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Integrated Technologies to Accelerate Process Intensification for Viral Vaccine Manufacturing

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Abstract

With the increasing world-wide demand for viral-based vaccines (VBVs) which includes attenuated and inactivated viral vaccines, as well as viral vector vaccines to protect against the coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), faster development times are required to progress VBVs more rapidly into clinical development and then to market. This has meant VBV manufacturing is changing and is being driven by the need for increased speed and greater flexibility. The requirement for greater flexibility has led to new types of manufacturing facilities which can accommodate a growing range of different types of VBVs and can be reconfigured easily to take high clinical trial attrition rates into account. To meet these challenges, vaccine manufacturers, for example those developing SARS-CoV-2 vaccines in cell culture are adopting strategies including process intensification as they believe this will help achieve higher product titers while reducing manufacturing footprint thus making larger numbers of doses of VBVs more readily available. To deliver on this, there is a need for products that can facilitate process intensification and operate under these conditions when manufacturing VBVs. To facilitate process intensification of VBVs including SARS-CoV-2 vaccine candidates, an integrated portfolio of technologies developed by Sartorius is detailed in this article.

Find out more: www.sartorius.com/vaccine-development

Trends in Vaccine Production

Recent outbreaks of viral diseases such as Swine Flu (H1N1), Zika, Ebola and the current SARS-CoV-2 pandemic are driving trends around speed, processing and flexibility with developers of viral-based vaccines (VBVs), which includes attenuated and inactivated viral vaccines, as well as viral vector vaccines. To increase speed to market, vaccine manufactures are continually trying to shorten clinical development timelines to reduce the amount of time to move their VBVs from pre-clinical development to first in human trials. This is reflected in having shorter process development timelines and is leading to an increasing use of Contract Manufacturing and Development Organizations (CDMOs), that specialize in this type of development and manufacturing work to help de-risk any possible failure in clinical scenarios. In terms of processing, there is pressure to reduce the footprint of manufacturing facilities, as well as increase their flexibility to accommodate rapid change over and enhance the supply chain.

Since many VBVs, including a number of viral vectors used for SARS-CoV-2 can be manufactured using cell culture (Philippidis 2020), this presents an area where new technologies could have a significant impact on production timelines and costs. Cell culture of VBVs has traditionally used expensive two-dimensional approaches with T-flasks and roller bottles. However, using suspension cell lines or adherent cells on microcarriers, cultivation can be performed in either stainless steel or single-use stirred tank bioreactors for faster, more flexible production.

Process Intensification of VBVs

An advantage of using cell culture to produce VBVs is that they could potentially be manufactured using process intensification. This is an approach to process development originally pioneered in the chemical industry by the Process Technology Group at Imperial Chemical Industries (ICI) in the UK. The aim was to reduce plant size while increasing productivity, thus decreasing the cost of goods (CoGs) by lessening capital investment and overhead costs (Nestola et al 2015). Today, multiple definitions of process intensification have been developed but all have the ultimate goal of increasing productivity.

Process intensification could be used for SARS-CoV-2 vaccine manufacturing, to utilize facilities with a smaller plant footprint and less scale up volumes to rapidly produce large number of doses required for mass vaccination campaigns. This is because there are more 2000 L scale bioreactors than 20,000 L good manufacturing practice (GMP) compliant bioreactors which can be accessed quickly. Therefore, utilizing an intensified cell culture process could improve overall manufacturing yield to produce 10-20 doses of vaccine/mL, making it possible to perform 2000 L runs and produce sufficient vaccine for small scale trials. For example, by increasing the final titer of VBVs by 1 log a potential scale up could be reduced from 20,000 L to 2000 L, which would have a significant effect on overall production timelines.

Using process intensification, allows a reduction in bioreactor size, and therefore the use of SU bioreactor for commercial production. VBV manufacturers could also improve their supply chain by becoming more flexible with ballroom style facilities and moveable skids, which allow rapid product changeover. Furthermore, using process intensification offers the possibility of remaining in the same facility throughout clinical development and potentially the initial years of commercial launch.

