guidelines further state that facilities should be designed to minimize potential contamination and limit exposure to objectionable microbiological contaminants as appropriate.

As mentioned previously, product type is a key factor in design. Biologically-derived products, made from complex source materials, such as mammalian or bacterial cells, are more difficult to purify and properly identify than synthetically-derived drug products or small-molecule products. Thus biologically-derived products (biologics) would require higher levels of protection from contamination since they are hard to purify and more difficult to manipulate and store.

Organizations have adopted an approach of “the process is the product,” or similarly, “the product is the process,” based on guidance statements from regulatory agencies such as the

FDA. This means that because the manufacturing process is directly related to the biological product, the process must be controlled in order to control product quality.

Other government agencies can affect facility design, such as the Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA). To protect people in the workplace, OSHA regulations address a wide range of issues, including walking/working surfaces, exits, fall protection, hearing protection, respiratory protection, machine guarding, etc., any of which can impact a facility's design. The EPA regulates soil, air, and water pollution, any of which could potentially result from manufacturing activities (including those in the biomanufacturing industry). Thus environmental controls must be incorporated into a facility's design. National, regional, and local laws relating to fire protection, electrical systems, and general building codes must also be met (Figure 2-2).



Sign Marking Exit Route

by Clerk-Free-Images
<https://pixabay.com/en/fire-safety-signs-symbols-exit-40631/>



Sign To Avoid Elevator in Case of Fire

<https://pixabay.com/en/not-use-elevator-information-44460/>

Figure 2-2. OSHA governs exits and exit routes in the workplace.

Biomanufacturing protection strategies depend first and foremost on attaining primary and secondary containment of hazardous process materials. Primary containment refers to the protection of personnel and the immediate environment from exposure to hazards. Secondary containment refers to the protection of the environment outside the facility. Containment efforts generally fall into one of these categories: facility design, equipment, or aseptic practices and techniques. This chapter covers the first two, while later chapters (*Environmental, Health, and Safety (EHS)* and *Microbiological Control chapters*) describe aseptic practices and techniques.

The United States Centers for Disease Control and Prevention (CDC) characterizes biological threats at four different levels. As a corollary to these levels, CDC has also assembled criteria that describe the minimum protective features necessary and relative to the degree of the hazard. These biosafety levels are administered in ascending order by the degree of protection afforded to personnel, the environment, and the community. They consist of combinations of protective features specifically designed for the operations performed, the routes of

transmission of the hazardous agents and the facility function. The specific protective features prescribed by CDC for each biosafety level can be found *at* www.cdc.gov.

Biosafety Level 1

The practices, safety equipment, and facility design and construction of this level are appropriate for undergraduate and secondary educational training and teaching laboratories, as well as for other laboratories where work is performed with organisms not known to consistently cause disease in healthy adult humans. Biosafety Level 1 provides a basic level of containment that relies heavily on protective practices and techniques but generally does not warrant special primary or secondary barriers.

Biosafety Level 2

The practices, equipment, and facility design and construction of this level are applicable to clinical, diagnostic, teaching, and other laboratories where work is performed with moderate-risk agents that cause human disease of varying severity. The primary risk to persons working with these agents is through percutaneous or mucous membrane exposures, or ingestion of infectious materials. **Biological Safety Cabinets (BSCs)**, safety centrifuge cups, along with primary barriers such as splash shields, face protection, gowns, and gloves are recommended. BSCs are an important type of biomanufacturing safety equipment utilized not only to provide protection from splashes and aerosols that can be generated during microbiological procedures but also to reduce potential material contamination. Secondary barriers, such as handwashing sinks and waste decontamination stations, must be available to reduce potential environmental contamination.

Biosafety Level 3

The practices, safety equipment, and facility design and construction of this level are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with agents that have the potential for respiratory transmission and which may cause serious and potentially lethal infections. Biosafety Level 3 places emphasis on primary and secondary barriers to protect personnel. Additional secondary barriers are also required, such as controlled access and ventilation that minimize the release of infectious aerosols.

Biosafety Level 4

The practices, safety equipment, and facility design and construction of this level are applicable for work with extremely dangerous agents that can cause life-threatening disease, may be transmitted via the aerosol route, or for which there is no available vaccine or therapy. The work with these agents must be performed in complete isolation through use of BSCs and full-body, air-supplied, positive-pressure personnel suits. The facility itself is generally a separate building or completely isolated zone with complex, specialized ventilation requirements and waste management systems to prevent release of viable agents into the environment.

The facility design is important in achieving the desired level of protection at a biomanufacturing plant. Appropriate designs strive to create a barrier between the hazardous biological agent and the external environment. The specific design will depend upon the degree of risk presented by the biological material.

Lower level hazards may only need to address inadvertent contact with the agent and thus require only emergency response considerations such as decontamination stations and shower facilities. Higher risk environments may require more robust containment features to ensure the agent cannot escape from the facility, such as:

- specialized ventilation systems
- air treatment to remove agents from the exhaust air
- highly controlled access
- facility segregation

Some general facility construction considerations include:

- construction materials are selected that resist degradation by the cleaning agents used in the facility and permit easy maintenance
- walls, ceilings, and floors are smooth, impermeable to liquids, and resistant to the chemicals and disinfectants normally used in the facility
- windows, building seams, floor, and wall penetrations are sealed
- changing rooms are located away from hazardous locations
- drinking fountains, sinks, and basins that permit non-contact washing
- emergency showers and eyewashes are located throughout the facility to ensure easy, unimpeded access
- plumbing and waste systems capture effluent for decontamination before being discharged
- light fixtures, air ducts, and utility pipes are arranged to minimize the horizontal surface area
- equipment, storage racks, and furniture are located in a manner that do not impede critical systems such as ventilation components, fire detection equipment, fire mitigation equipment, and emergency alarm actuators
- communication and emergency notification systems are provided at convenient locations, and exits/exit routes are clearly marked and unobstructed
- all surfaces are smooth and free of sharp edges
- floors are slip-resistant, and trip hazards are eliminated or minimized
- adequate illumination is provided in all operational areas
- exits and exit routes are marked

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- access into all facilities is controlled using lockable doors or electronic pass systems

Facilities that use more hazardous materials in the process may require the following:

- work area access is through a minimum of two doors prior to entering the room or through an airlock fitted with airtight doors
- outer and inner change rooms are separated by a shower
- when protective suits are worn in the operating area, a chemical shower is provided to decontaminate the surface of the suits before the worker leaves the area
- suit areas provide protection equivalent to that provided by Class III BSCs
- a double-door autoclave, dunk tank, fumigation chamber, or ventilated anteroom is installed to permit decontamination of supplies and materials entering or exiting the area
- a ducted exhaust air ventilation system is installed in a manner that creates positive pressure in the work area (i.e., air is drawn into the area from "clean" areas and out to "contaminated" areas)
- operating area exhaust air is directed to pollution control equipment and is not recirculated to any other area of the building
- pollution control equipment and external exhausts are positioned such that wind directional changes do not blow the exhaust toward air intakes
- one-piece positive pressure suits are ventilated by a life-support system that is protected by High Efficiency Particulate Arrestance (HEPA) filtration
- life support systems needed for positive pressure suits have redundant breathing air compressors and backup breathing air tanks
- emergency power sources are provided for the exhaust system, life support systems, alarms, lighting, entry and exit controls, and BSCs

Many municipalities around the world have established fire and building codes that set forth minimum criteria intended to prevent, control, and mitigate fires. Building and fire codes are generally adopted and are occasionally expanded by state and/or local authorities, with enforcement often administered by the local fire service. See the *Environmental, Health, and Safety (EHS)* chapter for more details.

