sartorius stedim biotech

Connecting Science, Technology and Business to Optimize Bioprocessing

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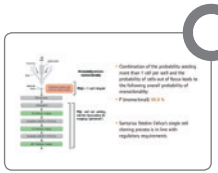

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Connecting Science, Technology and Business to Optimize Bioprocessing

An Overview of Sartorius Presentations from BioProcess International Europe 2017

Delivering Medicines to Patients across the Globe

by Miriam Monge

The market for biopharmaceuticals remains robust and analyst predict it will continue to grow strongly. The biologics pipeline is strong but becoming increasingly complex. There are thousands of biologics in the discovery to pre-launch phases of the lifecycle including mAbs, recombinant proteins, cell therapies, subunit vaccines and gene therapies. Bringing these products to market quickly allows drug manufacturers to maximize their market share in the face of increased competition in the pipeline often for the same indication and helps replace revenues being lost to the first generation of biosimilar products. Biopharmaceutical companies are increasingly seeking to address overseas markets and manage international supply chains (Figure 1).

Figure 1: Expansion of biomanufacturing capacity all over the globe

[1] discover more about ambr® 15

[2] discover more about mAbs

Engineers are developing and implementing new technologies, such as continuous processing, single-use technologies and flexible facilities to support the growth of the industry and address current challenges.

Biopharmaceutical companies can accelerate process development activities by outsourcing the development of cell lines to service providers enabling firms to move from DNA to the research cell bank stage in as little as four months. High throughput process development tools such as the ambr® 15 micro bioreactor system are proving to save considerable time during parameter optimization studies. Cobra Biologics, for example, has reported that they were able to save 6 weeks of development time by using the ambr® 15[1] system. Smaller biopharmaceutical companies in particular can benefit from seeking the advice of Sartorius Stedim Biotech's (SSB) Process Development Consultants to help them apply these tools and techniques that will allow them to reach the clinic more quickly.

To improve bioprocess efficiency, SSB clients are taking advantage of the company's process platform toolbox of technologies and services. These have been developed for mAbs[2], vaccines, ADCs and regenerative medicine workflows. They allow companies to adopt a consistent manufacturing approach to all their products within a category and implement a standardized supply chain.

Platform processes facilitate process transfers, enhance flexibility, increase predictability thus reducing risk and allow for optimized cost. SSB's advanced process modelling tools enable customers to understand Cost of Goods and the impact of certain process design and technology choices, modes of operations and production scheduling needs at different production scales. The Sartorius Integrated Solutions team has worked with clients such as Boehringer Ingelheim and Synthon to implement single-use mAb platforms from PD to commercial for efficient biomanufacturing.

Biopharmaceutical companies are implementing Quality-by-Design to help them define manufacturing design spaces that will allow them to achieve product critical quality attributes. SSB's BioPAT® process analytical technologies are QbD enabling tools that include single-use sensors, advanced real-time analytics, monitoring and control loops and multi-variate data analysis software. The BioPAT® MFCS/win[3] software is a central hub for data, analytics, chemometrics and control from cell line development through production for clinical trials and commercial manufacturing.

These bioproduction tools and services will be critically important in helping the industry evolve new business models and future-proof its commercial manufacturing networks in the face of increased competition, uncertain market demand and more potent, personalized medicines (Figure 2).

Figure 2: An integrated lifecycle concept speeds up drug development to IND and BLA

If you would like further information on these topics, please contact me at **miriam.monge@sartorius-stedim.com**

[3] discover more about BioPAT® MFCS

End-to-end Process Control Improves Biocompatibility, Integrity and Assurance of Supply of Single-Use Solutions

by Jean-Marc Cappia

Single-use systems are a dominant technology for the clinical production of biopharmaceuticals. Manufacturers are increasingly using single-use technology for the commercial production of their products to improve their processes, gain in process efficiency and expand capacity globally. Flexible facilities that make significant use of single-use technologies can be implemented quickly and require lower upfront investment than stainless steel plants. They have a lower footprint requirement and can generate up to 50 % less carbon dioxide due eliminating the energy-intensive need to clean and sterilize re-usable equipment.

