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Special Challenges in Production of Biopharmaceutical Dosage Forms

Michael J. Akers

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Biopharmaceutical products are potent, reactive, unstable, and expensive. As a consequence, all aspects of their handling, identity control, processing, packaging, and storage require utmost attention, if not perfection.

When mistakes occur during one or more segments of biopharmaceutical dosage form production, companies lose precious time and spend valuable resources investigating and controlling the impact of those mistakes on good manufacturing practice (GMP) attributes including safety, identity, strength, purity, and quality.

Because the stakes for biopharmaceutical manufacturers are high, production mistakes must be minimal or absent. Yet ensuring an error-free production process is a complicated task — especially when an increased need for well-trained staff to address multiple manufacturing process issues clashes with minimal opportunities for scientific exchange of information.

Indeed, research on biopharmaceutical manufacturing is rarely addressed in scientific literature or at conferences organized by professional educational organizations. Rather, research focuses on biopharmaceutical characterization, analytical method development, preformulation, formulation development, and stability or stabilization. A primary reason for the dearth of scientific data on manufacturing is that few, if any, academic laboratories focus on research involving manufacturing of finished products at a scale relevant to industry. Moreover, equally few individuals working full time in biopharmaceutical finished-product manufacturing facilities have the interest, or more significantly the time, to write an article or teach a course on the issues and problems they face. There likely also are proprietary considerations for which manufacturers restrict their employees, particularly manufacturing employees, from publishing or presenting new information.

This article seeks to provide practical information on the challenges inherent to production of biopharmaceutical dosage forms.

PRODUCT FOCUS: STERILE BIOPHARMACEUTICAL DOSAGE FORMS

PROCESS FOCUS: MANUFACTURING, FILL AND FINISH

WHO SHOULD READ: PROCESS DEVELOPMENT AND MANUFACTURING, FORMULATION DEVELOPMENT, QA/QC

KEYWORDS: STERILITY, FILTRATION, ASEPTIC PROCESSING, LYOPHILIZATION, MIXING, FILLING. TRAINING, BEST PRACTICES

LEVEL: BASIC

SPECIAL NEEDS OF BIOPHARMACEUTICAL PRODUCTS

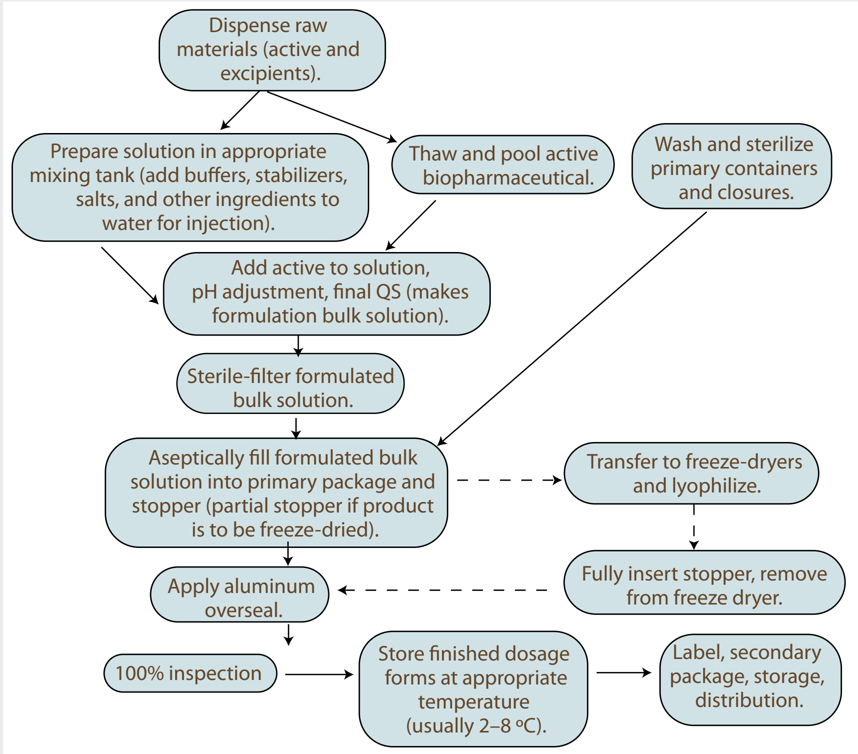
Biopharmaceutical finished dosage forms are especially difficult formulations to handle in a conventional manufacturing environment. Proteins can be sensitive to environmental and processing conditions, including temperature, mixing time and speed, order of addition of formulation components, pH adjustment and control, and contact time with various surfaces such as filters and tubing. The real test of compatibility between a biopharmaceutical and its process occurs during actual experimental batch preparations that precede process validation batch studies. Typically, it is hoped that conductance of scale-up studies will find few or no problems, making them confirmation-type rather than true exploratory studies to carefully evaluate the effects of processing variables on biopharmaceutical product activity, stability, and overall quality.