VBVs and other types of vaccine generally require long phase 3 trials where manufacturers have to produce a large number of doses for trials without knowing if their vaccine is going to be effective enough to become commercialized (Weinberg et al 2012). For phase 3 trials, manufacturers have to scale up production or move to a new facility to produce the 10,000 to 30,000 doses normally required. This is unlike a phase 3 trial for a monoclonal antibody (mAb) therapy, where patient populations are smaller and is a major difference between mAb and vaccine clinical studies and manufacturing. Using intensified processing means that a pilot facility could provide all the material for this clinical phase, which mitigates the risk of having to build a new facility, that would not be used if the VBV fails in Phase 3. The SARS-CoV-2 pandemic is also an exceptional situation, in which some clinical trials might be combined or accelerated, creating the need to have thousands or even millions of doses available in a very condensed timeline.

Process intensification also offers the opportunity for more localized production of VBVs in low to middle income (LMI) counties because it can provide more doses/mL, potentially making the cost per dose lower. This will help the transfer towards LMI countries, where having a fully closed, high titer process is essential to minimize GMP requirements, prevent unwanted contamination, and avoid the need for scale up. In this case, a scale out would be feasible and more easily manageable than a scale up especially in a setting where bioprocessing skills and knowledge may be lacking.

Process intensification for VBV production is built on three pillars, equipment, mode of operation and technology (Figure 1) and many manufacturers are assessing and adopting these pillars around process intensification generally in a step-wise approach.

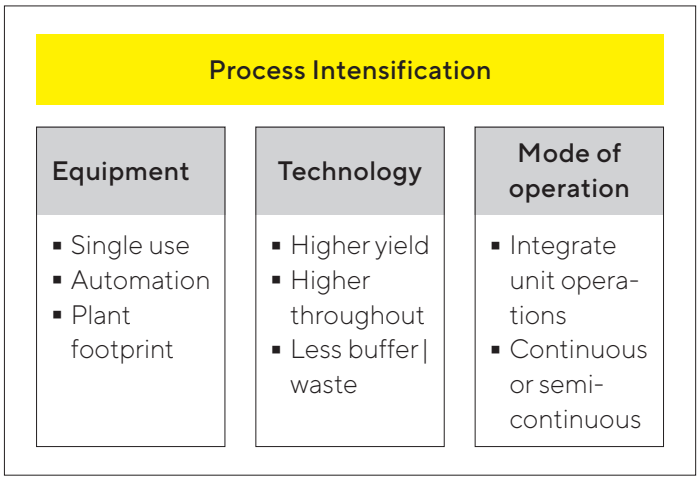

Figure 1: The three pillars of process intensification with VBVs

Upstream

Cell and Media Selection

Cell line and media selection are critical for intensified processing of VBVs because some cell lines, sub-clones and media perform better in intensified processing than others. There is published information about how to intensify Chinese hamster ovary (CHO) cell lines (Mueller 2019, Zijlstra, 2019), the cell line of choice for mAb production, but this is rarely utilized for VBVs and is not currently being used for manufacturing any SARS-CoV-2 vaccines.
Cell line: HEK293, Vero, MDCK: Virus: SARS-Cov-2, Adenovirus, Measles, MVA.

For VBVs, the most commonly used cell lines are human embryonic kidney (HEK293) cells, (mostly used for viral vectors), or Vero and Madin-Darby Canine Kidney (MDCK) cells for inactivated or live attenuated viruses. The cell culture process for VBVs is also different to that for mAb production as cells needs to be infected with virus to produce a VBV. If process conditions are not closely monitored | controlled and there is a slight difference in, pH, DO (dissolved oxygen) or temperature between batches, it could affect the virus' ability to infect the cells or the virus' genetic stability, suppressing expression of viral antigens, often resulting in lower VBV yields and potency.

One strategy to determine the optimum cell line, sub-clone and media combination for VBV intensified cell culture is to screen different media, feeds and sub-clones to determine the most suitable combination for maximum productivity early in the culture process, as this can significantly reduce development timelines during scale-up.

