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Single-use Systems for Vaccine Manufacturing Addressing Biocompatibility, Integrity and Supply Chain Issues

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Abstract

To meet global demand, it is predicted that next generation vaccines will be based on recombinant approaches and be produced in intensified single-use systems (SUS) to increase capacity at reduced costs. However, despite their benefits, SUS for vaccine manufacturing face a number of key regulatory challenges, which require greater reliance by the biopharmaceutical industry on SUS suppliers. This article details how Sartorius Stedim Biotech (SSB) is leveraging its quality strategy to address these issues by partnering with polymer and film suppliers to combine material science, film extrusion and bag making expertise, allowing in-depth characterization and process control of extractables/leachables substances and particles profiles of its SUS. The article also discusses why process controls, integrity testing and Maximum Allowable Liquid Leakage (MALL) specifications integrated with a solid global supply network will help the biopharmaceutical industry to achieve a more consistent quality supply of SUS for the production of safe, affordable vaccines.

Single-use Systems for Vaccine Manufacturing
Addressing Biocompatibility, Integrity and Supply Chain Issues

With global sales of human vaccines estimated to be over $30 billion in 2018 (1) and growing at 8 – 10% annually, vaccines are currently around 17% of the global biologic sales. The global market for vaccines is continuing to expand with more countries wanting to access and manufacture their own vaccines. Today, there are 10 blockbusters and around 480 marketed vaccines for 41 indications, as well as 750 in clinical and 1000 in pre-clinical trials. The vaccine market continues to be commercially lucrative but competitive with four major biopharmaceutical companies, 50 CDMOs, 300 small biotech companies and around 200 universities developing and producing vaccines, see Figure 1 for an overview.

The vaccine market is being driven by the need to continually supply the portfolio of existing vaccines and to develop new vaccines for unmet needs (such as unexpected pandemics or outbreaks of diseases for which a vaccine does not exist). However, biopharmas are facing a number of technical challenges with developing and producing vaccines, which include a lack of manufacturing capacity and changes to facilities required for switching from using egg-based production to using large scale adherent or suspension-based cell culture or bacterial fermentation. Traditionally, vaccines have been manufactured in mainly stainless-steel based production plants which have a CAPEX of around $500 million (2) to construct. These types of facilities have a risk of cross-contamination between batches and require considerable time and resources for steam-in-place (SIP) and cleaning-in-place (CIP). The next generation vaccines will be based on recombinant approaches and be produced on intensified single use platforms to meet the key objectives of cost reduction and capacity expansion.

