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Seasonal Vaccine Manufacturing

Baxter

Seasonal Vaccine Manufacturing: Three areas to evaluate when selecting an outsourcing partner.

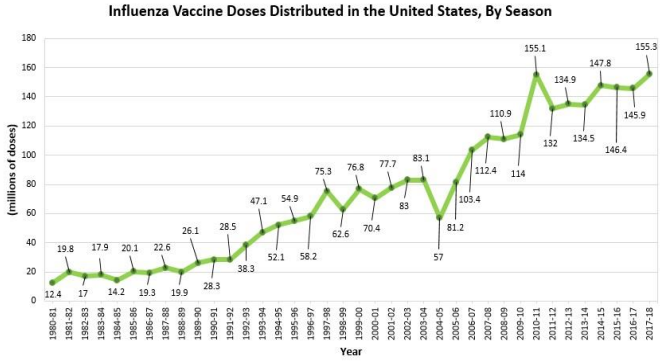
Introduction

The production of seasonal vaccines, such as those for influenza, presents unique challenges to manufacturers due to the necessary time constraints resulting from annual strain selection. The timeline for development of a seasonal influenza vaccine starts with a meeting by an FDA advisory committee in March[1] to decide which strains to include in the next season's vaccine which in turn must be produced, released, and distributed to pharmacies, clinics, and physician offices in as little as 6 months. The limited time span from strain selection to distribution requires most vaccine producers to rely on outsourcing partners to ensure timely production and supply.

Figure 1. Automated Plunger Rod insertion in Filled PFS units.

Source: Baxter Corporate Photo Library

Table 1. Taken from Reference 1.



The seasonal influenza vaccine market is projected to reach more than $4 Billion USD by the end of 2022[2]. It is a safe assumption that as demand for seasonal influenza vaccines increases, so too will the demand for contract manufacturing organizations (CMOs) to support its production.

Improvement

While service directories are filled with CMOs claiming vaccine fill-finish experience[3], the logistical challenges resulting from seasonal product are unique and it is important that outsourcing partners can ensure quality and on-time delivery.

Figure 3. Automated Syringe Inspection, Labelling and Packaging Lines can process 300 units per minute.

Source: Baxter Corporate Photo Library

What should sponsors look for when evaluating contract manufacturing services for a new seasonal vaccine program? Experienced outsourcing partners will have the right facility and technical capabilities, a culture of speed and execution, and shared expectations and commitment to continuous improvement.

Right Facility and Technical Capabilities

To ensure technical success without surprises, sponsors of seasonal vaccines programs should evaluate the experience of potential partners in the production of pre-filled syringe (PFS) products, vaccines and suspensions. The ideal CMO will have product development experience, will have worked with product owners to understand vaccine product's critical quality attributes (CQAs), and will be able to readily identify the critical process parameters (CPPs) within their control that may impact the CQAs. Examples of potential CPPs for vaccine production include recirculation, pumping mechanism, and temperature control. Suspension products may require intermittent or constant recirculation to ensure homogeneity of product potency throughout the filling process and an experienced CMO will have the experience to make a recommendation of recirculation parameters and mixing speed of the tank to ensure adequate dispersion of suspended solids. The CMO should have performed studies to understand the impact of mixing speed and solution level on the acceptability of the suspension remaining near the end of the filling process. Prior proficiency in monitoring in-process homogeneity of filled units within the production process using turbidimetric and spectroscopic techniques will ensure that mixing and recirculation processes can be optimized.

The production equipment available at the CMO can impact product quality. PFS filling lines were historically equipped with rotary piston pumps capable of filling up to 500 units per minute. Over the past decade, concern around sheer stress resulting in protein aggregation has led to in an increase in utilization of peristaltic pumps for biologic

products. Generally, piston pumps offer greater accuracy and speed, but advances in peristaltic pump head design, drive motors, and calibration algorithms have narrowed differences in performance for all but the most viscous formulations.[4] Efficiency and throughput are critical for seasonal vaccine manufacturing and in most cases are suitable for lines equipped with rotary piston pumps, but the availability of alternative fill mechanisms may be beneficial if development studies indicate that shear stress impacts product quality.

Figure 4. Syringes in Blister Packages awaiting sealing on the automated packaging line.

Source: Baxter Corporate Photo Library

A strong track record in aseptic production is critical to reduce risk of contamination. Some vaccine producers ship pre-formulated vaccine as a sterile bulk suspension, ready to fill without sterilizing filtration. In this case, the CMO should have extensive experience performing aseptic connections. Alternatively, experience with sterile filtration of formulated vaccine may be required. While disposable product contact equipment may be an option, durable equipment can be used in seasonal vaccine production to reduce cost. The CMO should have a robust cleaning validation program and to drive speed and efficiency, have the scientific knowledge to be able to apply a risk-based approach to cleaning validation. For example, once a residue detection method and cleaning validation process are developed and validated, they may not require revalidation following annual updates of strains in established vaccines. Evaluation of strain and formulation changes, in collaboration with the sponsor, may result in a risk assessment which does not require revalidation of residue detection methods and cleaning processes.