Optimization traditionally involves shake or spinner flasks to select the best combination of media | feeds and sub-clones. However, shake and spinner flasks provide no control over pH and DO, and the mixing environment is unlike that in a bioreactor. Additionally, these flasks are often manipulated by hand, making it difficult to perform feeds or sampling without introducing variability. Hence, their use can often result in different cell growth and viral protein expression profiles to those seen in scale-up.

Due to issues of cost, throughput, and resources, it is difficult for scientists especially those in academic laboratories where a number of SARS-CoV-2 vaccines are being developed to evaluate multiple sub-clones, media, and feed combinations for intensified processing. As a result, typical sub-clone and media ranking processes can involve several rounds of batch and fed-batch flasks to reduce an initially large numbers of combinations down to a manageable number (typically around six) that can be tested for process development in benchtop bioreactors. This manual approach can take several months to complete and is extremely labor intensive. Additionally, the final choice of sub-clone, media, and feeds maybe sub-optimal for process intensification and may not generate VBVs with the highest yield, making this approach unsuitable when timelines for robust process development need to be accelerated.

Methods of running intensified cell culture conditions in parallel at small scale are desirable to perform full Design of Experiments (DoE) of cell lines and media for VBV production. The use of automated microbioreactor systems capable of running as high inoculation fed-batch and | or perfusion mimics such as the Ambr®15 technology (Sartorius) which can monitor and control up to 48 micro-bioreactor cultures in parallel provide such a strategy.

Process Optimization

Process optimization and process understanding are key to ensuring a straightforward scale-up or transfer the process. Similar to clone and media selection, process optimization often uses glass benchtop bioreactors as models and requires a considerable amount of time for set-up, as well as labor intensive pre- and post-process cleaning and sterilization with every experimental run. However, automated single-use mini bioreactor systems such as the Ambr® 250 technology (Sartorius), can be used as models (250 mL working volume) for developing intensified fed batch and now perfusion cell culture (Figure 3) for VBV process development. The system is able to operate with suspension culture, as well as adherent culture using microcarriers, and studies have shown that these bioreactors can allow cell densities (between 1.8 and 3.5 × 10^6 cells/mL) with a high cell viability (> 90.5%) of BHK21 suspension cells for VBV production (Garcia et al 2019) and 1.5-5 × 10^6 cells/mL (95% viability) from an initial inoculum of 8.5 × 10^4 cells/mL with adherent Vero cells cultured on microcarriers (Cytodex 1, 4 g/L) for 13 days (Zoro et al 2017).

These studies indicate that mini bioreactors could enable process optimization studies for developing a SARS-CoV-2 vaccine with suspension or adherent cell lines because BHK21 cells have been used to produce a coronavirus vaccine candidate for Middle East respiratory syndrome (MERS) (Li et al. 2020) and the SARS-CoV-2 virus can replicates to high titer in Vero cells (Harcourt J. et al 2020). Since the Ambr® 250 bioreactors have similar geometries to larger stirred tank vessels such as Biostat® STR bioreactors, this could help develop process intensification conditions with the potential to improve the productivity of inactivate or live attenuated vaccine and produce multiple doses/mL of a SARS-CoV-2 vaccine which can be seamlessly transferred to pilot and manufacturing scale. Another application is the optimization of HEK293 which are a common platform the production of VBVs using adenovirus (Fedosyuk et al 2019).