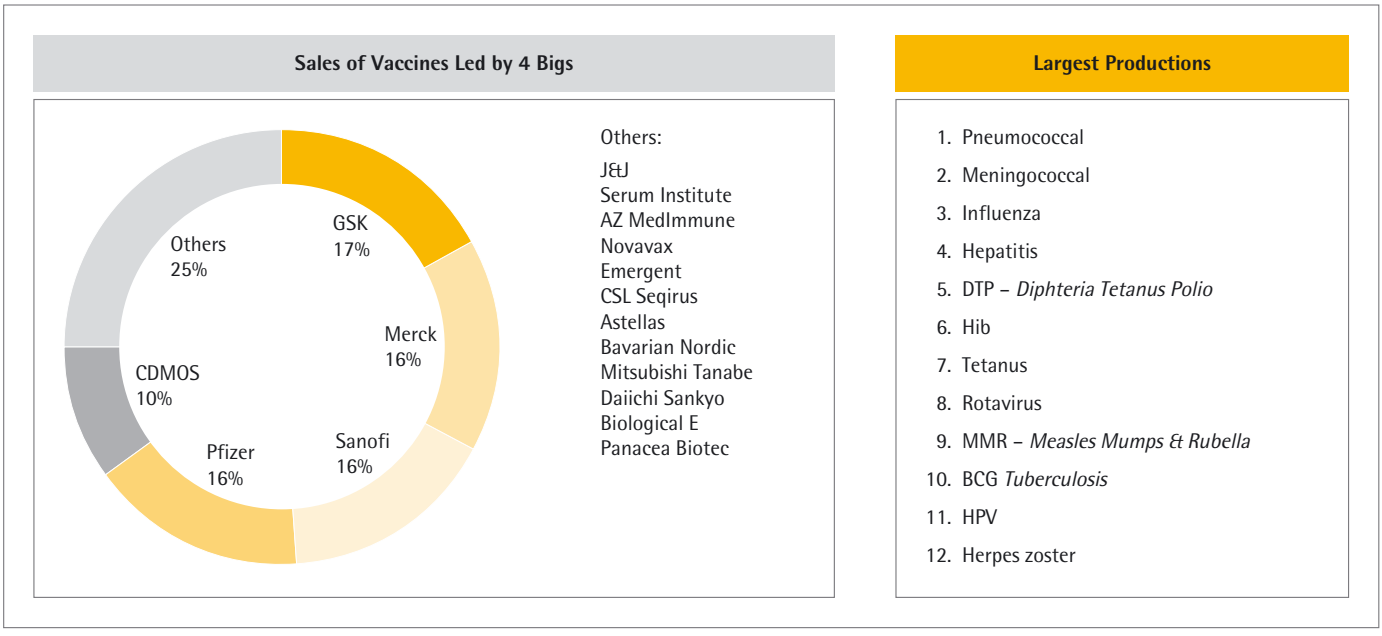

Figure 1: An overview of the global vaccine market by company and product.

Single-use for Vaccine Production

As part of process intensification, single-use systems (SUS) have become more mainstream and are now being used in all aspects of vaccine manufacture as a mean to increase capacity and reduce manufacturing costs. Implementing SUS in place of stainless steel, offers a range of CAPEX and OPEX as well as environmental benefits (3) (Figure 2).

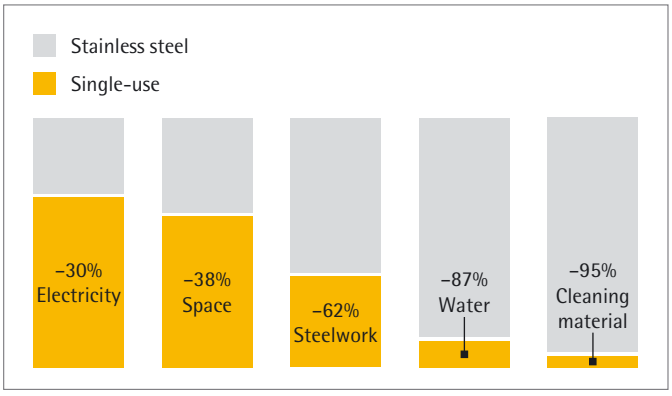

Figure 2: Benefits of SUS versus stainless steel for vaccine manufacturing

In recent years, SUSs have been developed for a range of vaccine manufacturing steps and using them in these steps can boost productivity by reducing the complexity and manufacturing costs, as well as eliminating CIP and SIP and associated activities. This offers greater flexibility and the basis for building more ballroom style manufacturing facilities with a large area that has no fixed equipment and minimal room separation.

The rise of SUS has meant that vaccine manufacturing as an end-to-end SUS process is becoming a reality (4). SUS plants offer a significantly shorter time frame to construct than stainless-steel, (usually around two years compared to four years) and can deliver the same quantity of vaccine as a traditional plant with a much larger footprint. For these reasons, many major vaccine development companies are adopting this concept. For example, APC and Bavarian Nordic have built a 500-L SUS pilot plant in Ireland for developing Bavarian Nordics' respiratory syncytial virus (RSV) vaccine candidate, MVA-BN RSV (5).

Key Challenges

While SUS undoubtedly offer many benefits in vaccine manufacturing, they also provide a number of key challenges and regulatory issues associated with single-use manufacturing (6). When applied to vaccine production, they include, firstly ensuring that SUS are biocompatible and have suitable leachables and particulates profiles to safeguard against unwanted contaminants in the final vaccine. SUS should also be free from leaks which can occur either during manufacturing, shipping and handling to assure SUS integrity to prevent leakage or microbial ingress. Finally, SUS must have a secure supply chain with a suitable period of change notification to enable continuous vaccine manufacture and avoid disruption of supply.

These guidelines have meant that biopharmaceutical companies and CDMOs producing vaccines have to be more reliant on SUS suppliers for greater transparency with their quality systems and supply chain. This in turn has meant SUS suppliers are expected to fully characterize their materials and processes, to control variability and understand the impact on the vaccine, as well as continuously improve their quality systems.

Biocompatibility

Industry bodies such as the American Society for Testing and Materials (ASTM), The American Society Of Mechanical Engineers (ASME), Parenteral Drug Association (PDA), Bioprocess Systems Alliance (BPSA), the United States Pharmacopeia (USP) and Biophorum Operations Group (BPOG) have issued guidelines and standards for the control of extractables | leachables and particles (7, 8, 9, 10, 11, 12) when implementing SUS and these are useful as guidance for biocompatibility quality assurance of vaccine production in SUS.

For a SUS supplier to control the particles and extractables in their products, they must have a complete knowledge of the materials and processes used to manufacture all the components of their SUS. This means, SUS suppliers have to build a strong relationship with their raw material suppliers (film and tube extruders and resin manufacturers) to ensure consistency of processes and materials. This knowledge allows SUS suppliers to fully characterize extractables, and control materials and processes to enable a reproducible extractables profile. Well characterized and reproducible extractables profiles ensure consistent biocompatibility and safety of SUS materials when producing vaccines.