Functional areas/unit operations

Biomanufacturing companies need to develop an understanding of the process as well as the product in order to effectively design and operate a facility. Tools used for Operational Excellence and Quality efforts, along with documents and technical drawings, can help designers better understand the process and its characteristics. These requirements can impact overall facility design, as well as individual processing rooms (functional areas/units) inside the facility.

Process characteristics that must be considered can include:

- ranges of variables
 - temperature
 - pH
 - pressure
 - level
 - flow
- environmental conditions
 - air quality
 - sterility
 - humidity

Product characteristics include:

- actual size of the manufactured product
- stability
- risk to workers
- environmental risks to the product
- decontamination strategies

The overall production process at a biomanufacturing facility can be broken down into stages, called functional areas or unit operations, such as:

- cell culture
- recovery/harvest
- purification
- formulation
- fill/finish

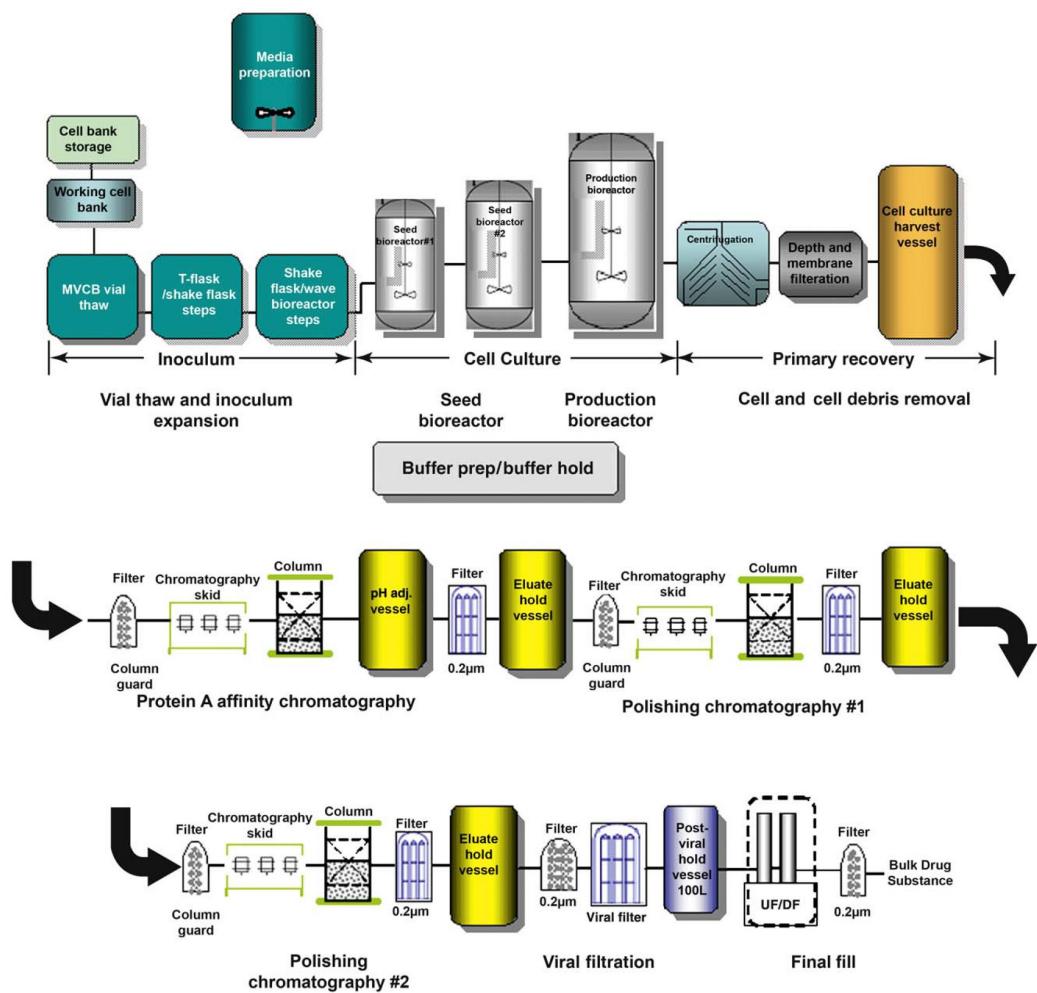
These unit operations can be housed and performed in one facility or separate facilities. For example, a company can grow and harvest the cells in one facility then ship them to another facility for purification and bulk filling of the product. The product can then be shipped to a third facility for filling into vials or syringes and packaging/labeling. These functionally distinct facilities can in fact be located in different cities, states, or countries. Figure 2-3 illustrates process flow, including required equipment and process time.

A common driving force behind the way in which unit operations are housed in biomanufacturing facilities relates to Good Manufacturing Practices (GMPs), or current GMPs (cGMPs) under FDA guidelines. GMPs are a set of standards that capture the best practices for manufacturing work. See the Quality Assurance chapter for more information.

Proximity to utilities and open or/closed processes are discussed later in this chapter. The general unit operations typically found in a biomanufacturing facility are discussed in the following section.

Unit operations layout can be determined by:

- proximity to utilities (either clean or un-clean)
- open or closed process requirements
- the criticality of the sequence of operations
- specific chemical and/or solvent usage
- product characteristics



Example of a process flow and associated equipment for large-scale production of monoclonal antibody (mAb) therapeutics.

From Shukla A.A., Thömmes J. (2010) Recent advances in large-scale production of monoclonal antibodies and related proteins. Trends in biotechnology, 28, 253–261. Figures 1 and 3.

Figure 2-3. Sample drawing of a process flow and its associated equipment

Raw material storage and handling

Raw materials can include basic items such as simple salts, media components, filters, tubing and bottles. Other raw materials depend on the product and process. Basic items are usually stored in a temperature and humidity-controlled warehouse. The warehouse is typically located adjacent to the raw material weigh/dispense area (see the next section) for ease of entry into the facility.