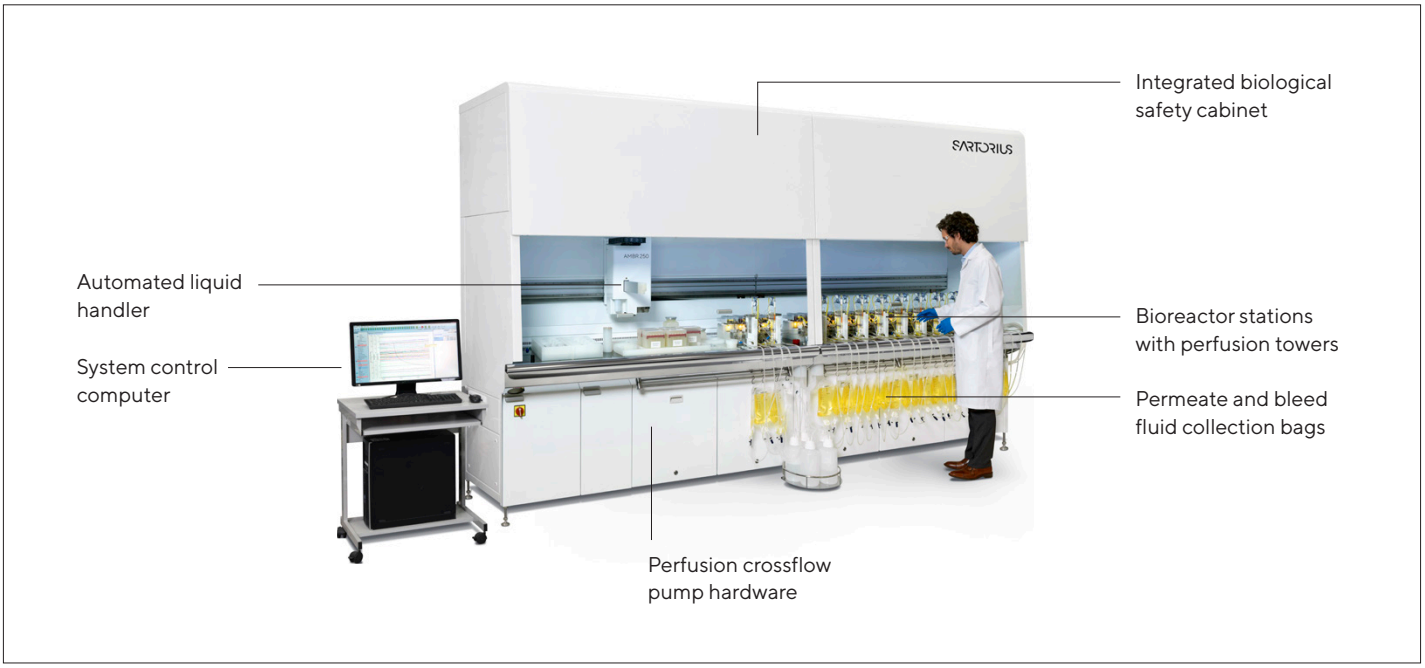

Figure 2: Ambr® 250 high throughput perfusion system

Intensified Seed Train and Scale-up

Intensified processes have been established for mAb based therapies (Zijlstra, 2014), which can be adapted as a low-risk approach for production of a SARS-CoV-2 vaccine candidate and an intensified seed train, which could be used is shown in Figure 3.

For VBV seed train process intensification and cell bank manufacturing services, which can produce high cell density vials to seed rocking motion (RM) bioreactors can be used. For example, Sartorius has cell banking equipment that uses an automatic closed single-use vial filling system, Fill-It which can fill 500 vials with up to 5mL at 50 × 10^6 viable cells/mL. These vials can then seed scalable RM bioreactors. For simple operation, these bioreactors should include an integrated perfusion membrane so that no external cell retention device is needed, for instance, the Biostat® RM, a fully GMP compliant, rocking motion bioreactor that comes with a range of single-use bioreactor bag sizes from 2 L up to 200 L, and a maximum 100 L volume. For process intensification at manufacturing scale, single-use stirred tank bioreactors which are capable of high cell density culture are required. Sartorius' Biostat® STR which scales from 12.5 L to 2000 L is being used at CanSinoBIO Biologics and the Institute of Bioengineering to manufacture China's first SARS-CoV-2 vaccine candidate (Ad5-nCoV) using an adenovirus-based viral vector platform. With process optimization, this bioreactor range could potentially be used for process intensification of this application in the future. Finally, for successful process intensification, RM and STR bioreactors need to include process control with PAT (Process Analytical Technology) tools to control and monitor conditions between batches. Technologies such as BioPAT® ViaMass for on-line cell counts which monitors and controls (exponentially growing) perfusion culture and allows automatic feeding and bleeding (Carvell et al 2016) can monitor on-line conditions for cell growth and infection in Biostat STR® bioreactors for example. MVDA (Multivariate Data Analysis) software can analyze the data from these sensors more easily for feedback control and modeling, which is essential for ensuring that all the parameters are tightly controlled during the virus production step.