Ensuring the compatibility of the materials of construction used in single-use systems with biological systems and products, improving process integrity and controlling supply chains are key challenges suppliers must addressed to allow the greater adoption of single-use processing systems in the commercial biomanufacturing environment. The industry is asking suppliers to better characterize raw materials and control their manufacturing processes more tightly to improve the quality and assurance of supply of single-use technology.

The development of the S80 film for Sartorius Stedim Biotech's (SSB) Flexsafe®[1] family of single-use bags was driven by a Quality-by-Design (QbD)[2] approach. R&D teams optimized the formulation and tested more than 25 different films against pre-defined critical quality attributes. All resins and the additives have been identified and the extrusion process is controlled within an established design space. This provides biomanufacturers with a guarantee of lot-to-lot consistency for cell growth, robustness and extractable and leachable profiles (Figure 1).

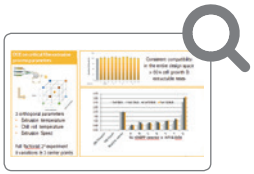


Figure 1: Film Extrusion DoE & Controls Guarantee Consistent Compatibility & Integrity across the Entire Design Space

[1] discover more about Flexsafe®

[2] discover more about QbD

SSB has implemented a Particle Prevent Program, P3 that aims to reduce particle contaminations by design. A continuous improvement program identifies particles and their sources. This allows the particle shedding properties of components to be reviewed and improvements made to minimize the impact on the bioprocesses operated by clients.

To ensure single-use container closure integrity is maintained throughout the lifecycle of the bag, SSB has implemented QbD and validated its production process to ensure consistent bag robustness. All bags are leak tested before leaving the factory and the firm can provide additional supplier integrity testing and a point of use leak test for pre-use integrity control. Both the supplier integrity test and point of use leak test are correlated to microbial ingress and liquid leakage based on the company's deep understanding of bacterial penetration and leak flow mechanisms.

Suppliers can provide a reliable supply of single-use technology with consistent quality by establishing partnerships and quality agreements with their suppliers (Figure 2), by locating their manufacturing network across multiple continents and by creating pre-designed solutions (PDS) tailored to process requirements.

SSB has implemented all three of these strategies. The company's standardized PDSs are helping end-users optimize their inventories while improving quality and assurance of supply. The use off-the-shelf and standard components covered by 24-month change notifications provide support to quality teams at the biomanufacturing site.

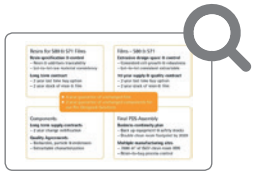


Figure 2: Partnerships & quality agreements with suppliers of materials, films & components

If you would like further information on the application of single-use technologies for commercial biopharmaceutical manufacturing, please contact me at **jean-marc.cappia@sartorius-stedim.com**

A Platform Approach to Viral Vaccine Manufacturing

by Kai Touw

The new generation of vaccines in pre-clinical development are quite different from those that companies market currently. A significant proportion of marketed vaccines belong to the live attenuated, toxoid and conjugated classes while subunit and recombinant vector classes dominate in preclinical development.

Companies are increasingly making the transition from stainless steel production equipment to single-use systems and fully flexible manufacturing operations. Seventy-five percent of all vaccines are in early stage process development. This is the right time for vaccine manufacturers to select scalable, self-contained processing technologies and a partner, with a robust supply chain, that can provide them.

Vaccine manufacturers can apply platform-processing approaches that can be scaled both up and down readily, use standard consumable designs and contain pre-qualified process steps. However, at Sartorius Stedim Biotech (SSB) we believe that the production platform concept is more than just the unit operations but extends to support and service functions that allow a firm to reach the clinic and the market quickly with a well-characterized process.