Often companies have a sophisticated, computer-based inventory system to track the raw materials' status (e.g., released by Quality Assurance, in quarantine, on test, etc.), quantity, and disposition (where the raw materials are consumed in the manufacturing process). The raw materials are generally stored on plastic pallets, as opposed to wooden pallets, to reduce the risk of contamination.

The raw material storage area is designed to be cleaned and dried easily to prevent the introduction of outside contaminants into the processing areas. Some raw materials, such as liquid nitrogen, are stored in large, bulk containers (tanks) either inside the warehouse or outside the facility. These containers are attached to a distribution system (consisting of piping, valves, and instrumentation) to move the materials to where needed. Equipment (tanks, pipes, valves) and instrumentation will be discussed later in the chapter.

Raw material weigh/dispense and media/buffer preparation

The unit operations given above are generally located near a material transfer room to minimize the movement of the materials within the facility. Raw materials are stored in containers that have been exposed to the inside of trucks, planes, and/or boats, so the possibility of outside contaminants entering a biomanufacturing facility increases when these containers are moved in and out of a facility.

To reduce this risk, companies often locate the weigh/dispense area in the raw material warehouse; materials are then transferred into cleaner, secondary containers which are moved into and out of the facility. A weigh/dispense area generally consists of calibrated scales, weighing instruments and tools (such as scoops, spatulas, and weigh boats), a weigh booth, and raw material handling equipment such as lifts and carts.

Media and buffer preparation areas are generally located near a refrigerated room if the solutions require storage at cooler-than-room temperatures. These preparation areas are sometimes centrally located in a facility because they provide solutions for the entire manufacturing process. Media and buffer preparation and holding vessels are designed for either cooling or heating depending upon the solution requirements.

Clean in Place (CIP) and Steam In Place (SIP) capabilities are added if large quantities of solutions (several hundred to several thousand liters) are prepared. This is to ensure the proper level of cleanliness is maintained. Transfer lines to the upstream and downstream processing areas of the facilities are often built in to transport these large quantities of solutions to their respective areas.

Inoculum preparation/cell culture

Typically, the inoculum preparation area has many open operations. Open operations can include:

- opening and closing medium bottles, flasks, and buffer solutions
- using sterile pipettes
- transferring cells and solutions from one container to another

These types of open processes require facility designs that can contain them using a variety of methods, such as using a Biological Safety Cabinet (BSC) in the inoculum preparation area (Figure 2-4). Workers wear sterile gloves and sleeves to work in a BSC so as to minimize contamination. Another way to control open processes is to conduct them in a classified environment, such as a Class 100 clean room. Clean rooms and room classifications will be discussed later in this chapter.



Figure 2-4. Biological Safety Cabinet

Cell culture operations are designed to contain a vessel in which cells are grown, piping and/or tubing to supply and transfer gases (e.g. oxygen, carbon dioxide, and compressed air), media and other solutions for cellular growth. The vessels used to grow cells are referred to as bioreactors, reactors, or fermenters. These equipment types can be designed for CIP/SIP or transferred to a validated washer or autoclave depending on the size (see **Validation** chapter for more information). In the fermenter stage of the process the operations are normally closed, so equipment such as BSCs are normally not required. Inoculum preparation and cell culture areas are designed to be located in either the same room or adjacent rooms within a facility.

Recovery and harvest

A variety of techniques are used in this unit operation, including homogenizers, centrifuges, and depth filtration **and sterile filtration** systems. Generally these processing steps and techniques are performed in closed systems with minimal exposure to the environment. These areas are designed for cleanability. CIP capabilities are added if the equipment is too large to clean in a validated washer/autoclave. Cold rooms or refrigerators/freezers are placed nearby if the product is not stable at room temperature.

Purification

In the purification unit operations, steps can be performed either at room temperature or at a controlled temperature depending on product stability. If temperatures must be controlled, the area must be designed to accommodate these conditions without adding any contamination risks to the process. Equipment in this area includes chromatography columns and associated chromatography skids, as well as cross flow and dead-end filtration devices and skids.

Purification processing areas are generally located near the recovery/harvest areas for ease of transport.

Fill/Finish

The finished product is created in the fill/finish unit operations. Since this is the final step in the manufacturing process, the processing is performed in a tightly controlled environment. The area, called an aseptic processing area, is designed for the maximum protection from outside contaminants. Filling machines, lyophilizers (freeze-drying machines), and formulation/filling vessels are used to transform the purified product into a usable product. Note that the aseptic processing area is located at the center or core of the room. It is located away from adjacent materials, people, and services areas. This design minimizes the probability of any contaminants entering the core area.

Material and Personnel Flow

Biomanufacturing facilities are designed to adequately accommodate the processes and associated equipment used in manufacturing the product. They are also designed to provide both proper access for personnel (e.g. operators, technicians, maintenance staff, and quality department staff) as well as the ease of movement of raw material and products. Architects, engineers, designers, and other staff members work together to ensure the facility and its areas are designed in a way that promotes the creation of a safe, effective, pure, and high quality product. This must be achieved using the most optimum process flow. See ***Operational Excellence*** chapter for information on how process flows can be optimized in a safe, hygienic, and environmentally friendly manner.

Prevention of contaminants in aseptic processing areas is a key principle when biomanufacturing facilities are designed and built. This principal is even more significant in the final fill/finish processing area, in which the product and container closures are exposed; adjacent rooms require aseptic support activities such as gowning, autoclaving, washing, and material transfers.

Thus material and personnel flow is critical to minimize product and process contamination. Material flow is generally unidirectional, with the flow moving from less clean areas to cleaner ones. Personnel gown and de-gown in separate rooms and airlocks are used to segregate different air qualities within a room.

A few general concepts can summarize how personnel and material are designed to flow through a biomanufacturing facility. One concept is that general flow through a facility should prevent product cross-contamination and environmental contamination. Personnel must not introduce contaminants into the product as they move from one area to another. Another important concept is that process or operational waste should be removed from the facility without contaminating the product. Devices such as one-way pass-throughs can assist in this type of transfer. For personnel flow, items such as step-over benches, door interlocks, or time-delays are used to segregate different clean areas and to prevent or reduce pressure gradients and two-way access into controlled areas.

Room Classifications

Biomanufacturing processes require clean rooms, aseptic processing areas in which contaminants are limited or controlled. A clean room is any room or area in which an attempt is made to limit, control, or eliminate the amount of airborne contamination. The word "attempt" is important to note, as a totally clean room does not exist (i.e. a room can never be truly uncontaminated—there are only degrees of cleanliness). Clean room design must be properly implemented during construction and maintained and updated throughout the life of the facility.