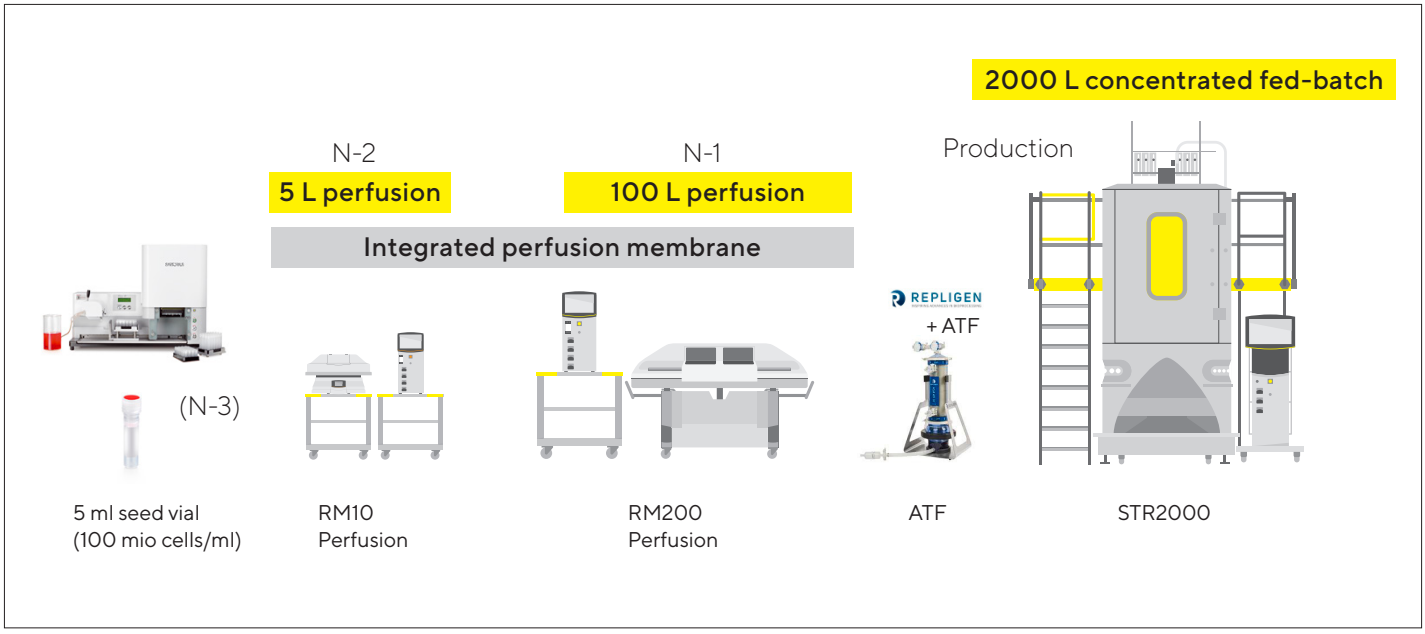

Figure 3: Intensified seed train and scale up for manufacture of VBVs

Downstream

Purifying a mAb produced in intensified cell culture is more straightforward than a VBV and downstream processing of VBVs is currently where bottlenecks occur. VBVs need to be purified generally from a cell lysate and where lytic viruses are being produced there is a large amount of debris associated with high cell densities and virus titers that requires a range of technologies to remove the debris, a classic example of this is adenovirus. However, if enveloped viruses including SARS-CoV-2 , Modified Vaccinia Ankara (MVA) and measles are being produced, cell lysis does not occur, and debris is less of an issue. These VBVs are instead more shear stress sensitive and this must be taken into consideration during downstream operations. (see Figure 4 for a workflow of technologies that could be used to purify VBVs cultured in intensified cell culture).