Each biopharmaceutical molecule and its final formulation must be evaluated for compatibility with production environmental conditions, processing steps, and equipment. But the industry has learned several precautionary "rules of thumb" over the years that will aid in assuring successful production with minimal problems.

The processes required for preparing sterile products constitute a series of events beginning with the procurement of approved raw materials (e.g., drugs, excipients, vehicles) and primary packaging components (e.g., containers, closures) and ending with a sterile product sealed in its dispensing package. Unit processes involved in manufacturing finished sterile dosage forms include compounding and mixing, filtration, filling, lyophilization (freeze-drying), closing and sealing, sorting and inspection, labeling, and final packaging for distribution.

Figure 1 presents a schematic overview of the entire manufacturing process for solution and lyophilized dosage forms. Each step must be controlled carefully to ensure product quality, particularly for relatively unstable and interactive biopharmaceuticals. Each process should be validated to ensure that it is accomplishing what it is intended to do.

Figure 1: Processing solution and freeze-dried biopharmaceutical dosage forms



Basic Requirements for Successful Processing

The many factors that must be in place for successful production of stable and high-quality biopharmaceutical finished dosage forms include appropriate personnel, practices, and processes.

Personnel: Clearly, it is essential that personnel responsible for assigned duties be capable and qualified to perform them. This is much easier said than done, however. Although training programs at most companies are quite good, two subjective aspects of personnel training cannot be guaranteed.

First is ensuring that procedures taught are truly learned before it is too late. Although examinations can be administered, written tests typically do not cover all aspects of a procedure, and it may be possible for personnel to guess the right answers to pass an exam. Conversely, true learning can be validated with a greater deal of certainty through "hands-on" testing, when a procedure must be carried out in actual practice.

A second aspect of training is making certain that personnel actually do the right thing, even when they have learned the proper procedures. For example, operators may know the right things to do to maintain aseptic conditions, but they may not always do everything correctly all of the time. Consequently, it is as important to assess personnel attitudes as it is to evaluate their level of knowledge.

Ingredients: Strict adherence to identity control, either by performing an in-process test to verify a component or having a good documentation system for checking the certificate of analysis data, can help ensure that ingredients used in compounding a product have the required identity, quality, and purity. Quality parameters include zero to extremely low bioburden and endotoxin levels. Purity parameters include assay methods such as high-performance liquid chromatography (HPLC) or enzyme-linked immunosorbent assay (ELISA) and physical integrity checks (e.g., color, odor, and appearance of powder).

Processes and Procedures: Workable processes must be understood and followed to make products that meet potency, purity, and quality requirements. Because a production environment must be suitable for performing critical processes, the importance of matters such as orderliness, cleanliness, asepsis, and avoidance of cross-contamination cannot be stressed too highly. A number of steps are necessary to ensure that procedures are effective:

• Critical processes must be validated to ensure that equipment used and processes followed will bring about a finished product with the expected qualities.

• Adequate quality-control procedures are necessary to confirm that finished products have the required potency, purity, and quality.

• Appropriate stability evaluations can establish that drug products will retain their intended potency, purity, and quality until the determined expiration date.

• Separation of quality control from production responsibilities will encourage independent decision making.

• To prevent mix-ups, adequate conditions and procedures must be instated and enforced.

When problems occur, thorough procedures — with documentation — must be in place for investigating and correcting failures or problems in production or quality control.