The clean room environment is created and maintained by controlling the air that is supplied. Traditional air handling systems, Heating/Ventilation/Air Conditioning (HVAC) filtration systems, are of prime importance in biomanufacturing facilities. They remove large particles and provide air that is adequate for routine manufacturing. HVAC systems are quite expensive and constitute a large portion of the overall total facility cost. Some factors that affect HVAC costs are:

- the size of the aseptic processing area if applicable—the larger the aseptic processing area, the costlier the HVAC system
- complexity of the HVAC design
- HVAC integration with other areas of the facility, including process equipment (e.g. some downstream processing equipment requires extremely clean areas)

In addition to controlling cost and particulate emissions, HVAC systems also play an important role in the regulation of a facility's temperature and humidity.

Standard HVAC filtration capabilities, however, are not adequate for aseptic processing due to the inefficacy in reducing sub-micron airborne contamination. Thus High Efficiency Particulate Air filters are used as part of a biomanufacturing facility HVAC system to establish and maintain a high quality of clean air in "controlled" areas, such as clean rooms (Figure 2-5). HEPA filters remove 99.97% of particulates that are 0.3 microns or larger in size. A micron is a term which is

used interchangeably with “micrometer,” or 1/1000th of a millimeter (0.001 mm). For comparison, a cross-section of a human hair is approximately 100 microns in size. The **Microbiological Control** chapter addresses specific information relating to particulates and HEPA filtering.

The air handling system also changes the air inside the room, effectively purging the air of particulate matter generated *within* the clean room. Therefore, the number of air changes per hour in a clean room is also controlled.



by CSIRO

https://commons.wikimedia.org/wiki/File:CSIRO_ScienceImage_482_HEPA_Filter.jpg

Figure 2-5. A HEPA filter

HEPA filters are constructed of a continuous sheet of boron silicate microfiber paper (the filter media) similar to fiberglass. The microfiber is pleated in an accordion-like fashion around aluminum separators, and the entire filter is framed in metal. Channels are created and air flows into the pleats and through the filter media. In addition to removing nearly 100 percent of particles in the sub-micron range, the filters also provide an essentially uniform-velocity curtain called “laminar flow.” Laminar flow helps “wash away” airborne particulate that is generated within the clean room, thus helping to prevent work area contamination. HEPA filters are tested for leaks and inspected on a regular basis.

Additional features that are designed to maintain this environment include:

- construction materials
- air classifications
- pressure differentials
- airlocks
- restricted entry
- flow of people
- flow of materials

Materials used for constructing clean rooms must be durable, smooth, hard, rust resistant and easily cleaned and disinfected. Any material that crumbles, has many cracks and crevices, or cannot be properly cleaned and disinfected should not be used in clean rooms. For example, floors are typically concrete, having either an epoxy/polyurethane surface coating or a sheet vinyl covering with no joints or seams that might support microbial growth or allow insect intrusion. Floors, walls, and ceilings should be joined or coved so that each is a continuation of the other. There should be no cracks at the wall corners, wall/ceiling corners, or the point at which the wall and floor meet. Stainless steel and plastics are commonly used construction materials in clean rooms since they can be cleaned, disinfected, and sterilized.

Clean rooms are designed with special features that provide a working environment in which the level of airborne microbial and particulate contaminants is significantly reduced. In such an environment particulates are controlled using HEPA filtered air that is continuously circulated through the work area. Air classifications are used to describe the various environments within a clean room. These classifications are based on the amount and size of particulates which exist in the work area.

The classifications are:

- Class 100 environment contains less than 100 particles (greater than 0.5 microns in size) per cubic foot
- Class 10,000 environment contains less than 10,000 particles (greater than 0.5 microns in size) per cubic foot
- Class 100,000 environment contains less than 100,000 particles (greater than 0.5 microns in size) per cubic foot

For example, the work area under a laminar flow hood or laminar flow canopy where aseptic processing is performed is a Class 100 environment. The room in which the hood or canopy resides is a Class 10,000 environment, and the hallway outside the room may be a Class 100,000 environment. Thus a lower-classification of room indicates a cleaner environment.

Once the proposed steps in the manufacture of a new drug product have been defined, air classification requirements for the clean room can be found in regulatory agency standards. Air classification requirements differ for products to be sterilized in their final container versus a product prepared by aseptic processing. The requirements also differ between regulatory agencies. Table 2-1 summarizes some of the room air classifications for products manufactured by aseptic processing.

Table 2-1. Air Classifications

| Air Quality (0.5 micron particles/ft ³) | Typical Area | FDA Classification | European Classification | ISO Classification ^a | Typical Dress Code |
|---|---|--------------------|-------------------------|---------------------------------|--|
| Outside | Facility Parking Lot | N/A | N/A | N/A | Street clothes |
| Unclassified | Laboratories Warehouse | N/A | N/A | N/A | Per facility guidelines |
| Controlled | Clean Corridor | N/A | N/A | N/A | Per facility guidelines, such as laboratory coat, hairnet, shoe covers |
| Class 100,000 | Clean, non-sterile processing, personnel and equipment airlocks, and support areas leading into the background room/area for aseptic processing | Class 100,000 | Class D | 8 | Clean garments |
| Class 10,000 | Filling Room, Background room for aseptic processing | Class 10,000 | Class C | 7 | Sterile garments |
| Class 100 | Aseptic processing, sterility testing, and point of filling | Class 100 | Class A | 5 | Sterile garments (sterile gloves/ sleeves while working in a BSC) |

^a ISO 14644-1 designations provide uniform particle concentration values for clean rooms in multiple industries.

In summary, Class 100 is the critical zone in which sterilized drug products, containers, or closures are exposed to the environment. Class 10,000 is usually for the rooms (clean area) surrounding the critical zone. Class 100,000 is for support or manufacturing areas with no sterilized product/component exposure. Controlled and Unclassified designations are for areas surrounding the clean room.

The flow of air from one room to another within a clean room is controlled by **air pressure differentials**. Positive air pressure is used to keep the most critical processing rooms free from airborne contaminants that may be present in adjacent rooms. A clean room is designated as being under positive pressure when it has a higher air pressure than an adjacent room. Therefore, the direction of the flow of air is from the room with higher pressure to the room with lower pressure, creating an air barrier. Clean rooms are designed so that the most critical processing area has the highest air pressure, and the least critical area has the lowest pressure. For example, a laminar flow hood in which the aseptic processing occurs has the highest air pressure, the room in which the laminar flow is located has a slightly lower air pressure than the laminar flow hood and the adjacent room has an even lower pressure.

