

CHALLENGES AND SOLUTIONS IN BIOLOGICS PRODUCT MANUFACTURING

Source: Singota Solutions

Singota® Solutions is a CDMO located in Bloomington, Indiana, USA that specializes in Parenteral, Early Phase Drug Development and Aseptic Filling projects.



Development of biologic therapies can present a number of unique challenges for formulation scientists and process engineers. Unlike many small molecule products, most biologics require a parenteral route of administration. Formulators therefore must develop a suitable means to deliver the product via injection which entails addressing a variety of potentially complex challenges related to the unique properties of the biologic substance being delivered. Issues such as the stability of the biologic material in a solution state must be considered along with the overall practicality of a formulation in terms of manufacturing, storage, transport, and administration.

While it may be possible to develop a formulation that meets the desired finished product characteristics using laboratory techniques, it is imperative that each formulation is carefully evaluated to confirm it is practical for industrial-scale manufacture.

A significant number of new biopharmaceuticals currently are the product of innovation at small to medium-sized biopharmaceutical companies. Many such firms are virtual in the sense that they rely on third parties to carry out the production of clinical trial materials. Frequently, these companies will have in-house staff that are experts in drug discovery and perhaps are able to meet the need for formulated products to support pre-clinical activities. However, many if not most will rely on third-party contract manufacturing organizations to carry out GMP manufacturing of their clinical supplies of finished products.

A typical starting point for outsourcing would be for the sponsor to select a CMO based on an assessment of capabilities relevant to the production of the type of product needed. Once a CMO is selected, it is then necessary to begin the transfer of the formulation technology developed during pre-clinical activities to the manufacturing organization.

In some instances, the pre-clinical formulation may be deemed inappropriate for scale-up either because it is impractical for larger scale production or because it would be unsuitable for human administration. In these cases, selection of a CMO that offers formulation development capabilities (a CDMO) would be a logical choice. Conducting formulation development within the same organization that will eventually be responsible for scale-up and GMP manufacture (as opposed to relying on a stand-alone development laboratory) helps ensure that the formulation selected is scalable and suitable with existing manufacturing techniques/equipment.

The process of assessing whether a formulation is ready for scale-up can be a critical step that determines the ultimate success or failure of initial plant-scale production activities.

Many issues faced by manufacturers of Phase I clinical supplies can be traced to an inadequate understanding of the manufacturing process and failure to take into account challenges associated with scale.

The main challenges associated with scale-up and manufacture of the first clinical supplies of an aseptic drug product can be thought of as falling into one of three categories: formulation, fill/finish, or post-production.

Formulation:

As previously noted, many drug discovery companies approach their first GMP production with a formulation that was initially developed to support pre-clinical activities. As such, they usually have at least a basic manufacturing process suitable for lab-scale production of small batches of finished product. It is usually preferable to maintain the same formulation when the drug proceeds to the initial Phase I study in humans such that the same concentration, excipients, diluent, and so forth are used. This approach lessens the chance that a change in formulation might alter the performance of the active biologic in human subjects compared to results derived in animal studies.

A CMO/CDMO will typically be provided a process description that details formulation components and compounding techniques that were used to generate pre-clinical supplies. From this point forward, the manufacturing organization must evaluate the formulation and manufacturing process to determine whether it is feasible for direct scale-up or if changes are required. Generally, addition or substitution of different formulation components would not be considered in order to avoid altering the properties of the final formulation. The manufacturer would typically conduct laboratory scale trials of the pre-clinical compounding procedure to confirm that the process is amenable to plant-scale manufacturing.

Variables that may be assessed include:

- Order of addition – the sequence of introducing the vehicle/solvent (e.g. water), active ingredient, and excipients (e.g. buffering agents, cosolvents, surfactants, bulking agents, thickening agents) to the formulation
- Mixing – speed, time, mixer type/geometry
- Formulation stability – is the formulated product sufficiently stable during manufacture (e.g. thermal stability, sensitivity to manufacturing atmosphere (oxygen, peroxide, light, etc.))
- Materials/equipment compatibility – how does the formulation interact with manufacturing equipment surfaces (e.g. stainless steel, silicone tubing, polyethylene, glass)