[1] discover more about BIOSTAT STR®

[2] discover more about kSep® Systems

SSB has focussed recently on the development of end-to-end, single-use platforms for viral vaccine production. The upstream process features our industry leading BIOSTAT STR® [1] single-use bioreactor technology while microcarrier removal be performed with the kSep® [2] single-use centrifuge (Figure 1).

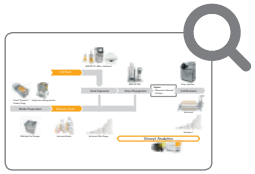


Figure 1: Upstream Viral Vaccine Platform

Upstream processes can be developed in the ambr® micro-bioreactor platform and are fully scalable to our 1000 L bioreactors and beyond. Virus manufacturers can use this same platform regardless of whether they have suspension or adherent cell culture processes. The platform design takes into consider-ation the necessary biosafety requirements needed for the production of viruses and viral vectors.

During the development of the viral vaccine platform SSB appreciated that there was not going to be a one-size-fits-all solution for complex products such as viruses. We have adopted a flexible and modular approach that allows technologies to be interchanged easily depending on the virus to be processed (Figure 2). The platform features technologies such as automated, self-contained, cross-flow systems and our Sartobind® membrane adsorbers.

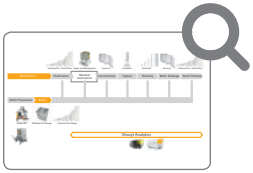


Figure 2: Downstream Viral Vaccine Platform

Process analytical technologies such as the BioPAT® Viamass[3], capable of determining the ideal point of infections in bio-reactors, and the ViroCyt[4] at-line virus quantification equipment, further augment the performance of the platform.

SSB is providing a full service portfolio to support its viral vaccine platform. This includes solutions for virus screening and adaptation, process development consultancy services, process engineering and Cost of Goods modelling. Furthermore we can provide guidance on bio-analytical testing and the design of a control strategy.

A case study describing the performance of the platform for the production and purification of adenovirus is available from here[4].

If you would like further information on the viral vaccine platform, please contact me at **kai.touw@sartorius-stedim.com**

[3] discover more about BioPAT® Viamass

[4] discover more about production of adenovirus

The Development of a Platform Technology to Address Challenges in Cell Line Development

by Cornelia Lindner

The Cellca CHO expression platform comprises of a host cell line, expression vector, media system and upstream process design. The platform uses a DHFR selection system and the host cell is a CHO DG44 cell line capable of growing in suspension in chemically defined, animal component-free media and achieves high cell densities, high yields and excellent product quality. A standard fed-batch process with defined media and feeding strategy is used to culture the cells. The process is reproducible and robust with no need for media or process optimization. Sartorius Stedim Cellca has demonstrated the scalability of the expression platform from the ambr® 250[1] microbioreactor system through to the BIOSTAT STR® 2000[2] single-use bioreactor. The expression platform is robust and produces reproducible results in rocking motion and stirred tank bioreactor formats.

A range of biopharmaceutical products have been expressed in the expression platform including mAbs, bispecific antibodies, Fc-fusion proteins, Fabs and biosimilars. In most cases a product titre of 3 g/L or greater is achieved. Three recent biosimilar projects have shown that, after process optimization, product critical quality attributes from Cellca clones have very similar profiles to those of the originator molecules.

[1] discover more about ambr® 250

[2] discover more about BIOSTAT STR® 2000

Furthermore, a review of 14 recent projects showed that, overall 90 % of the “top four “ project clones were stable and that, for any given project, at least two of the “top four” clones were stable over a nine-week period.

Sartorius Stedim Cellca is continuing to develop its CHO expression platform still further. Recently, the company validated their method to prove the monoclonality of the generated cell lines. The method uses the BD FACSAria™ Fusion flow cytometer in combination with the Cellavista non-invasive imaging system (Figure 1). The probabilities that there is more than one cell per droplet during cell sorting and that a cell has not settled into the focal plane for imaging are very low and combine to give an overall probability of monoclonality from the method of 99.9 %.