Figure 2-6 illustrates room air pressure differentials (using + signs to indicate air pressure) and the direction of air flow for a filling room. The pressure differentials are closely monitored using instruments called pressure sensors to measure these differentials. To help maintain the air pressure differentials and to minimize the potential for contaminants to enter the aseptic processing area, it is important that doors between each room are kept closed.

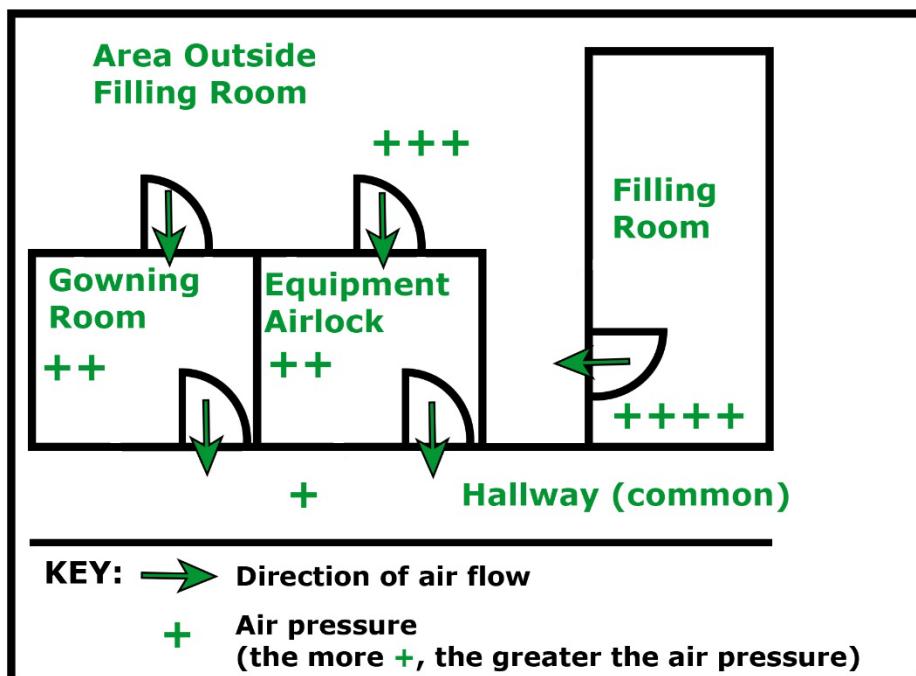


Figure 2-6. Example of room air pressure differentials and direction of airflow for a filling room.

To ensure that aseptic processing activities are performed in areas with the appropriate air quality, clean rooms often use airlocks. An **airlock** serves as a barrier between an outside, uncontrolled environment and an inside, controlled environment. Thus airlocks are barriers designed to prevent airborne contaminants in one area from entering another area. Equipment and personnel entrances typically have airlocks to prevent outside air (and its potential contaminants) from entering the clean room.

A gowning room is usually the entrance to the clean room for people and is designed as an airlock. Specifically, an airlock consists of two doors with a space between them containing HEPA-filtered air. To prevent the flow of outside air into the clean room, only one of the two doors may be opened at a time. Some facilities have airlocks equipped with alarms, lighted signs, or interlocks to prevent opening both doors at the same time. An interlock is an electronic device that physically prevents both doors from being opened at the same time.

Typically, personnel flow within a clean room is uni-directional—individuals enter the clean room through an entry airlock and leave through an exit airlock. Separate airlocks are used to assist with the unidirectional flow of personnel and equipment. Figure 2-7 illustrates the airlocks and personnel and equipment flow in a fermentation suite.

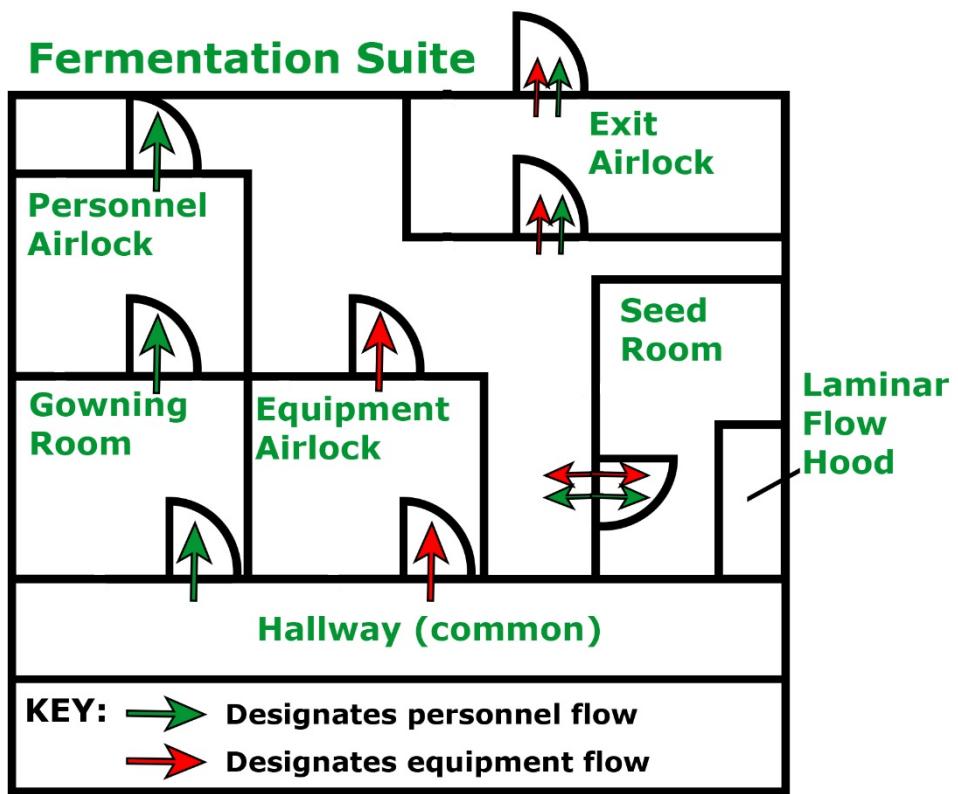


Figure 2-7. Airlocks and personnel/equipment flow in a fermentation suite

The possibility of contamination due to either particulate matter or airborne microorganisms increases as the number of people increase in a facility. Thus access to clean rooms must be limited and strictly controlled. Only personnel required to perform or support a particular process are allowed to enter the clean room through controlled entrances and exits. Card key readers and similar measures at personnel airlocks, combined with a limited number of entrances and exits, help to control the number of people able to access a clean room. Within a clean room there should be separate spaces designated for clean and dirty manufacturing equipment. These spaces help prevent product contamination by the inadvertent use of dirty equipment during processing.

Facility Security and Access Controls

Biomanufacturing is a multi-billion dollar industry. Intellectual property (e.g. product and process trade secrets) must be maintained and protected from industrial espionage. Biomanufacturing is also a potential target of terrorist groups or similar organizations.

