Overview

Engineering Unit

Biomanufacturing Engineering Requirements

A successful and productive biomanufacturing facility must meet and adhere to certain engineering requirements. The purpose of the engineering unit of this text is to introduce a number of concepts that are vital to both the achievement of the facility's overall goals and the implementation of a successful strategic plan as they relate to these particular requirements. This unit will examine the engineering requirements as they apply to facilities, metrology and validation, environmental, health and safety hazards, and operational excellence.

Biomanufacturing is similar in many ways to other manufacturing industries. In a general sense raw materials are brought into a facility (either a single building or complex of buildings) where equipment, tools, systems and methods are utilized to process those materials into a quality product as effectively, consistently, and efficiently as possible. The product is then packaged and distributed. A successful facility takes into consideration not only the physical design of the facility but also factors such as material and personnel flow; room classifications within the facility; facility security and access controls; process equipment, instrumentation, and control systems; process utility systems; facility sustainability; and process documents and drawings. The ***Facilities*** chapter examines each of these areas in detail.

Where biomanufacturing (and the manufacture of all types of pharmaceuticals) can differ from other types of manufacturing is in the stringent government regulations and quality standards that must be met to produce a safe, effective, and pure product. Government agencies such as the United States Food and Drug Administration (FDA) strictly regulate the production of all categories of pharmaceuticals. All those working in the facility must ensure that their work is performed in compliance with all applicable governmental regulations and that the facility's own quality standards are continuously adhered to. The quality group (or unit) of the facility plays an important role in ensuring adherence. Two methodologies that are essential to satisfying these quality and regulatory requirements are **Metrology** and **Validation**.

Metrology is the fundamental method by which objects and phenomena are measured, along with the means for assigning values to measurements and the certainty of these assigned values. Validation involves the practices and procedures for checking and verifying that the equipment, process, and methods used in biopharmaceutical production perform as expected. The ***Metrology*** and ***Validation*** chapters examine these methods as they relate to the government regulations and facility standards in the biomanufacturing industry.

In addition to the standards relating to a facility's end product, industrial facilities institute **Environmental, Health, and Safety (EHS/HSE/SHE)** policies and procedures to keep employees safe and healthy and reduce or eliminate workplace hazards; protect the facility, equipment, product from harm; and ensure the environment (water, air, and soil) in and around the facility are not polluted by the facility's materials, processes, and products.

Government agencies such as the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA) also enforce regulations related to workplace safety and health as well as the environment. The ***Environmental, Health, and Safety*** chapter examines the efforts and roles of both the facility and the government agencies in ensuring compliance and adherence to these regulations and guidelines.

As with all other manufacturing industries, those involved in biomanufacturing employ systems and methods to continuously evaluate and improve the manufacturing process. These efforts are typically referred to as **Operational Excellence (OE)** and play an important role in the improvement of the overall operations of any facility. Aiding in reducing waste and driving for consistency, OE is a philosophy that requires an organization to continuously strive for lean operations while concurrently adding value to both the overall business as well as the end product. OE methodology and OE-based decisions must be part of a successful biomanufacturing facility's daily operations. The ***Operational Excellence*** chapter details this philosophy and related efforts.

The Engineering Unit of this text is divided into five chapters, each addressing a specific area of importance to the overall biomanufacturing process. The remainder of this section summarizes what one should expect within each chapter.

Facilities: Chapter 2

The FDA provides general guidelines that impact the design and operation of biomanufacturing facilities. These guidelines state that buildings and facilities used to manufacture drug 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 the manufacturing process. The guidelines also require facilities to be designed to minimize potential contamination and limit exposure to microbiological contaminants.

The process of manufacturing involves taking raw materials into the facility and moving the material through various stages of processing before a product emerges. These stages in a biomanufacturing facility can include:

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

A process within a facility is typically divided into different units (groupings of equipment and tools) that are used to perform a specific step or part of the process. Utilities such as gases, water, and electricity are brought into the facility and incorporated into the process as needed. Air supply systems and filtering are crucial to operations, especially for areas that must be kept "clean," or free from contaminants. The facility and the units it contains are designed to optimize the flow of materials in the process and ensure that designated clean areas are properly controlled.

Documentation and drawings play an important role in the design, construction, and maintenance of a facility. Documents, such as Standard Operating Procedures (SOPs) and equipment specification manuals and technical drawings, such as Piping and Instrumentation Diagrams (P&IDs), can assist facilities/metrology technicians in properly and efficiently operating and maintaining the facility, its units, and equipment and tools. These can also aid teams from quality, validation, EHS, and other groups in better understanding the process and performing their jobs properly.

Metrology and Validation: Chapters 3 and 4

For the biomanufacturing industry, metrology and validation are vital to each other as well as to the manufacturing process as a whole. A key concept with metrology is traceability. Traceability means that measurement results or values of measurement standards can be related to other references, such as established national and international standards, in an unbroken "chain" of measurements. The results can be compared to other measurements from previous time periods, locations, or situations. Traceability is vital for ensuring regulatory compliance and that quality standards are consistently met. Traceability can be achieved through calibration, a process where a measuring instrument's value is compared to an established measurement standard.