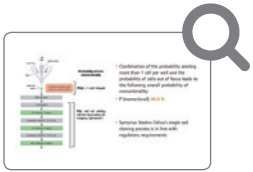


Figure 1: Validation of Cellca's Single Cell Cloning Approach

The company has developed a new pool generation approach called CLD 2.0 (Figure 2). The approach saves four weeks of development time by using increased MTX concentrations during the generation of mini-pools. Experiments with three difficult-to-express products showed that, on average, clones generated using the CLD 2.0 method produce higher titers when compared to those generated using the standard method.

Figure 2: CLD 2.0 A new pool generation approach

The clone selection process has been improved by replacing 25 mL shake flask cultures with the ambr® 15[3] microbioreactor system. The ambr® 15 allows clones to be evaluated under conditions that are more representative of those cells will experience at larger scales. Scientists have demonstrated that the ambr® 15 is more predictive than shake flask experiments with respect to cell growth, product titer and metabolic profiles in a 5 L benchtop bioreactor.

[3] discover more about ambr® 15

Finally, Sartorius Stedim Cellca is further investigating new methods to boost product titers from the CHO expression platform. Firstly, they have identified a novel signal peptide that showed increased titers in transfection pools by a minimum of 28 %. Secondly, the team have experimented with a new promotor that improved titers in four out of five tested projects (by between 29 % to 176 %) when compared to the standard promotor.

If you would like further information on the Cellca CHO expression platform please contact me at **Cornelia.Lindner@Sartorius-Stedim.com**

Fully Single-Use Virus Filtration during Manufacturing

by Birte Kleindienst

Engineers designing downstream processes should select an appropriate virus filter to match their specific application. Sartorius Stedim Biotech (SSB) has developed the Virosart® HF [1] filter specifically for the processing of monoclonal antibody and recombinant protein solutions derived from mammalian cell culture.

Increasingly, biopharmaceutical companies are seeking single-use solutions that they can apply readily in commercial manufacturing environments. Single-use technology allows rapid batch turnaround times, flexibility and lower capital costs. To allow biomanufacturers to benefit from single-use technology SSB has integrated the Virosart® HF filters into filter transfer lines (Figure 1).

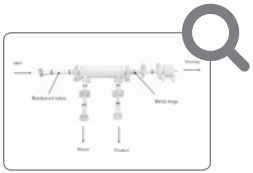


Figure 1: Concept of Filter Transfer Line

These transfer lines are delivered sterile following gammairradiation to the production site and can be easily connected into single-use assemblies. Their design has been optimized to allow them to handle the higher operating pressures of 2.0 to 3.0 bar typically needed for the virus filtration steps. For example, stable reinforced tubing has been used to allow operation up to 3 bar and metal rings have replaced cable ties to strengthen connections. Clients can choose between Opta® [2] and AsepticQuick® connections for processing within a sterile environment or TC connectors when controlled bioburden is all that is required.

Biomanufacturers require that their single-use virus filters can deliver high capacities, are scalable and allow for high step yields. However, they must also deliver robust retention performance across a range of flux rates, operating pressures and conditions during which the pressure is interrupted or pulses.

[1] discover more about Virosart® HF

[2] discover more about Opta®

SSB has shown that the Virosart® HF can successfully filter mAb concentrations of 10 g/L up to 15 g/L to a capacity of 8 kg/m² process solution. The performance can be improved by protecting the virus filter with Virosart® Max[3] and optimizing conditions such as the pH of the feed stream. Virosart® Max is a pre-filter specially developed for the virus retentive filters combining adsorption & size exclusion. Throughput data shows that the Virosart® HF is fully scalable from 5 cm² to 0.8 m². Due to its void volume optimized capsule design, 3 L/m² of buffer flush allows a product recovery of 99 % to be achieved[4].