Security entails managing risk. Risk, in these terms, is vulnerability plus a threat. Vulnerability is a hole in the security, while a threat is a person or group that will take advantage of that vulnerability. Security depends on deterrence, detection, assessment, communications, and response.

Security measures address risks at a biomanufacturing facility by:

- limiting access from individuals outside the organization (e.g., access and perimeter control)
- performing personnel control
 - screening potential new hires prior to hiring
 - restricting access to certain areas by existing staff members
- establishing operations and procedures (e.g., monitoring and threat response plans)
- setting up communications

Security measures can include:

- security forces (e.g., guard posts and patrols)
- access barriers (e.g., gates, fences, and doors)
- alarm and monitoring devices (e.g., cameras and motion sensors)
- lighting systems
- communication systems
- pass-protected entrances and exits (e.g., badges, key cards, or biometric scanners such as thumbprint or retinal scanners)

A facility will also have cyber or computer security in place to protect technological assets. Cyber-security measures include preventing unauthorized computer access (using passwords and "firewalls") and monitoring computer access and usage.

Process Equipment, Instrumentation, and Control Systems

Having established the physical aspects of a facility and the respective areas within, the following section addresses the equipment, instrumentation, and control systems used in the production process.

Equipment is the machinery and other items used to perform various parts of the process. The more common types are:

- vessels
- piping
- valves
- motors
- pumps
- compressors
- fans
- reactors
- columns
- boilers
- laminar flow hoods
- filters
- centrifuges
- autoclaves
- refrigerators/freezers
- conveyors
- filling, sealing, packaging, and labeling machines

A facility may or may not have all of these types of equipment, and the arrangement of the equipment is based on the process and the facility specifics. While this section will provide a general overview of equipment, specific types of equipment (e.g. reactors, columns, and filters) will be discussed in later chapters.

Vessels

A vessel is a generic term for any container that stores materials in liquid, solid, and/or gas form or is involved in the processing and treatment of those materials. Vessels can include tanks, drums, cylinders, bins, and hoppers. Reactors, discussed later, are a specific type of vessel.

Piping

Typically cylindrical in shape, piping consists of varying lengths of tubing made of materials such as steel, iron, plastics, etc., that carry materials (usually in liquid or gas form) from one location to another. Along with valves, piping is one of the most common pieces of equipment found in a facility.

Valves

Valves are devices that are attached to piping or equipment to control the flow of liquids or gases. There are a wide variety of valve types that can start/stop or throttle (open or close in increments) the flow. Valves are vital to process control. They can be remotely opened or closed to control variables such as flow or level.

Motors

Motors are electrically-powered devices that are often used to drive rotating/moving equipment such as pumps, compressors, fans, mixers, blowers, and conveyor systems. Motors are usually powered by alternating current (the type from power lines as opposed to direct current from batteries). Motors turn electricity into a rotational motion that subsequently powers other types of equipment.

Pumps

Pumps are an important type of equipment to process operations. They are used to move liquids through the system, such as into or out of a tank. There are many different types of pumps, but they all use either rotational or centrifugal force to induce flow in liquids.

Compressors

Like pumps, compressors are also an important type of equipment in process operations. Compressors are used to move gases (air, oxygen, nitrogen, etc.) through a system. Compressors can supply filtered and/or pressurized air or breathing air (for certain types of respirators). Pressurized air can also be used to control valves (pneumatic controls).

Fans

Industrial fans are similar to household fans, using spinning blades to circulate air. However, industrial fans are much larger and more robust than household types. Air circulation plays a critical role in a facility in reducing contaminants and potentially harmful fumes.

Reactors

Reactors are specialized vessels in which reactions are initiated and sustained. In general terms, materials placed in a reactor are subjected to various conditions, such as temperature and pressure, to create and sustain a reaction. Some reactors have a mixer or agitator inside to stir the vessel contents.

Bioreactors (Figure 2-8) are used to promote biological conditions within the reactor's environment during the fermentation stage of a process. Bioreactors are further discussed in later chapters.



Figure 2-8. Production bioreactor

Columns

Columns are used to separate and purify materials. In process operations they are typically configured as a cylindrical tower containing a physical phase inside that performs the separation/purification. The mobile phase (containing the material to be separated/purified) passes across the stationary, physical phase in the column. Columns are further discussed in later chapters, including the ***Quality Control: Biochemistry*** chapter, where they are used as part of the chromatography process. Chromatography is a range of physical methods used to separate and/or analyze mixtures.

Boilers

Boilers are a type of vessel that uses heat and pressure to create steam. In the biomanufacturing industry, steam is vital to cleaning processes and purging operations. Steam can also be used to drive certain types of rotating and moving equipment.

Laminar flow hoods

During certain steps in the manufacturing process, the product is exposed to the environment. However, this exposure takes place in controlled areas using various types of aseptic equipment to prevent product contamination. This equipment includes laminar flow hoods (Figure 2-9), laminar flow canopies, and BSCs. Laminar flow hoods, laminar flow canopies, and laminar flow rooms provide protection to the product so as to prevent contamination, whereas BSCs provide protection to both the product and the person working under the BSC.

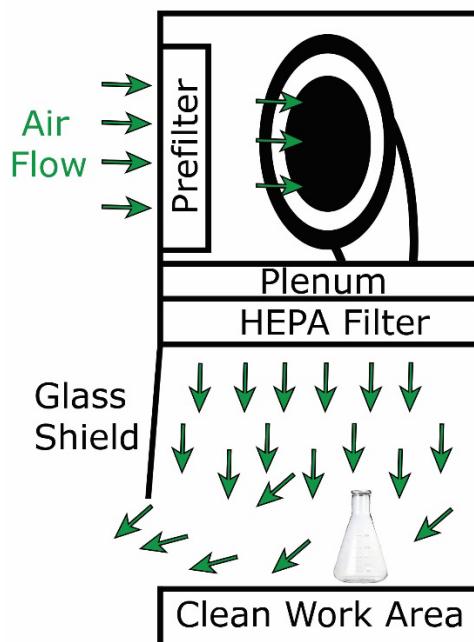


Figure 2-9. Laminar flow hood

Filters

Filtration is a key part of biomanufacturing processes as they help maintain product purity and quality. As mentioned previously, HEPA filters are used to prevent airborne contamination. Process filtration is further discussed in the ***Upstream Processing*** and ***Downstream Processing*** chapters.

Centrifuges

A centrifuge is a piece of equipment that is spun by a motor at high speed and uses centripetal force to separate a mixture (normally dispersed in a liquid) into its denser and lighter components.

Autoclaves

An autoclave is a device that uses high temperature and pressure steam to sterilize equipment and tools (Figure 2-10). Autoclaves are discussed in more detail in later chapters.