Traceability and calibration play key roles in validation efforts and the overall quality management system. The FDA, the primary regulator of drug and biologic products marketed in the United States, has defined a number of important terms for the pharmaceutical and biopharmaceutical industry, including validation:

> The process of *demonstrating*, through *documented evidence*, that a process, procedure, piece of equipment, analytical method, or facility will *consistently* produce a product or result that meets *predetermined* specifications and quality attributes.

Therefore, biomanufacturing organizations must prove that their production process will consistently create a product that meets all of the specifications or quality attributes that have been established for that product. To do so organizations must ensure the following:

- facility, equipment, and utilities perform properly
- analytical methods used in the quality control laboratory are performed properly
- each step of the production process contributes to a final product that meets all of the quality attributes and specifications

Validation is an independent check on the performance of a system and ultimately the entire manufacturing process. If each step in the process is performed properly, the entire process should produce a product that meets predetermined specifications. If not, there is a step in the production process which is not adequately understood or is not performing properly.

Environmental, Health, and Safety (EHS): Chapter 5

Employees in a biomanufacturing facility can be exposed to a variety of hazards as they perform their daily tasks. Hazards are actions, materials, or situations that can harm or kill people, destroy products, equipment, buildings; threaten a nearby community; andor impact the environment. Risk assessment and management, as discussed in operational excellence, is also a key tool in evaluating the safety profile of a workplace and identifying potential hazards.

Facilities will have an Environmental, Health, and Safety program in place to eliminate or reduce these hazards. Potential hazards fall into one of the following generally-recognized categories:

- physical: environmental factors such as temperature, pressure, noise, trips and falls, electricity, etc.
- chemical: substances in either a solid, liquid, or gas form that can cause health problems, death, and environmental pollution (e.g., acids, solvents, and cleaning agents)
- biological: living or dead organisms that can cause health problems, death, and or environmental pollution (e.g., bacteria, viruses, allergens, and toxins)
- ergonomic: stresses created on the human body by repetitive tasks, improperly designed or adjusted workspaces, incorrect use of tools and equipment, etc.

Because of the sensitive nature of biomanufacturing, physical and cyber security measures are used to protect the process and products from industrial espionage, terrorism, etc. Physical security includes restricted access to the facility, areas and rooms; video monitoring; employee login/logout; and other such procedures as deemed necessary by the facility. Cyber security involves hardware/software security (e.g., firewalls and biometric readers such as thumbprint ID), restricted Internet access, password protection, and other similar measures.

An EHS program employs various types of controls to create and maintain a safe, healthy, and environmentally sound workplace. These include:

- elimination of the hazard by design or substitution (e.g., implementing a closed process to prevent worker exposure to hazards or choosing a safer cleaning agent over another)
- engineering controls (e.g., erecting barriers around hazards or installing ventilation in areas where fumes are present)
- administrative controls (e.g., protective practices and techniques such as hearing protection programs, safety training, and ergonomic practices)
- Personal Protective Equipment (PPE) (e.g., gloves, safety goggles, face shields, lab coats, hard hats, respirators, and non-skid footwear)

In the United States, OSHA promotes and enforces safety and health standards for the workplace. It can conduct inspections and investigations and propose penalties for noncompliance with standards. The EPA, on the other hand, provides research, monitoring, standard-setting, and enforcement activities to ensure environmental protection.

Operational Excellence: Chapter 6

Operational excellence efforts, which grew out of the quality movement and its approaches, play a critical role in the continuous improvement of biomanufacturing operations. Operational excellence relies on various techniques and tools to evaluate the efficiency, consistency, and effectiveness of processes in a manufacturing facility.

An important concept behind operational excellence is lean manufacturing, or focusing on eliminating waste and providing quality products at a value to customers. Process controls are used to reduce variation and ensure the quality of the products produced. In a general sense, process evaluations and changes are made by:

- defining a problem and its effect
- measuring the current process performance level
- analyzing the cause of problems
- improving the process by installing permanent countermeasures
- follow-up and confirmation of the success of solutions
- controlling the improvements and ensuring previous errors are not repeated

Risk assessment and analysis is a key tool for operational excellence efforts. It involves the probability of various events (or threats) occurring and assessing the potential impact of each. Managing risk is important to the continuous improvement of a process. Failure Modes and Effects Analysis (FMEA) and Corrective Action and Preventive Action (CAPA) are examples of tools to identify and mitigate such risks.

Operational excellence within a facility creates a culture that promotes optimized, effective processes and values the company’s ongoing quality assurance/quality control programs. As a result of these programs, the facility produces products that are safe, effective, pure, and of high quality and that reflect current Good Manufacturing Practices (cGMP).