Effects of Processing on Product Quality

The stability and quality of a biopharmaceutical product in a finished dosage form also can be affected by a number of processing conditions.

Agitation Rate and Duration: Shear effects (e.g., high rates of mixing) are known to cause foaming, denaturation, aggregation, or oxidation of biopharmaceuticals. Such potentially irreversible problems can be prevented through use of the proper types of mixing equipment and adherence to validated mixing procedures.

Order of Ingredient Addition: The order of mixing for ingredients may affect a product significantly, particularly in a large-scale production where attaining homogeneity requires considerable mixing time. Typical compounding problems include incomplete dissolution of sparingly soluble components, excess foaming during the mixing procedure, problems in a pH adjustment (e.g., over- or undershooting pH target, having to go back and forth), addition of components too quickly before the water-for-injection solvent has cooled, and mistakes in quantities added or order of addition.

Adjusting pH by adding an acid, even though diluted, may cause excessive local REDUCTION in a product's pH.

pH Adjustments: Adjusting pH by adding an acid, even though diluted, may cause excessive local reduction in a product's pH. In this instance, adverse effects may be produced before the acid can be dispersed throughout the entire volume of product. In addition, missing the target pH during adjustment of large volumes of product will require back-titrations with extra volume of acid or base, potentially affecting solution ionic strength. This, in turn, could affect the stability of a protein.

Filtration: Because many biopharmaceuticals are known to bind to filters, selecting the proper filter for sterilizing a finished product requires validation studies to assure product–filter compatibility. That includes ensuring that a drug does not bind to a filter and that it does not cause filter leachables. Potential problems can be prevented or minimized once understood through experimentation with alternative filter material choices or by predicting the amount of solution to be passed through a filter to saturate the binding sites.

Filtration and Filling Conditions: Rates of filtration and filling, if not controlled properly, could lead to adverse shear effects on a biopharmaceutical. Although examples of this possibility are not published, rates of filtration and filling must be studied during process validation. Process tubing used in transferring product from mixing tanks to filter assemblies, holding tanks, and filling apparatuses are hydrophobic surfaces and that can cause protein aggregation.

Freeze-Drying Parameters: Biopharmaceuticals that are unstable in solution over the long-term may remain stable throughout their shelf lives in a solid state by freeze-drying (lyophilizing) the product. However, freeze-dry processing steps — including the rates of freezing and drying — may themselves cause physical and chemical instability of a biopharmaceutical. To stabilize biopharmaceuticals during lyophilization, formulation ingredients such as amorphous sugars, amino acids, or polymers, act as cryoprotectants and/or lyoprotectants. These ingredients aid in stabilizing proteins by controlling the rate of freezing or assuring that product temperatures are below the critical temperatures (e.g., glass transition temperature) during the primary drying stage.

Environmental Conditions: Controlling temperature, humidity, air (oxygen), microbial content, and processing time is critical to assuring that a biopharmaceutical remains stable during manufacturing. Often, biopharmaceutical manufacturing requires strict time limits (hours) between the time an active component is added to a solvent to the time it is filled into a final primary package and properly stored. Oxygen-sensitive proteins require minimizing the presence of oxygen by sparging the solvent with inert gases (nitrogen or argon) and overlaying the container headspace with the inert gas. Although it is impractical for processing environments to be too cold, temperatures in manufacturing rooms should be controlled in the range of 15–20 °C.

Materials Compatibility: Biopharmaceuticals are extremely interactive with surfaces of all types. They can potentially bind or interact with mixing tank stainless steel surfaces as well as polymeric surfaces of filters, tubing, and pump diaphragms. Development studies must be done to understand the degree of these interactions and to design the formulation and process to minimize them. Often, a slight excess of active ingredient is required because it is known that some active will be lost during processing through adsorption to manufacturing equipment surfaces.

Changes Over the Years

In its pursuit of CGMPs, the biopharmaceutical industry in recent years has shown initiative and innovation in extensive technological developments and improvements in quality, safety, and effectiveness of sterile dosage forms. Such innovations are largely driven by special considerations manufacturers must take to produce stable biopharmaceutical products. Examples include developments in cold-chain distribution and storage at temperatures ranging from 2 °C to 8 °C, down to –70 °C; and design and construction of modular facilities, which offer greater accuracy of equipment and robustness and improved accessibility for service and cleaning. Other improvements have occurred with containers and closures, mixing and filling processes, aseptic processing, and enhanced automation and materials.