Harvest and Clarification

For downstream clarification of VBVs produced in intensified cell culture by either enveloped, shear sensitive viruses for example the SARS-CoV-2 or measles virus or lytic non-enveloped viruses including adenoviruses, cell harvest and clarification can become a bottleneck. High cell densities (>-20 × 10^6 cells/mL) present a number of challenges because increased cell numbers produce an increase in host cell proteins (HCPs), DNA and protein aggregates, which can foul and clog filters, requiring sizeable filter areas and large buffer volumes for VBV purification.

The most common option to help remove excess DNA before filtration is to use nuclease, but this is an expensive enzyme, and if a large amount of DNA is present then grams of nuclease could be required making the manufacturing process prohibitively expensive. One alternative to using nucleases with lytic viruses, such as adenoviruses being used to produce SARS-CoV-2 vaccines candidate is to use flocculants and centrifugation.
Centrifuges that operate by balancing out centrifugal force and medium flow to keep cells contained in an expanded bed are recommended, as these exert lower sheer forces on the viral product to minimize loss of infectivity. If classic filter trains do not work or a huge surface area is required, centrifugation is advised as the first step in cell harvest for high cell density as it reduces the filter area, eliminating pre-rinse steps to efficiently separate cells out, enabling the use of smaller footprint facilities where less buffer volume and buffer storage are required. A suitable centrifuge for this application is the kSep® single-use, sterile centrifuge (Sartorius) which has been shown to efficiently clarify high cell density mammalian cell cultures (> 200 × 10^6 cells/mL). This type of system is ideal for enveloped viruses, however when lysis occurs, additional experiments and the use of flocculants should be considered because this centrifuge operates at a maximum g-force of 2000 G, which may be an insufficient force to sediment all the debris.

