School of mechanical and aeronautical engineering

Business, Manufacturing

Facilities and equipment use in bio-manufacturing

In process development and manufacturing, the biopharmaceutical industry requires high flexibility in its production facilities. These suites must be able to produce clinical material or even drug substances for the market. Biomanufacturing processes requires a physical building or set of buildings to house them, usually these buildings are called facilities or site. These facilities are somehow like other types of manufacturing facilities. Raw material is used for the process, using various equipment and tools, then it is send for packaging and distribution. Some example of the bio-manufacturing facility used that are like other type of manufacturing site are: shipping/receiving, warehouse/storage, control rooms/areas, utilities (air, gases, water, electricity), security etc.

Although there are some facilities in bio-manufacturing are similar to other types of manufacturing, there are some features, process and products that are unique to the bio-manufacturing industry. These facilities are built and designed to prevent contaminations. This design is based on the regulations set by government agencies like the United States Food and Drug Administration (FDA).

Process equipment are usually constructed using materials like stainless steel or plastic. Stainless steel equipment can be washed and reused again while plastic equipment is disposed after single used. Products manufactured for medical or food use should be produced in facilities designed and operated according to Good Manufacturing Practice (GMP) regulations. The level of contaminations and number of particles or microorganisms in the

cleanroom must be control under a certain number. Sterilization and aseptic processing equipment are required for production of injectable products.

Facilities design and regulatory framework for bio-manufacturing

Facilities design is a key component of process component. How do they decide the design of the bio-manufacturing facilities? There must be certain general guidelines for them to determine whether the design fits the requirement. To assist the organisations and companies, FDA has come out with the general guidelines for the facilities use for bio-manufacturing industry.

- Process and product characteristics
- Process complexity
- Sole product or multiple products
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These guidelines state that buildings and facilities used in Active Pharmaceutical ingredients (APIs) should be located, designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage manufacture. There are also other government agencies that can affect the facility design like Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA). EPA is an agency of the federal government of the united states which was created to protect human health and environment by writing and enforcing regulations. EPA regulates the air pollution, water pollution and the environment, therefore environment control needs to be take into consideration for the facility design. OSHA is a multidisciplinary field

concerned with the safety, health, and welfare of people at work. So, to protect the workers, OSHA address to a few workplace safety rules like exits, hearing protection, fall hazard sign, bio hazard sign which will also affect the facility designs too.

Biomanufacturing protection strategies depend on attaining primary and secondary containment of hazardous process materials. What is primary containment? Primary containment is the first container in direct contact with biohazardous material as well as protection of personnel and the immediate laboratory environment from exposure to infectious agents. What is secondary containment? Secondary containment is the protection of the environment external to the laboratory from exposure to infectious materials and is provided by a combination of facility design and operational practices. Containment efforts generally fall into one of these categories: facility design, equipment, aseptic practises and techniques.

In the United States, the Centres for Disease Control and Prevention (CDC) came out with levels of biological threats which are called the biosafety level. It is a set of biocontainment precautions required to isolate dangerous biological agents in an enclosed laboratory facility. There are total of four levels. The contamination ranges from the lowest level which is biosafety level 1 (BSL-1) to the highest level biosafety level 4 (BSL-4). This level of biological threats is used to determine the minimum protective features necessary for the degree of the hazard.

Biosafety level 1: This is the lowest of the four, BSL-1 applies to laboratory settings in which personnel work with low-risk microbes that pose little to no

threat of infection in healthy adults. The practises, safety equipment, facility design and construction at this level are appropriate for undergraduates and secondary education training and teaching laboratories.

Biosafety level 2: This biosafety level covers laboratories that work with agents associated with human diseases (i. e. pathogenic or infections organisms) that pose a moderate health hazard. The practises, safety equipment, facility design and construction at this level are applicable to clinical, diagnostic, teaching or other laboratories where work is performed with moderate-risk agents that might cause human disease of varying severity.

Biosafety level 3: BSL-3 laboratory typically includes work on microbes that are either indigenous or exotic, and can cause serious or potentially lethal disease through inhalation. The practises, safety equipment, facility design and construction at this level applicable to clinical, diagnostic, teaching, research, or production facilities in which works are done with agents that post a potential for respiratory transmission which may cause lethal infections.

Biosafety level 4: As the highest level of biological safety, a BSL-4 lab consists of work with highly dangerous and exotic microbes. The practises, safety equipment, facility design and construction at this level are applicable for work with extreme dangerous agents that could probably cause life-threatening diseases or might be transmitted through the aerosol route.

Qualifications

Facilities Qualifications:

Facilities Qualification validates the overall manufacturing / testing / production environment. The requirement is as usual driven from the product processes. Where the product process calls for specific room condition, as defined in ISO 14644 and was in FS209E, the engineers must design the respective process area to enable these conditions to be achieved and maintained.