Containers and Closures: Improvements in selection of containers and closures, as well as in their cleaning and sterilization, are helping to minimize surface interactions with potential extractables and enhance sterility assurance. This is a critical issue, given that containers and closures will be in prolonged, intimate contact with the product and may release substances into or remove ingredients from it. Rubber closures can be especially problematic (leading to problems with sorption, leachables, or air and moisture transmission) if improperly evaluated for compatibility with a final product. Careful assessment and selection of containers and closures are essential for final product formulation to ensure that a product retains its purity, potency, and quality during the intimate contact with the container throughout its shelf life. Moreover, use of containers and closures with minimal or no siliconization can minimize or eliminate potential hydrophobic surface interactions with sensitive biopharmaceuticals.

Mixing and Filling: Improved mixing and filling technologies also are helping to increase quality assurance. Advanced mixing technologies allow for efficient compounding of a final solution while minimizing shear effects that could produce foaming of the product
and/or surface denaturation of the biomolecule. Meanwhile, fast and efficient filling technologies (up to 500 units filled per minute) increase speed, but remain gentle on the product to minimize shear effects.

Aseptic Processing: The surge of potentially heat-labile products from biotechnology and an inability to terminally sterilize them has accelerated development of barrier–isolator technology. When perfected, such technology — which helps control the environment with respect to temperature, humidity and, if necessary, anaerobics — enables the processing of protein and peptide solutions to occur under a much higher degree of sterility assurance than is now achievable with conventional aseptic processing. The main features of barrier–isolator technology are its abilities to sterilize, not just sanitize, environments to which sterile solutions are exposed during filling and stoppering and to remove direct human contact with exposed sterile solutions.

Automated Processes, Disposable Materials: The biopharmaceutical industry has made myriad other improvements to streamline production and improve quality assurance.

• Freeze-drying technologies, including automated loading and unloading, may minimize potential

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for inadvertent contamination of the product.

• Controlling particulate matter can be assured through the combination of valid cleaning procedures, dedicated equipment, tight control of air-handling systems, excellent training in aseptic techniques, and automated or semiautomated visual inspection machines.

• Weight checking, inspection technologies, and labeling and finishing operations also are being automated.

• The use of disposable materials helps reduce risk of cross-contamination and the need for cleaning validation. Although still in its infancy, this technology is likely to become state-of-the-art, particularly for product mixing and holding.

Ensuring Best Practices

All scientists, engineers, and manufacturing and quality personnel must be aware of the various issues involved in the manufacturing arena that can affect the stability and quality of biopharmaceutical products. Among the more relevant areas of concern are shear rate and stress during compounding, filtration, and filling; adsorption onto process tubing and filter surfaces; and the effects of time and temperature during each step of a manufacturing process.

It is beyond the scope of this article to compare the properties of various well-known therapeutic proteins and other biologicals, given that no two biopharmaceutical active ingredients are alike with respect to stability, compatibility, and reactivity properties. Some proteins are extremely unstable and incompatible, whereas others are relatively stable and nonreactive. Consequently, I've presented a "worst-case scenario" approach to addressing major potential problems in handling and processing biopharmaceuticals in a large-scale manufacturing environment.

Obviously, each biopharmaceutical active ingredient must be well characterized during product and process development for its physical and chemical properties, including all factors that affect potency and stability. "Quality by design" is the best practice for building a foundation that ensures production of high-quality biopharmaceutical finished dosage forms.

To that end, formulation scientists and process engineers must work together to design and implement experiments that help them determine processing effects on protein stability and establish an appropriate control strategy. Subsequently, production management, operators, and maintenance staff along with quality control and quality assurance experts must work together to follow the proper and correct procedures for producing top-quality biopharmaceutical finished products.

Michael J. Akers, *PhD, is senior director, Pharmaceutical Research and Development, Baxter BioPharma Solutions, Bloomington, PO Box 3068, 1-812-355-7188.*