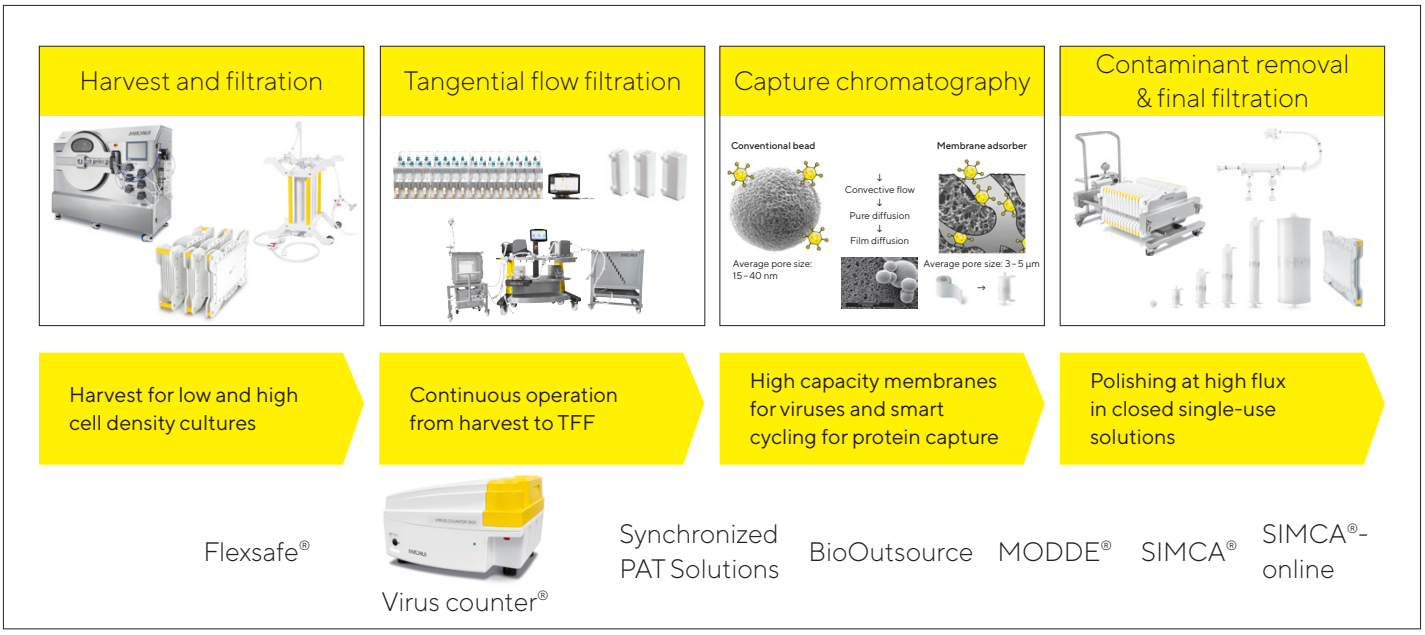

Figure 4: Technologies for intensified downstream purification of viruses for VBV production

Following centrifugation, filtration is generally required for clarification, and the use of filters without any virus adsorption properties is essential to avoid loss of infectivity. An inorganic filter aid with high capacity such as Sartoclear® (Sartorius) can be used for purification of VBVs from very dirty cell supernatants but since this filter has adsorptive properties, operating conditions such as pH and salt have to be fine-tuned, to avoid virus adsorption at this stage. A Sartopure® PP3 filter (Sartorius) can also be used for clarification as many viruses will not adsorb to it, due to its very low specific absorption properties. This filter has been shown to achieve 100% virus recovery and high throughput for adenovirus processes (Boulais et al 2018), indicating it could be suitable for purification of a SARS-CoV-2 vaccine candidate produced by intensified processing. There is currently no plug and play harvest and clarification solution for all VBVs and scientists need to test different flocculants and filters to find the optimum combinations for use in their intensified processes.

Purification and formulation

Fast production is now a major driver for producing a SARS-CoV-2 vaccine in an intensified process and reducing the amount of buffer is critical to manufacturing in smaller sized facilities. Purification of high titer VBVs propagated requires technologies that have high binding capacities and low fouling capabilities. If these types of technologies are not adopted, large buffer volumes will be required, which need larger storage and manufacturing areas. The challenge is always to develop simplified purification processes that use as little buffer volume as possible. For example, the initial purification steps can use ultrafiltration with Tangential Flow Filtration (TFF) membranes which offer low fouling, high throughput, and a higher cutoff membrane of 300kDa. TFF membranes are available in two different materials, cellulose-based Hydrosart® and polyethersulfone (PESU) polymer-based. Hydrosart® has the unique property of being very hydrophilic thus preventing viruses from adsorption to the membrane. Both membrane types allow removal of low molecular weight impurities, to reduce the numbers of subsequent unit operations.

When using high titer VBVs, it is important to select the right buffer formulations for purification and there are small scale systems such as the Ambr® crossflow system (Sartorius) which allows scientists to perform high throughput screening of buffers to evaluate viruses, buffer combinations and process control conditions. This helps improve early stage R&D productivity and efficiency, while helping to reduce buffer volumes required for the screening experiments.

With high binding capacity in mind, membrane adsorbers can be used in place of conventional resin-based affinity chromatography for purification of VBVs (Weigel at al 2016). Membrane adsorbers with beads that have large pore sizes (3-5 µm) are recommended as these provide maximum ligand accessibility for viruses and eliminate the need for diffusion through resin pores. Membrane adsorbers with large pore sizes such as Sartobind® Q can operate at volumetric flow rates that are typically 20-fold higher than classical resins and studies with adenovirus have shown that compared with resins, they can achieve a 10-fold higher viral binding capacity using 58% less buffer, without compromising virus purity (Abrecht et al 2019).