Retention experiments with MuLV, MMV and PPV show that LRVs of greater than 5 were readily achievable with each virus type. Retention is independent when reaching flux decay of 70 %. Further experiments with PP7 demonstrated that the retention characteristics of the filter are scalable between 1.7 cm² to 2.4 m² devices. The retention of PP7 was shown to be independent of low and high operating pressure when tested at 0.1 bar, 1.0 bar and 5.0 bar.

In a particularly interesting set of experiments the impact of pressure interruptions on PP7 LRVs were studied. Three studies were performed in duplicate to understand whether a multi-step pressure reduction profile, rapid pressure changing profile or pressure release profile would reduce the retention efficiency of the Virosart® HF. However, the LRV remained consistent between fractions taken throughout each profile (Figure 2).

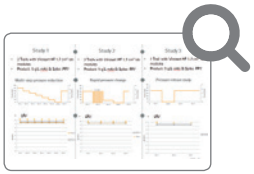


Figure 2: Independence of pressure interruptions on the LRV

Finally, the impact of pulsation created by a peristaltic pump on the retention performance of the Virosart® HF was tested. No impact of pulsation on retention was found with absolute PP7 retention of 6.5 LRV.

For more information about the Virosart HF® and these experiments please contact Birte Kleindienst at **birte.kleindienst@sartorius-stedim.com**