Only by knowing the exact composition of raw materials in a SUS and the manufacturing processes involved, can a fully characterized extractables profile be obtained.

Extractables | leachables

At Sartorius Stedim Biotech (SSB) over 300 components of SUS are subject to extractables testing over a range of test periods using stringent, worst-case scenario in-house test conditions (13) (see Table 1). Critical components are also tested using the BPOG extraction recommendations, again over a range of times (see Table 2).

In House Extractables	1 Day	7 Days	21 Days	70 Days	70 Days
40 °C		100% EtOH – WFI			1M NaOH – 1M HCl
Bags, impellers, sensors, valves & tubings	–	–	•	•	•
Bioreactors, fittings & connectors	–	–	•	–	–
Sterile connectors	–	•	–	–	–
Filters & needles	•	–	–	–	–

SSB data compiled in solution-related extractable reports

Table 1: Conditions used to generate an extractables profile for standard SUS components

BPOG Extractables	1 Day	7 Days	21 Days	70 Days	70 Days
40 °C t0 at RT		50% EtOH – 0.5N NaOH – 0,1M Phosphoric acid WFI – 5M NaCl – 1% Tween 80			
Flexsafe®, Flexboy® Celsius® Bags	•	•	–	•	•
Sartopore® Filters	•	•	•	–	–

Table 2: Conditions used to generate an extractables profile for critical SUS components

In-house and BPOG protocol derived data are used to supply different levels of documentation, reports and services.
An extractables guide for standard and custom SUS products uses in-house data. Process extractables reports relating to specific vaccine processing conditions use in-house data and data derived from the BPOG extraction protocol and can be used for risk and toxicological assessment.

To produce extractables reports of specific SUS made of standard components requires using scaling or partitioning models which depend on the contact time of the components with the vaccine. Leaching of extractable products from SUS is controlled by diffusion or equilibrium and depends on the contact time the vaccine has with the SUS. For example, short contact times cause extractables to diffuse and so extractable data are calculated for this type of SUS component with a surface scaling model (14). Long contact times will produce equilibrium and SSB uses a more complex partitioning model for scaling extractables data here. Using these approaches, SSB is developing a data-base and IT tool to calculate extractables for assemblies made of multiple components in multiple process conditions. Moreover, SSB is developing full mechanistic modular models to predict leachables in dedicated process steps or throughout an entire downstream process (15). These Fate-of-Leachables models will not only allow prediction of potential leachables in biopharmaceutical production, which is based on batch processing but also in other methods such as . intensified processes or in cell and gene therapy applications.

Particles
SSB applies 100% visual defect inspection (VDI) to all 2D and 3D SUS bags (Figure 3). Inspectors are trained to detect loose particles and particles embedded within SUS plastic materials. Additionally, on a regular basis representative samples of SUS assemblies are flushed internally with water (destructively tested) and sub-visible and visible particulates in the water extracts are measured and trends are noted. This "visible particle test" (VPT) is a qualified method for quantifying particles greater than 100 microns using membrane microscopy. In addition to setting action limits, the VPT along with particulate chemical | physical identification methods facilitates identification of particulate sources within SUS manufacturing. This data enables SSB's "particle prevention program" (P3) and continuous improvement in SUS cleanliness. All these efforts (VDI and VPT) allows risk management and reduces the risks from particulates in SUS applications for vaccine manufacturing (16).

Figure 3: SSB operative inspecting bag chambers before assembly (left) and SSB operatives examining assembled products (right) for visible particles

Testing Integrity

Based on the USP <1207> (17), industry bodies such as the ASTM and BPSA are working on proposed standards (18, 19) and have issued guidelines (20) for testing SUS integrity in relation to both leakage and microbial ingress. These act as useful guidance for quality assurance of SUS for vaccine production.

For a SUS supplier to ensure microbial integrity of their SUS, they must have methods to validate their sterile product manufacturing and to detect leakages with physical tests that correlate defect sizes with microbial ingress. This means they must be able to identify a hole size which would allow the entry of microbes into the SUS under different sets of process conditions. They also need to provide tests that can be done at the SUS supplier's site and at the point of use in the vaccine manufacturing facility. This ensures there are no leaks or contamination of the vaccine at plant as this can costs millions of dollars in lost revenue and a shortage, if an entire production batch has to be discarded.

Leakage and microbial ingress

SSB use Quality by Design (QbD), process control and quality control to assure SUS integrity. Controlling the extrusion process into its design space established in collaboration with film and resin suppliers ensures SUS are being constructed of strong materials of consistent robustness and quality. As process control, SUS bag chambers are then visually inspected, and leak tested using pressure decay testing methods. Liquid shipping validation is also performed according to the most stringent ASTM D4169 standard tests (21) to assure SUS bags for example, are capable of being used for shipping vaccines.

