

APPROACH TO SIMPLIFYING ASEPTIC CONTRACT 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.

Anyone responsible for the management of the supply chain to support a pharmaceutical or biologic clinical trial can appreciate the challenges associated with an unexpected or otherwise urgent need to produce clinical drug product. Many factors can conspire to make a rapid response to such an urgent supply situation challenging. From a need to transfer sometimes complex manufacturing processes and test methods to availability of specific manufacturing components, it can be a daunting problem to identify, select, and engage a CMO/CDMO willing and able to meet the myriad of challenges. What measures then can a CMO take to help its clients respond when time is of the essence?

This article is the first in a series that describes some of the challenges and solutions available to pharmaceutical/biotech companies and their supply chain partners in the CDMO realm to ensure that critical clinical supply materials are ready when they are needed and how one CDMO, Singota Solutions, has positioned itself to meet these challenges.

Numerous factors contribute to the ability of a CDMO to mobilize resources in order to produce clinical materials in a timely and efficient manner. In a broad sense, these might fall into three general categories:

1. Items within the control of the NDA/BLA sponsor (the pharma/biotech company)
2. Items outside the control of either party
3. Items within the control of the CDMO

Let's briefly consider each category.

Items within the control of the NDA/BLA sponsor:

These factors might include the supply of the API/bulk biologic material, knowledge of the dosage form (for example the amount and tolerance per dose, exact route of administration) and frequently, but not always, technical details needed to support manufacturing (for example the formulation components/procedure and test methods). A sponsor will often know exactly what they need and how to make it although they may also rely on a CDMO to develop some or all the required know-how. For the purposes of this article, we will focus mainly on technology transfer situations rather than development activities. Whether developed by the customer or the CDMO (or perhaps a third-party laboratory), this includes the technology required to enable a CMO to successfully manufacture a product for its client.

Factors outside the control of either the sponsor or the CDMO:

These items are many, varied, and may depend on the nature of the product involved.

Examples could include availability of excipients and other manufacturing materials or ancillary supplies, and regulatory approvals (beyond FDA, these might encompass environmental and other governmental authorizations such as import/export permits if overseas shipments are involved). While neither party may have direct control over these factors, it is important that both work towards understanding what they may be and anticipate the impact they could have on the success of a project, especially the timeline.

Items within the control of the CDMO:

While a CDMO may rely on its client to provide product-specific information and supplies as outlined above, they are largely in control of many other factors that will influence the outcome of any project. Factors within the control of the CDMO include:

- Equipment (e.g. properly designed, maintained, and qualified manufacturing and related equipment)
- Schedule
- Personnel
- Quality systems
- Supply chain (e.g. readily available quantities of pre-qualified materials)

Singota has demonstrated capabilities that optimize their services which provide their clients the ability to meet urgent needs for clinical supplies of aseptic drug product.

Manufacturing Technology

When selecting the aseptic manufacturing system Singota would install for aseptic fill/finish operations, the team assessed several technologies. From the outset, it was obvious that whatever filling equipment was chosen, it would be important to employ state-of-the-art isolator technology rather than traditional cleanroom or RABS systems since isolators have become the industry standard for aseptic manufacturing.

The products Singota handles typically involve exceptionally valuable active ingredients whether they are of synthetic or biologic origin. As such, Singota needed to ensure that its aseptic filling line provided the utmost capability in sterility assurance.

Further, since most of Singota's projects are aimed at either clinical supplies or niche, high-value/low-volume therapeutics, it was obvious that selection of a distinct filling technology was key. For Singota, the technology needed to provide repeatability, limit line loss, and emphasize precision over speed.

While there are many choices for high-speed parenteral filling lines, there are significantly fewer choices for equipment specifically designed to fill smaller batches where line losses are minimized, and precision and security of the batch are maximized.

Finally, because of its CDMO role and focus on clinical manufacturing, it was important to Singota to select a technology that provided as much flexibility in terms of dosage size and form (e.g. vial, syringe, cartridge) as possible without compromising other important attributes.

After an extensive assessment of the available options, Singota selected the Vanrx SA25 system. This fully integrated manufacturing technology incorporates state-of-the-art gloveless isolator technology, integrated vaporized hydrogen peroxide decontamination, a unique robotic filling system, and a fully automated control system with built-in monitoring and recording of all key system parameters.

All-in-one systems that include the filling equipment, isolator, and VHP decontamination capabilities provide a major advantage in the simplicity of operations. Rather than requiring three separate systems to be integrated and operated in concert, each with its own set of operating parameters, Singota's system is operated as a single unit with a single control system. Once the isolator is cleaned and programmed for a manufacturing run, the system operates without in-process human intervention. All major operations are carried out either by a robotic filling system or the onboard logic which controls VHP sanitization. This system ensures that each run is carried out with the utmost of precision and repeatability.

There are a limited number of activities that must be carried out by operators in the course of setup and manufacturing when using the SA25. These include:

- Programming the control system with a batch recipe (e.g. container type/size, fill volume, batch size, frequency of weight checks)
- Installation of pre-sterilized product path (e.g. sterilizing filters, transfer tubing, receiving bag, fill needle)
- Loading and unloading pre-sterilized components to load/unload carousel periodically during manufacturing

Once the system is set up and loaded, the operator ensures the system performs as expected and uses the control panel or robots to address any alarms that might occur. The system does not require in-process human intervention unless a catastrophic event occurs. Worst case scenario, only one tub of vials/syringes/cartridges is ever at risk since all other tubs are in sealed-off parts of the isolator.

The balance of the functions necessary to complete a batch of drug product is carried out by the SA25. These include:

Setup:

- VHP sanitization of isolators (one isolator with two separate chambers; load/unload carousel and filler)
- Pump calibration
- Loading of components (by an operator) into decontamination staging isolator which contains a carousel that holds tubs of pre-sterilized, nested containers and closures
- Sanitization of exterior of tubs of pre-sterilized, nested containers and closures



Manufacturing (Performed by two robots within primary isolator):

- Transfer of nested components from decontamination staging isolator to filling isolator
- Unsealing of nested components
- Vial, syringe, or cartridge filling
- Stoppering (in a separate sealed-off, attached isolator) after gas overlay, if needed
- Transfer of filled, sealed product from filling isolator to decontamination staging isolator
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Post-Manufacturing (Performed by Operator):

- Removal of tubs of filled vials/syringes/cartridges from decontamination staging isolator
- Opening/closing of viable particulate monitoring plates

The SA25 digitally records key parameters throughout the manufacturing process. Among these parameters are:

- VHP cycle performance
- Fill weight checks
- Pump calibration data/actions
- Fill/reject count
- Non-viable particulate counts

All data is stored electronically in the memory of the SA25 and following batch completion, the data may be downloaded and printed for inclusion in batch documentation. The digital data is stored in accordance with Singota's record retention policy. As required by FDA and EU guidelines, the control system is CFR Part 11 compliant. This electronic record-keeping relieves operators of much of the burden of manual record-keeping and all but eliminates the possibility of human entry errors for the parameters the machine measures and records. Additionally, this automation greatly reduces the size and complexity of batch records and hence simplifies post-manufacturing batch record review.

In summary, Singota's filling service featuring the Vanrx SA25 workcell provides its clients with a highly robust, repeatable aseptic filling process that can be ideal for virtually any clinical or small-volume therapeutic manufacturing need.

Next in this series of articles, we will discuss how Singota uses pre-sterilized manufacturing components to enhance its aseptic filling operations and how this benefits its clients.

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.