- In-process control analysis – sampling and analytical procedures to ensure the formulation meets required parameters prior to subsequent activities (filtration/filling, intermediate assay, pH, etc.)
- Sterilization technology – is the formulation a candidate for terminal sterilization (e.g. heat or irradiation) and if not, what type of sterilizing filter is compatible with the formulation

Many biologic formulations are simple solutions that require only a rudimentary set of instructions for the addition of formulation components and mixing. Assessment of this type of process is typically straightforward and requires minimal laboratory effort to arrive at a definitive process description that can be translated into a manufacturing batch record. However, certain biologics can require elaborate multi-step formulation processes including chromatography, ultra-filtration, and a myriad of other techniques. In the case of such complex formulation techniques, the transfer of technology from the development lab to the manufacturing facility usually entails an elaborate, multi-stage effort that may include several intermediate scale trials prior to initiation of GMP production.

In some cases, especially when working with a formulation that requires highly specialized techniques and/or equipment, it may be preferable to conduct the final formulation process of the bulk solution at the same facility that manufactured the active ingredient and shipping this formulated bulk material to the drug product facility in a ready-to-fill state. Advantages of this approach include a significant reduction in the efforts associated with both the formulation process as well as eliminating or reducing the need to transfer certain analytical methods. In some cases, formulated bulk solution may be more stable than the isolated biologic material due to the presence of stabilizing agents in the formulation, and therefore formulating at the time the biologic is initially isolated in the bulk active facility may be advantageous. Disadvantages of this approach could include changes in the physical properties of your bulk solution. Shipping the bulk solution and potentially exposing it to environmental conditions and/or increasing the time between formulation and filling can cause agglomeration of biological formulations. Agglomeration or denaturing of the biological ingredient can significantly impact the intended performance of the formulation or impact its ability for downstream processing (e.g. filtration). Understanding the shipping lanes of your bulk solution could be as important as the solution itself.

Fill/Finish:

Once a final formulation is established, it is necessary for the finished dosage manufacturer to begin to establish a process to dispense the formulated bulk to individual containers and to determine the proper components of the container closure system. Biologics may present unique challenges not typically encountered with small molecules. Careful consideration should be given to the way the active ingredient responds to the conditions it will encounter during fill/finish activities.

Biologics can be particularly sensitive to stresses associated with dispensing. Shear forces, thermal stress, and oxidation resulting from exposure to oxygen or common decontamination agents such as hydrogen peroxide should all be evaluated before finalizing a finished product manufacturing process.

Heat-sensitivity: Large molecules can be particularly prone to thermal degradation through denaturing or unfolding. Determining sensitivity of a product to elevated temperatures will allow the manufacturer to select appropriate measures to protect the product during the proposed manufacturing process. It is common for biologics such as antibodies or proteins to be stored below room temperature (either refrigerated or frozen). The manufacturer must determine whether the formulation can withstand temperatures it is likely to encounter in the manufacturing environment (typically controlled room temperature) over the timeframe required to manufacture and inspect. In some cases, it may be necessary to hold the sterile bulk formulated batch in refrigerated reservoir upstream of the dispensing pump in order to avoid prolonged exposure to higher temperatures. Similarly, it may be necessary to specify that sealed containers be moved promptly to refrigerated storage rather than being held at room temperature for an extended time following filling.

It should be relatively straightforward to assess temperature sensitivity through a laboratory evaluation whereby the formulated bulk is held for a specified time under simulated manufacturing conditions, sampled, and tested to determine if the material has been adversely impacted. Such assessment should take into account the anticipated maximum amount of time required from the point the active is introduced to the formulation process to the time the batch is completely filled and transferred to refrigerated storage. The assessment should also consider the time necessary to conduct the required visual inspection of the finished product. It is also important in this type of assessment to account for potential manufacturing delays in determining appropriate processing conditions.



Data that extends the processing window will give assurance that the formulation has not been impacted, should a delay or an unforeseen event occur.

Oxidation: Biologic materials may exhibit extreme sensitivity to oxidizing agents and therefore when developing a finished product process, it is necessary to assess the impact that exposure to the manufacturing atmosphere may have on the formulation. The two most obvious sources of oxidation potential are atmospheric oxygen and the sanitization agents used to clean and disinfect manufacturing equipment.

