23 Bulk pharmaceutical and biopharmaceutical plant design considerations

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When designing and building a bulk pharmaceutical plant, there are many things to be considered that are different from biopharmaceutical or finished pharmaceutical facilities. In this chapter, we shall review some of the design parameters and considerations and shall contrast biopharmaceutical with bulk pharmaceutical plants.

23.1 Basis of comparison

There are basic differences, as well as many similarities, between bulk pharmaceutical and biopharmaceutical facilities. Biopharmaceuticals are microbial or mammalian cell generated products, usually manufactured in batch fermenters. Bulk pharmaceuticals may be derived from a wider variety of sources, including fermentation, organic synthesis, or extraction of naturally occurring materials. Both types of operation require multipurpose flexible processing operations, that can handle a diversity of operating steps and equipment, although biopharmaceutical processing generally is on a smaller scale. It is unusual for bioreactor systems to be larger than 2000 l, although production systems are as large as 10 000 l. Bulk manufacturing reactor systems can be as large as 35 000 l, with some bulk fermentation equipment reaching 100 000 gallons (380 000 l) in size. Both operations require supporting recovery and purification systems to take the crude reactor or fermenter product to a purified bulk stage. In some cases the bulk product is sterile, but in the large majority of cases it is not. Sterilization of the product is needed prior to packaging in the final dosage form. Because of the need for purification steps, direct support space for purification equipment and process utilities is required close to the reactor operations.

Bulk pharmaceutical and biopharmaceutical facilities are normally designed to handle multiproduct campaigns, where several batches of one product or intermediate are manufactured before cleaning the system and beginning another product. Production volumes, which are relatively small, dictate this approach to operations. Even in large bulk systems, the newer active pharmaceutical ingredients are more potent than older drugs, and thus require lower therapeutic dosages resulting in lower overall production quantities.
A bulk facility may be designed for a single product, but that product may require several dissimilar manufacturing steps before reaching the final bulk material. This also leads to campaigning of operations. A few biopharmaceutical and many bulk pharmaceutical products are manufactured in continuous systems. Continuous fermentation equipment is available for bioreactions and many types of continuous reactors are used in bulk organic synthesis and purification. The trend is away from continuous systems in bulk operations due to the reduced product quantities needed and the specialization that those systems imply. It is uneconomical to install expensive equipment that will be idle for a large percentage of the operating year. On the other hand, more continuous bioreactors are being manufactured, because the number and quantities of biopharmaceuticals are increasing.

The major points of discussion in the remainder of the chapter will be the following:

- Facility layout
- Processes and unit operations
- Equipment and piping systems
- Types of material and materials handling
- Heating, ventilation and air conditioning system (HVAC) and utilities systems
- Waste disposal and handling
- Safety considerations
- Regulatory considerations

23.2 Facility layout

23.2.1 Bulk pharmaceuticals

Bulk pharmaceutical manufacturing facilities may be as varied as the kinds of chemical reactions that they utilize. It is important to remember that a bulk plant is basically a chemical production facility, where the products happen to have an end use as a pharmaceutical. There are no ‘universal’ types of equipment arrangements that work for all processes. Some typical bulk pharmaceutical processes include fermentation and isolation of fermentation products, synthetic chemical reactions, extraction of naturally occurring materials, and microencapsulation or other physical processes. In many locations a large portion of the plant may be outdoors, with only the final product isolation, drying, and packaging in an enclosed area.

Bulk plants may utilize batch, continuous, or semi-continuous processes or possibly a combination of all three. The type of processing is generally a function of the required output of the facility, with high volume products frequently being made in a continuous system, although batch processing is also used for large product volumes. Batch plants provide versatility, allowing many different products and intermediates to be manufactured with a