Figure 2-10. Autoclave

Refrigerators and Freezers

Industrial grade refrigerators and freezers operate using the same principles and mechanics as household types. Industrial units, however, are much larger in size and capacity. They also differ in that they utilize both sensors to monitor temperature and other conditions and alarms in case of equipment failure or other issues.

Conveyors

A typical conveyor in a facility is a moving belt driven by a motor and used to transport materials from one part of a facility to another. A facility can also use a variation on the design of the conveyor or other similar device to efficiently move materials as needed in a process.

Filling, sealing, packaging, and labeling machines

These machines are typically automatic devices used for packaging product into sterile containers that can be distributed to other locations. In biomanufacturing processes, these are maintained in aseptic conditions to ensure product purity and quality.

Instrumentation and process control

The remainder of this section will discuss the devices and systems that are used to monitor and control the production process.

Process instrumentation consists of devices that operators and technicians use to monitor and control various conditions of a process—process variables. The main types of process variables are:

- temperature
- pressure
- level
- flow
- analytical

Though the first four process variables are self-explanatory, analytical variables are more involved and include both quantitative and qualitative properties of a material, including but not limited to the following:

- pH
- chromatography
- color/optical measurements
- density
- viscosity

Analytical measurements of biomanufacturing products are critical as they aid in determining product efficacy, safety, purity, and quality; an organization's Quality Department relies heavily on these analytical measurements.

Instrumentation typically falls into one of the following categories:

- sensing (checking the process variable)
- indicating (displaying the variable's value)
- transmitting (sending the value to another location, such as a workstation for viewing on-screen)
- recording (logging the historical values over time, or trending)
- controlling (generating a response to a variable; for example, closing a valve if a level in a tank is getting too high)

It is vital to understand process variables and their relationships. This can assist in understanding the overall process and ensuring that an effective, quality product is being produced. Similar to a doctor checking vitals of a patient, the vitals in a production process indicate the product's health and aid in determining whether corrective actions must be taken.

Manufacturing processes can be controlled and monitored by a variety of methods, ranging from manually controlled to near full automation. Most biomanufacturers use some type of automation controls for critical operating parameters (i.e., process variables). An example of a critical operating parameter is the percentage of dissolved oxygen in a bioreactor.

Instrumentation feeds data like pH or temperature into a control system so that operators and technicians can monitor the process remotely, make adjustments, and respond to process

alarms. This computer-based system is typically called a **Distributed Control System (DCS)**. A similar system, referred to as a Building Automation System (BAS), is linked to the facility's HVAC systems, alarm systems, and other environmental controls.

Process Utility Systems

Utilities such as air, water, gas, and electricity are vital to the biomanufacturing process. Utility systems are generally divided into two categories, **Process Systems** and **Process Support Systems**. Each utility system plays a unique role in a biomanufacturing facility. Since purified water and clean steam are normally used as part of the manufacturing process, they are considered process systems. Process support systems, on the other hand, are utilities such as breathing air, chilled water, instrument air, potable water systems, and plumbing systems (e.g. floor drains).

Since process systems are those that can directly contact the product, the construction materials used for the equipment that stores/distributes these utilities must not cause product contamination. For example, nitrogen gas can indirectly or directly contact the product depending on the application. Stainless steel piping and storage vessels are generally chosen for nitrogen gas storage and distribution because of its inert properties (it does not react with other substances and will not explode or cause a fire). Stainless steel piping and components are also used for purified water storage and distribution.

Table 2-2 displays typical biomanufacturing utility systems and their respective categories.

Table 2-2. Process Utilities

| Utility System | Category |
|----------------|-----------------|
| Purified Water | Process |
| Clean Steam | Process |
| Nitrogen | Process |
| Air | Process |
| Oxygen | Process |
| Carbon Dioxide | Process |
| Helium | Process Support |
| Breathing Air | Process Support |
| Potable Water | Process Support |
| Chilled Water | Process Support |
| Instrument Air | Process Support |

Water For Injection (WFI) is a type of high quality water made by filtering and distilling potable water (water fit for drinking). This purification process results in a significantly lower level of microbial contamination than that of tap water. Once WFI is manufactured, storage must be provided in holding tanks to accommodate constant usage needs. A circulating loop maintained at a high temperature (65°C – 80°C) must be provided to maintain flow throughout the points of use of the WFI system. This minimizes the opportunity for microbial contamination.

WFI is tested periodically to ensure that it has less than 20 Colony Forming Units (CFUs) per 200 mL of water and contains no bacterial endotoxins; this is determined using a test called Limulus Amebocyte Lysate, or LAL. Furthermore, WFI must be free of added substances (e.g. chlorine found in tap water) and not contain any of the following objectionable bacteria: *Pseudomonas aeruginosa*, *Burkholderia cepacia* or coliforms.

For these reasons, the United States Pharmacopeia (USP), a public group that sets these standards, specifies that water used as an ingredient in the manufacture of sterile pharmaceuticals and for cleaning equipment must meet its stated standards for WFI.

Facility Sustainability

Once biomanufacturing facilities are designed and operational, the focus shifts to sustainability. Thorough and adequate cleaning of a facility is an important aspect in lowering the risk of product/process contamination. Typically all surfaces of a facility are cleaned on a daily or per shift basis. Ceilings, walls, and floors are normally cleaned less frequently but may be cleaned daily depending on how critical the unit operation is.

Rooms are sanitized with a disinfecting agent, which is sometimes sterile-filtered, and all excess sanitizing agents are wiped down to prevent pools of stagnant liquid from promoting bacterial or fungal growth. Viricides, bactericides, and sporicides are all used as disinfecting agents and can be used on a set, rotating basis, such as once per month, for added protection.

Preventive maintenance is another critical component required to maintain and sustain a biomanufacturing facility. Preventive maintenance involves routine, predetermined inspections of equipment, HVAC, and utilities to prevent any potential breakdowns and to reduce the risk of contaminants being introduced into the product.

General housekeeping procedures are also important to ensure facility sustainability. Housekeeping can prevent cross-contamination in facilities that produce single and multi-products. It can also aid in preventing product/batch/lot mix-ups and safety issues. Housekeeping procedures can be documented in Standard Operating Procedures, Master Batch Records, and preventive maintenance work orders. For example, the first step in a Master Batch Record could state, “Ensure work area is clean and free of clutter before proceeding”.

Standard Process Documents and Drawings

Standard documents and drawings are created to describe a biomanufacturing facility, its processes, and its resources. Some of these are created during facility design/equipment installation, while others are created before process operations start. These documents and drawings are maintained through the life of the facility and modified as necessary. They can be

utilized to help meet regulatory agency requirements and implement quality policies and high-level procedures.