Ready-to-use membrane adsorbers are ideal for virus capture with VBVs as they are quick and easy to operate because column packing, as well as cleaning and related validation activities are eliminated. They also have a small footprint and are single-use, which reduces cross contamination risks, and can lead to significant time and cost savings. For example, Sartobind® Q has been used for adenovirus purification and has achieved a loading capacity of 6.4×10^{13} virus particles/mL of membrane and reduced DNA concentration in the process stream to 0.7 ng DNA/dose (Boulais A. et al 2016). Similar results were obtained by GSK, where scientists reduced DNA by a log reduction value (LRV) of >4, and product recovery ~90% (Abrecht et al 2019), indicating that this membrane adsorber could be used for purification of a SARS-CoV-2 vaccine produced by intensified processing.

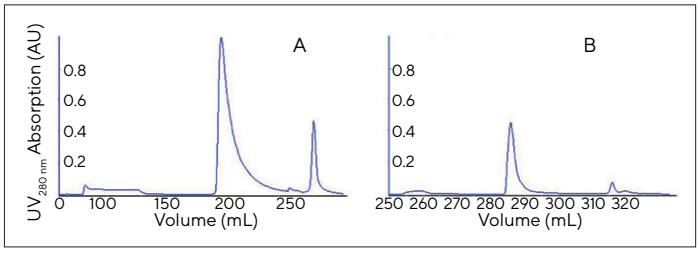

Figure 5: UV 280-nm chromatograms from reference resin (a) and Sartobind membrane (b); experiment was conducted with a 20-mL Q resin column and a 3-mL Sartobind Q (8-mm bed height). Resin and membrane first were sanitized with NaOH 1 M, then equilibrated with Tris-NaCl buffer. Virus load was 1.7×10^{12} virus particles (VP)/mL, and step elution used the same Tris buffer with increased NaCl concentration.

For final polishing and formulation of high titer viruses, membrane filtration using stabilized cellulose membranes is suitable as these membranes are hydrophilic, which limits fouling while maximizing membrane flux performance and virus yield. Membranes which can be used include Hydrosart® (Sartorius) which has previously been shown to have an improved chemical stability coupled with adenovirus recovery of up to 90 % (Boulais et al 2018). The hydrophilic nature of the membrane also prevents adsorption of the virus or important components in the final formulation buffers. These membranes come in scalable single-use cartridges and/or self-contained units, which can be used with automation on movable skids indicating that this membrane could be used as a flexible method of producing clinical to manufacturing batch sizes of an adenovirus based SARS-CoV-2 vaccine produced by intensified processing.

Virus Analytics

To optimize downstream capture and purification steps, monitoring of inlet and outlet virus concentration and quality is required to select the best purification parameters. This can be achieved by Q-PCR or using no-wash staining assays, for example Combo Dye® reagent or the antibody-based ViroTag® (Artinger et al 2016), which can be detected automatically in flow cytometer-based technology such as the Sartorius Virus Counter® 3100 system (Figure 6). Speeding up the analytical response and understanding of which experiments should be prioritized, reduces analytics downtime, allowing faster process development timelines.

Virus counter® 3100 instrument

Software 21CFR Part 11 support

Reagents Combo Dye® and ViroTag®

Figure 6: Virus counting technology

Summary

Intensified processing enables VBV manufacturers to utilize single-use technologies and manufacturing facilities with increasingly smaller footprints, which could be used to rapidly produce vaccines for the current SARS-CoV-2 pandemic. However, it does require upstream and downstream tools that are capable of culturing and processing high cell densities and high virus titers.

In summary, developing an intensified process for a VBV should start with the end in mind, first selecting the optimum media and cell line, to intensify the process and seed train. Then selecting the appropriate technologies in the downstream to ensure the highest virus recovery, using chromatography membranes and single-pass ultrafiltration and diafiltration, as well as monitoring and controlling the process with rapid viral quantification, PAT and MVDA data analysis software. Starting intensified processing with the end in mind, could help ensure rapid manufacturing of large numbers of doses of VBVs such as a SARS-CoV-2 vaccine produced by intensified cell culture in a fully closed process that could be run in a small bioprocess facility. Sartorius offers a range of proven upstream and downstream technologies, which when connected and optimized have the potential to deliver this vision.

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