Leakage and bacterial ingress into SUS depend on factors including process conditions, properties of the liquid in the SUS and the size of the defect. Microbial ingress cannot occur without liquid flow (22). To determine the Maximum Allowable Leakage Limit (MALL) for SUS, SSB is performing, based on existing data derived from studies using micro tubes, experiments with representative defects in SUS material to create their own predictive models. These models can be used to predict MALLs for any process condition, such as storage (gentle handling) and shipping conditions, where vibrations, shocks and accelerations can occur (Figure 4).

For most stringent conditions the models have been used to determine the MALL of 2 µm for liquid leaks or microbial ingress in any process conditions.

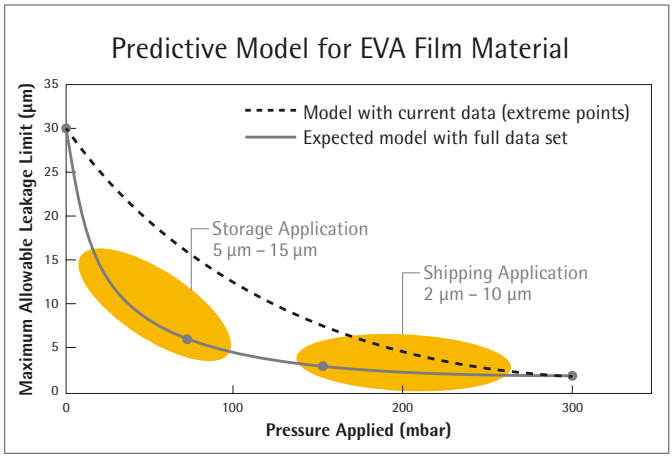

Figure 4: Predictive model of MALL for EVA film material

Quality assurance

With SUS bag chambers, SSB uses a pressure leak test that detects 40 – 90 µm defects and discards 400 ppm of products which have defects from its manufacturing operations. For a complete SUS assembly used in critical applications, SSB uses a Helium-based Supplier Integrity Test (SIT) which detects 2µm defects. At the vaccine manufacturing plant, SSB recommends an additional point of use integrity test, using the FlexAct® BT, before beginning production with its SUS bags. This detects 10 µm defects that can occur during transportation and handling.

Supply Chain

To provide constant quality SUS to vaccine manufacturers globally, SUS suppliers have to work in partnership with resins, films and components manufacturers to ensure material specifications and traceability, extrusion design space, consistent material quality and change control. Additionally, SUS suppliers have to have stringent quality assurance with a rigorous testing regimen in place to maintain SUS sterility, as well as manufacturing sites in different territories. These sites should operate to the same standards and all produce similar critical SUS so that there is always a contingency level of critical products available.

SSB has established partnerships and quality and supply agreements with their critical suppliers to achieve the highest levels of quality and most stringent change control in the SUS industry.

SSB has full control over all the parameters of its S80 and S71 film materials most frequently used in SUS for vaccine production (Table 3), a rigorous testing regimen (Table 4) and has SUS production at four different sites globally, all of which are continuously expanding to meet demand from vaccine manufacturers.

Levels of control	Resins Specification	Resins Control	Extrusion Design Space	Extrusion Control
S80 & S71	Yes	Yes	Yes	Yes
Other films	Yes	Yes	No	Yes
	No	Yes	No	No
	No	No	Partial	Partial
	No	No	No	No

Table 3: Levels of control SSB has with suppliers of the films for its SUS

QC Test frequency	SSB	Other suppliers		
Bioburden	Weekly Representative sample	No	Quarterly	Quarterly
Endotoxin		Quarterly		Yearly
Sub visible particle				Quarterly
Bag leak test	Yes	No	Yes	No

Table 4: SSB's quality testing schedule

Conclusions

Integrating SUS in vaccine manufacturing enables biopharmaceutical companies and CDMOs to utilize more environmentally friendly manufacturing facilities with increasingly smaller footprints and the flexibility to perform rapid changeovers at different scales with a range of vaccines. However, SUS in vaccine manufacturing also has a number of key regulatory issues, which requires greater reliance by the biopharmaceutical industry on SUS suppliers. By leveraging a quality strategy where SSB partners with polymer and film suppliers to combine material science, film extrusion and bag making expertise, as well as end to end process controls allows an in-depth characterization and control of extractables | leachables substances and particles profiles.

Further process controls combined with SSB's integrity testing strategy and MALL specifications and its solid global supply network will help the biopharmaceutical industry to achieve more consistent biocompatibility, integrity and assurance of quality supply of SUS for vaccine manufacturing to an expanding, competitive global market.

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