To ensure on time delivery, high-speed automated inspection, packaging and labeling systems are essential. Automated inspection processes must be validated specifically for each product and this can be challenging for semi-transparent fluids and suspension products. For seasonal influenza products revalidation might not be required for

subsequent campaigns if the product change is limited to strain substitution. Vaccine developers should seek a service provider with strong experience in automated inspection of PFS and experience validating automated inspection of difficult to inspect products.

Because of the short production timeline for seasonal products, many major seasonal vaccine manufacturers will utilize their internal capacity as well as multiple CMOs. To meet requirements of the Drug Supply Chain Security Act[5] (passed as part of the Drug Quality and Security Act) the CMOs should now be prepared to meet serialization requirements and have information technology systems supporting serialization that can communicate with the sponsor's system to ensure that the serial numbers applied are unique and traceable across the network of product manufacturing sites utilized.

Lastly, because of the time-critical nature of seasonal vaccine production, sponsors may seek to mitigate risk by selecting a CMO with redundancy in their manufacturing systems. Redundant filling lines, supplied with separate water and HVAC systems, can provide back-up capacity, though sponsors should balance their desire for risk reduction with the cost of performing process validation on a second line. Implementation of a second redundant packaging line is simpler because of fewer validation requirements and can provide risk mitigation as well as increased throughput.

A Culture of Speed and Execution

The unique time constraints associated with seasonal products require a culture of speed and focus on execution. Best practices in supply chain logistics are critical for timely start of the campaign and delivery of materials. These include having redundant suppliers for PFS components qualified in their supplier quality system. The CMO should have suppliers prepared to react and deliver quickly. For example, packaging artwork requires FDA approval (21 CFR 601.12(f) which can create delays in the packaging process. Good communication with the packaging material vendor can reduce the time required for delivery of printed labels and packaging material after artwork approval from weeks to several days. Provided the CMO has sufficient appropriate cold storage, the inventory of filled units can be built up as work-in-progress (WIP) materials while awaiting artwork approval. Upon approval, the stored filled units can be quickly inspected, labeled, and packaged using

redundant automated lines to expedite delivery.

The quality team must also demonstrate the culture of execution while maintaining focus on compliance and product quality. A dedicated team of consistent reviewers who are familiar with vaccines can expedite review and release of documentation. A collaborative relationship between the quality team and the sponsor will speed closure of investigations and non-conformance reviews (NCR) which would otherwise delay batch release.

The facility should have a plan to staff seasonal campaigns quickly and shift resources as project demand moves from filling to packaging. Ideally, this is accomplished through cross-training so that experienced personnel familiar with the product can move seamlessly between manufacturing tasks to best meet product resource demands.

Shared Expectations and Focus on Continuous Improvement

Successful collaborations require mutually agreed upon expectations which should start in the contracting process. Seasonal products have unique contractual requirements such as the inclusion of provisions for a flexible start window for filling and packaging operations. A well-managed CMO can offer dynamic scheduling within the flexible start window allowing for manufacturing start within 48 hours of notice by the vaccine sponsor. The sponsor and CMO should proactively prepare for a fast start to the campaign by pro-actively assessing any changes to the vaccine and the impact this may have on any validated processes such as product contact equipment cleaning, updating and validating any API release testing procedures, and conducting product specific training for manufacturing operators and laboratory analysts.

Additionally, during the seasonal planning period the CMO supply chain team should be communicating with vendors to ensure supply of components.

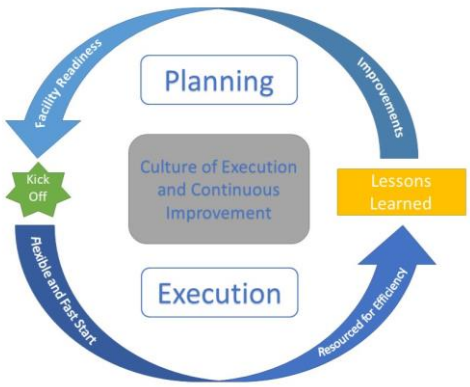
On time delivery during the campaign season requires year-round planning. The facility change control process must be monitored, during the campaign, to avoid changes to the lines or facility that could result in a regulatory supplement that requires agency prior approval. Maintenance of filling and packaging lines used for a seasonal campaign product should be performed during the season prior to the campaign to avoid any preventable service interruptions.

Each campaign should end with a lessons learned review by the sponsor and the CMO of what went well, what didn't go well and areas for improvement. Any areas for improvement can be incorporated during the planning process for the following campaign.

Conclusion

The time-sensitive nature of high-volume seasonal vaccine products creates challenges in their production. When vaccine developers evaluate external drug product manufacturing partners they should look beyond manufacturing capabilities. While the right facility and technical expertise are important, consistent quality and on-time delivery require a culture of speed and execution, shared expectations, and a focus on continuous improvement.

Figure 2: Culture of Execution and Continuous



References

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Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois, USA 60015
United States: 1-800-4-BAXTER International: 1-847-948-4770
Email: biopharmasolutions@baxter.com www.baxterbiopharmasolutions.com

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