Oxygen is obviously ubiquitous in any manufacturing environment and it would be difficult if not impossible to render a manufacturing room or isolator oxygen-free. However, techniques may be employed to render the headspace inside a vial, syringe, or cartridge essentially free of oxygen by either backfilling any headspace with an inert gas such as nitrogen or reducing the headspace volume by adjusting fill volume and proper placement of closures (e.g. the plunger in a pre-filled syringe). It is typically straightforward to determine whether oxygen poses a threat to the finished product and to develop appropriate means to overcome this issue provided the manufacturing equipment employed can perform a gas overlay when necessary.

Sanitizing Agents: The aseptic fill/finish industry has been moving away from traditional cleanroom facilities over the last decade and has adopted isolator technology in a successful bid to improve sterility assurance. While isolators have significantly enhanced manufacturers' ability to establish clean (Grade A/ISO 5) manufacturing environments for the manufacture of sterile products, such isolator technology has introduced an additional challenge that must be considered when manufacturing products that are prone to oxidation.

Isolator-based manufacturing lines are typically sanitized immediately prior to use by exposure of the isolator interiors to a sterilant gas, typically vaporized hydrogen peroxide (VHP). VHP is highly effective in killing microorganisms but is a strong oxidizing agent that can react with many products both small and large molecule alike. For this reason, it is imperative that manufacturers be able to effectively remove the sterilant gas from their isolators once a sanitization cycle is complete. Most, but not all, modern isolator systems are able to achieve residual peroxide levels on the order of one part per million, which is usually below a level that would be of concern from a product quality standpoint. It is prudent, however, to be able to assess the degree to which any individual formulation is susceptible to peroxide degradation in a laboratory setting prior to introducing that product to a manufacturing setting involving the use of peroxide sterilant gas.

In rare cases, it may be necessary to employ additional measures to achieve sub ppm levels of peroxide when working with exceptionally sensitive molecules. **Shear Sensitivity:** Some biologic materials and certain types of formulations are especially prone to damage from shear forces that result from dispensing through certain types of pumps. For this reason, it is generally preferable to use a mixing method during formulation to achieve the desired homogeneity properties without causing stress on the active ingredient. Additionally, a dispensing method must be selected to fill containers that imparts as little shear force on a formulation as possible. The most common dispensing method for biologic finished dosage form production is the peristaltic pump since they generate relatively low shear force. However, it remains necessary to specify appropriate pump settings to ensure that the formulation is not adversely impacted by the filling process.

Parameters that should be considered before finalizing a manufacturing process for dispensing include tubing type (e.g. material of construction, inner diameter, wall thickness), roller speed, stroke length, occlusion setting, occlusion geometry, and drawback if necessary. These settings may be determined in a laboratory setting using the same type of pump that will be used during manufacture or on the actual production filling line in advance of GMP production.



Once settings have been determined, samples of the formulation should be dispensed and then analyzed to confirm that the properties of the product have not been altered by the dispensing process. In addition to addressing shear concerns, the pump study should also confirm that the proposed pump parameters achieve the desired dose accuracy and precision, which will save time and product during manufacturing by avoiding in-process pump adjustments and recalibrations. When possible, it is advisable to utilize filling technology that includes a feedback loop between the filling line's weight check load cell and the dispensing pump such that automatic adjustments can be made with minimal line stoppage or operator intervention.

Post Production:

Following completion of the fill/finish part of a biologic product batch manufacturing process, there are several steps that must be carried out before a product is ready to administer to patients. These activities include inspection, analytical/microbiological release testing, labeling, packaging, and transport.

Inspection: Regulatory guidelines require that all injectable products undergo a thorough inspection before release. Such inspection may be performed visually or by automated inspection equipment. In either case, it is necessary to develop an appropriate inspection regimen that is capable of detecting defects. Such defects may be obvious and include damaged glass (cracks, chips, etc.), defective seals, or visible particulate matter. Other defects may be more difficult to detect. Certain biologic materials may exhibit subtle light-scattering properties known as opalescence which can complicate the inspection process by giving the illusion of the presence of particulate matter. Because some biologic materials tend to form agglomerates during manufacturing and/or storage, it is important to understand whether this property is an issue with any given product and account for it in the development of inspection criteria, which in turn are used to train visual inspectors or program automated inspection equipment.