Standard documents in a facility include:

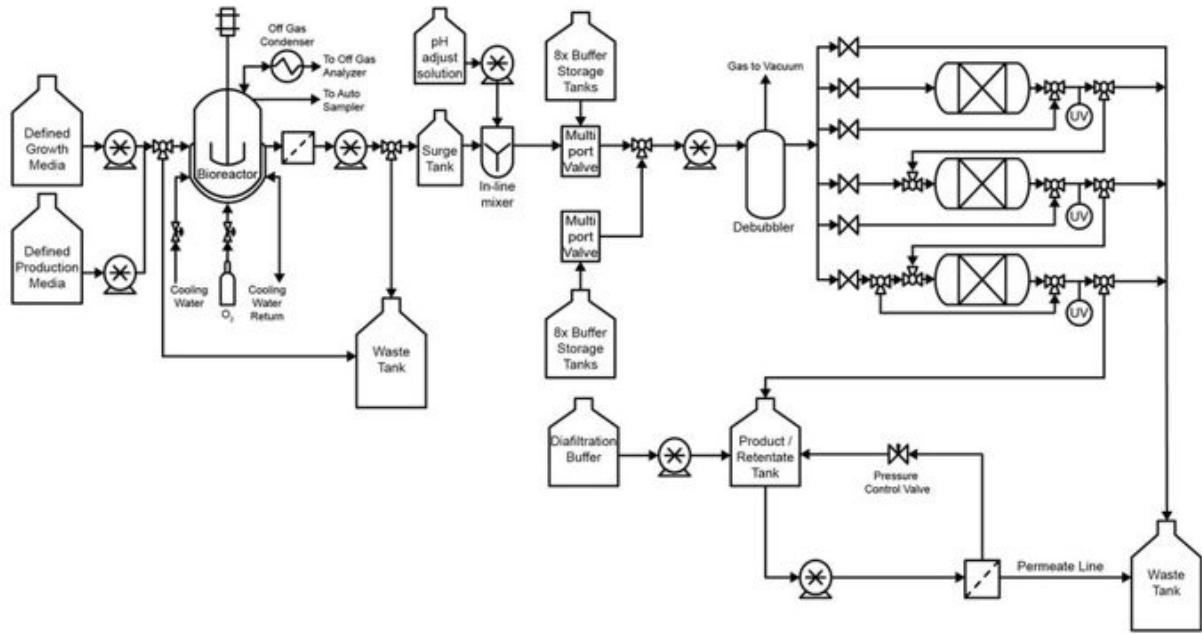
- **Standard Operating Procedures (SOPs):** a written and approved step-by-step procedure that describes ways in which to accomplish a task or set of tasks. SOPs are version-controlled and an important part of cGMPs as regulated by the FDA.
- **Work Instructions (WIs):** similar to SOPs and the more commonly accepted terminology in ISO 9001 certified sites. Typically SOPs are more general in nature than WIs.
- **Material Safety Data Sheets (MSDS):** a document required by OSHA's Hazard Communication standard that describes key safety, health, environmental, and other crucial information about a chemical. A MSDS is provided by the chemical manufacturer/distributor.

OSHA requires employers to make MSDSs available to workers as part of its Hazard Communication regulation, or HazCom. For more details refer to ***Environmental, Health, and Safety (EHS)*** chapter.

A type of standard drawing used to describe a biomanufacturing facility is a Process Flow Diagram (PFD). These types of documents are used throughout the life span of the facility but are critical at the design phase. A typical PFD displays the processes required for each unit operation. Facilities are designed based on unit operational flow. Each unit operation will require certain types of equipment and specific space, which are each depicted in a PFD. PFDs are also useful for operator and technician training as well as reference materials during regulatory inspections.

Another standard type of drawing is called a Piping & Instrumentation Diagram (P&ID). Figure 2-11 depicts a typical P&ID. P&IDs contain a high level of detail (more so than a PFD). This document displays the location of piping and instruments associated with a particular system or unit operation. P&IDs include all instrumentation, equipment, size of process piping, vents, sampling lines, and slope direction. Operators, engineers, maintenance, validation, and other facility staff members use this type of drawing for a variety of purposes, including system design, hazardous operation analysis, control sequencing, training, review, modification, and system troubleshooting.

Since biomanufacturing is a highly regulated industry, a wide variety of other types of documents and drawings are required. These are discussed further in later chapters.



Example of Detailed piping and instrumentation diagram (P&ID) for the InSCyT system.

From Crowell, L.E., et al. (2018) On-demand manufacturing of clinical-quality biopharmaceuticals. Trends in biotechnology, 28, 253–261. *Nature Biotechnology* Supplementary Figure 1.

Figure 2-11. Sample P&ID

Check Your Knowledge

1. Which of the following government agency's regulations can impact the design, construction, and operation of a biomanufacturing facility?
 - a. FDA
 - b. OSHA
 - c. EPA
 - d. all of these
2. The practices, safety equipment, and facility design/construction for biosafety level _____ are applicable for work with extremely dangerous agents that can cause life-threatening disease; may be transmitted via the aerosol route; and for which there is no available vaccine or therapy.
3. Which area has many open operations, such as opening and closing medium bottles, using sterile pipettes, etc.?
 - a. raw material dispense
 - b. inoculum preparation
 - c. fill/finish
 - d. none of these
4. Which classification of room would be used for a point of filling operations?
 - a. 100
 - b. Class 7
 - c. 100,000
 - d. Class B
5. The flow of air from one room to another within a clean room is controlled by air pressure_____.
6. Risk, related to facility security, is _____ plus a threat.
 - a. espionage
 - b. control
 - c. access
 - d. vulnerability
7. What type of equipment is used to push a liquid through a system?
 - a. pump
 - b. compressor
 - c. pipe
 - d. valve

-
8. Which of the following is NOT an example of an analytical process variable?
 - a. pressure
 - b. pH
 - c. density
 - d. viscosity
 9. What type of system is a clean system? _____
 10. Water for Injection must contain less than _____ CFUs per 200 mL of water.
 - a. 5
 - b. 10
 - c. 15
 - d. 20
 11. A _____ drawing contains a high level of detail about a process.

Activities

1. Research the FDA requirements related to facility design where intermediates and APIs will be produced. Write a two-page summary of the regulation.
2. Locate five everyday examples of these types of equipment around your home, car, or school: valve, pump, compressor, vessel, and reactor. Present the examples to your classmates.
3. Write a Standard Operating Procedure for a simple activity that you commonly perform (you can research examples on the Internet or in your workplace). After writing the SOP, ask a classmate, family member or friend to perform the SOP as written. Afterward, review what elements were clear, unclear, or missing. Make changes to the SOP.
4. Include Boston Globe Genzyme facility activity