Equipment Qualifications:

Equipment qualification or validation as required by the FDA, requires verification documentation to start with the Validation Master Plan (VMP) and flow through a series of documents that define the scope and tasks required to successfully execute your equipment validation task. Under equipment qualifications, there are three qualifications: Installation Qualification (IQ), Operation Qualification (OQ), Performance Qualifications (PQ). With these three qualifications, there is a degree of flexibility as regard to the content of these documents.

Ø Installation Qualification (IQ). This term is associated with equipment. It is conducted according to an approved installation qualification protocol or plan. IQ is defined by FDA as establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’s approved specification and that the recommendations of the supplier of the equipment are suitably considered. IQ is a verification of alignment with design specifications

Ø Operation Qualification (OQ). This term is associated with equipment too. It is performed to verify operation within specified parameters like temperature, pressure etc. OQ should be accomplished by established and approved protocol that describes all aspects of the testing of the equipment in detail. OQ can be defined as the compilation of pragmatic evidence that a process can consistently produce regulatory controlled product to within predetermined specifications. OQ is a verification of alignment with functional specifications

Ø Performance Qualification (PQ). PQ should be accomplished by an established and approved protocol that describes the acceptance criteria to be met to successfully accomplish the performance qualifications. Performance Qualifications are a collection of test cases used to verify that a system performs as expected under simulated real-world conditions.

Validations for facilities, equipment and utilities:

FDA Definition:

“ Validation is a process of demonstrating, through documented evidence, that a process, procedure, method, piece of equipment, or facility will consistently produce a product or result that meets predetermined specifications and quality attributes.”

For a new or upgraded facility, commissioning and facility validation is the foundation for assuring success in further manufacturing process validation. Before manufacturing process is validated, an approved facility, utilities and the equipment to support its manufacturing operations have to be in place.

Stages of qualification/validation:

Qualifications stages begin with the facility design, equipment design or the process then progress to the ability of it to produce a product meeting the predetermined product specifications. After completion of the required qualifications or validations stage for equipment/system “ cements” that equipment or operation in a validated state. Re-validation might be required if there is any changes to equipment or operation.

Project team. First step of establishing a project is to form a project team with decent skills that are suitable for the project. The choosing of representative from each group in a organisations will based on the project scope, resource equipment and key stakeholder. Stakeholder can mean a stall with process, validation or engineering. To make sure that project is going according to the initial plan, communication, planning and coordination between team mates are important.

Risk assessment (Impact assessment). A risk analysis or risk assessment will be conducted once the design qualifications are done. Risk assessment is the most important tools to determine the amount of validation required. As mention in the risk assessment section, the level of commissioning and qualification needed is determine by the function of the facility, equipment or utility.

Validation planning. Organisations must define an approach towards validation like what is to be validated, how is it to be validated, who is to validate it, who is to approve the validation, when it must be revalidated. A project validation master plan (VMP) should be developed in the initial stages

to define the overall validation philosophy and methodology to be used throughout the project. This is to allow validation master or the project to plan the resources and the schedule requirement etc.

Functional area/Unit operations:

It is important for biomanufacturing companies to develop an understanding of the process as well as the product so to effectively design and operate the facility. Tools used for operational excellence and quality effort aids designer to better understand the process and characteristics. Biomanufacturing facility can be broken down into few stages:

- Cell culture
- Recovery/harvest
- Purification
- Formulation
- Fill/finish

Biomanufacturing Clean work area operation:

Controlled process and aseptic process are crucial to biomanufacturing industry. At the heart of aseptic processing is the need to keep viable particulate matter, specifically bacteria and yeast, from contaminating the product. Human are the primary source of microbes (Skin, hair), so it is important to make sure proper attire is wore, it must be the correct fitting and personal protective equipment that must be worn in a clean work area or cleanroom. Entry of people, raw materials and exit of waste are carefully controlled to reduce the entry of contaminations into the clean work area. Materials that are brought to the clean work area should be sterilized or

disinfected before entering the clean work area. As microbes and contaminated particles are moving freely in the air, the HVAC system (Heating, ventilating and air-conditioning) is designed to constantly filtering air through high efficiency particulate air filter.

Equipment/Facilities cleaning and maintenance

Cleaning and maintenance of the facilities/equipment is to prevent malfunctions which could possibly lead to contamination of the product. A written procedure for cleaning and maintenance of equipment/facilities should be established and followed strictly. Items that should be included in the written procedure:

- Cleaning and sanitizing schedules
- A detailed description of cleaning
- Protection of clean equipment
- Inspection of equipment prior to use
- Removal of previous batch identification
- Responsibility for equipment cleaning and maintenance