When employing visual inspection techniques, training operators to recognize both standard and product-specific characteristics is of paramount importance. Insufficient understanding of product characteristics and/or inadequate training of inspectors can give rise to poor inspection results by either missing true rejects or rejecting product unnecessarily.

An additional challenge presented by some biologic products is their extreme temperature sensitivity. In cases where the product must be refrigerated or frozen promptly upon completion of filling, it is necessary for the manufacturer to develop a detailed plan to coordinate filling and inspection activities in order to avoid exceeding temperature control parameters.

Release Testing: As with all GMP products, biologics are required to undergo a rigorous regimen of release testing at the conclusion of manufacturing. Requirements will vary from product to product but generally will include certain specialized assays in addition to mandated compendial tests required of all injectable formulations.

A key consideration for temperature-sensitive products is the coordination of sampling activities with the production process such that test samples are handled in a manner that is consistent with the bulk of the batch. This means they remain representative in all respects despite being separated physically from the main portion of the batch destined for patient administration.

Labeling: Labeling a biologic is typically no different than labeling any other injectable product. Although, in the case of cold-chain products, it is important to select label materials that will be able to withstand low-temperature storage. In the case of products that will be stored in a frozen state, it is normally desirable to subject finished product to as few freeze/thaw cycles as possible.

Ideally, labeling should occur promptly after the completion of inspection and prior to transfer to frozen storage. Determining how a product reacts to freeze/thaw cycles is an important part of the pre-manufacturing development process.

Packaging: As with labeling, the requirements for packaging a biologic product do not typically differ significantly from those of other injectables. For clinical trial materials, it is often the case that labeled vials, syringes, or cartridges will be stored in bulk and only assembled into secondary packaging (e.g. cartons) as needed to support a particular clinical trial. This strategy will help reduce the overall storage space needed and may be particularly helpful in the case of frozen or refrigerated products where storage space tends to be more limited than in the case of controlled room temperature warehousing.

Transport: Biologics can be particularly sensitive to certain conditions they may encounter during shipping. Temperature excursions, vibration/shock, and atmospheric pressure changes all have the potential to adversely impact finished product by causing changes to the biologic material itself or by jeopardizing container closure integrity. For this reason, it is important to evaluate the propensity of any finished product to be impacted by shipping and to devise a plan to protect the product while in transit.

In the case of clinical trial materials, it is often most expedient to elect to ship finished product via one of several "white glove" services whereby a dedicated courier picks up a shipment and transports it in a temperature-controlled truck to its final destination. Where overseas shipment is necessary, similar services are available to shepherd a shipment through transit and customs clearance. Use of carefully engineered temperature-controlled shipping containers is usually the best choice for air transit.

In order to guarantee that a particular product shipment has been handled properly, shippers will ordinarily include temperature and shock sensors inside the packaging. The shipping and receiving facilities should agree in advance on a protocol to cover the retrieval of the monitoring devices.

Prior to submission of a Biologics License Application (BLA), it is necessary to conduct a shipping simulation study to demonstrate to regulatory agencies that the proposed shipping mode will not adversely impact the finished product. To satisfy this requirement, product sponsors will carry out an extensive study to simulate the conditions a product will encounter in transit. Such studies will include an evaluation of temperature, vibration, shock, and pressure changes over a worst-case period of time in order to confirm that the proposed shipping protocol is appropriate.

Conclusion:

Biologic products present unique challenges for sterile injectable manufacturers and it is imperative that the many unique properties of each product be evaluated before initiating production activities. Choosing an organization that has the right infrastructure and most importantly the right experience to anticipate and overcome issues any given product may present is of paramount importance. The cost, both financial and time-related, is such that sponsors of new biologic products cannot afford to take chances when it comes to designing a finished product process and selecting a capable and experienced manufacturing organization to produce their clinical trial supplies of injectable products.

Singota Solutions is a US based CDMO in Bloomington, Indiana. Singota specializes in formulation development and aseptic fill finish for injectable projects. Once a formulation is established, Singota utilizes state of the art robotic filling technology and focuses on smaller batch size requirements. For more information, visit Singota.com to explore how Singota has established itself as a one-stop solution for all your developmental needs.

Contact solutions@singota.com to schedule a meeting with our business development team to further discuss your current or future projects.