[3] discover more about Virosart® Max

Figures

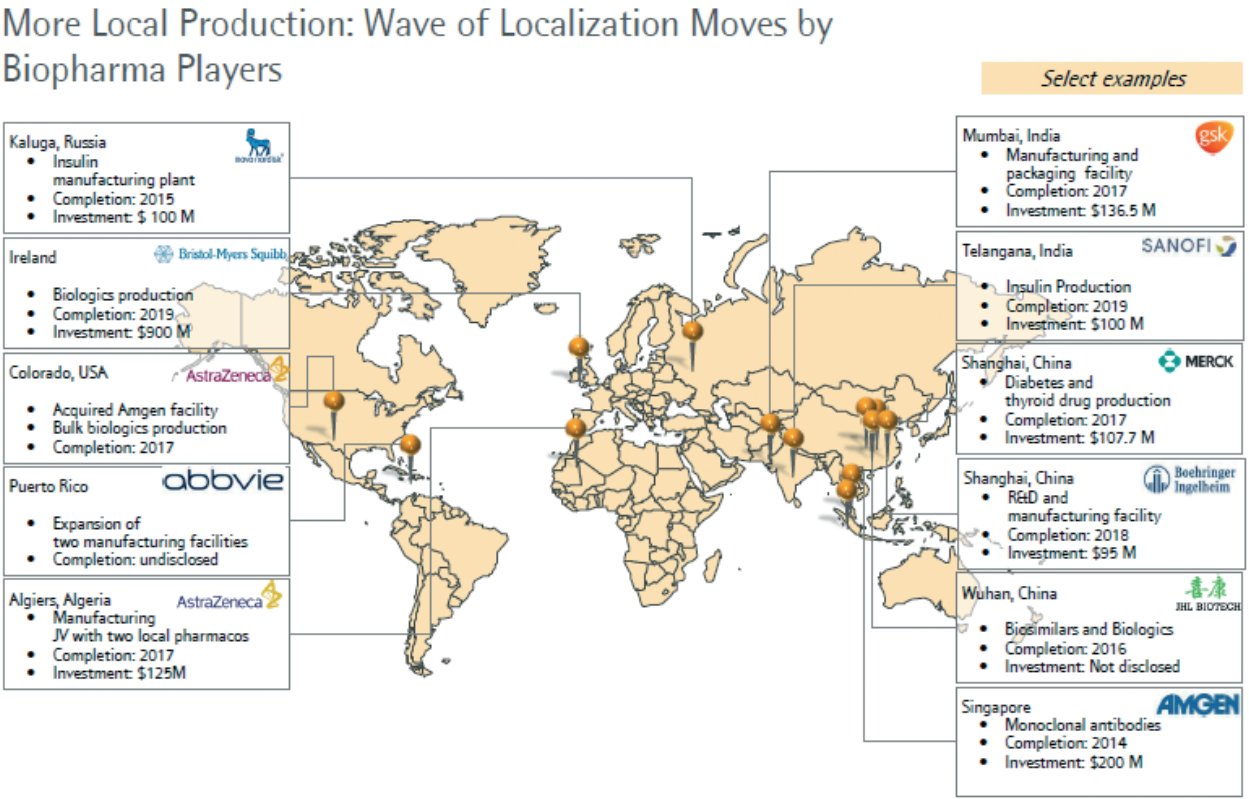


Figure 1: Expansion of biomanufacturing capacity all over the globe

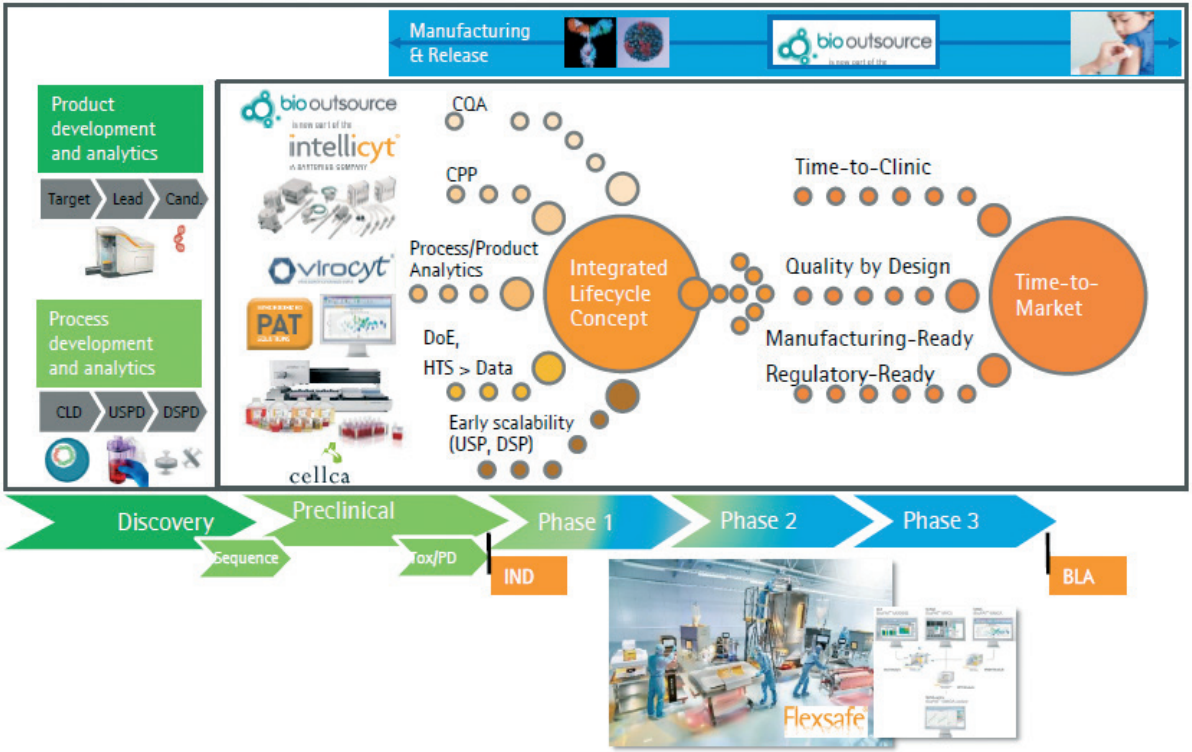
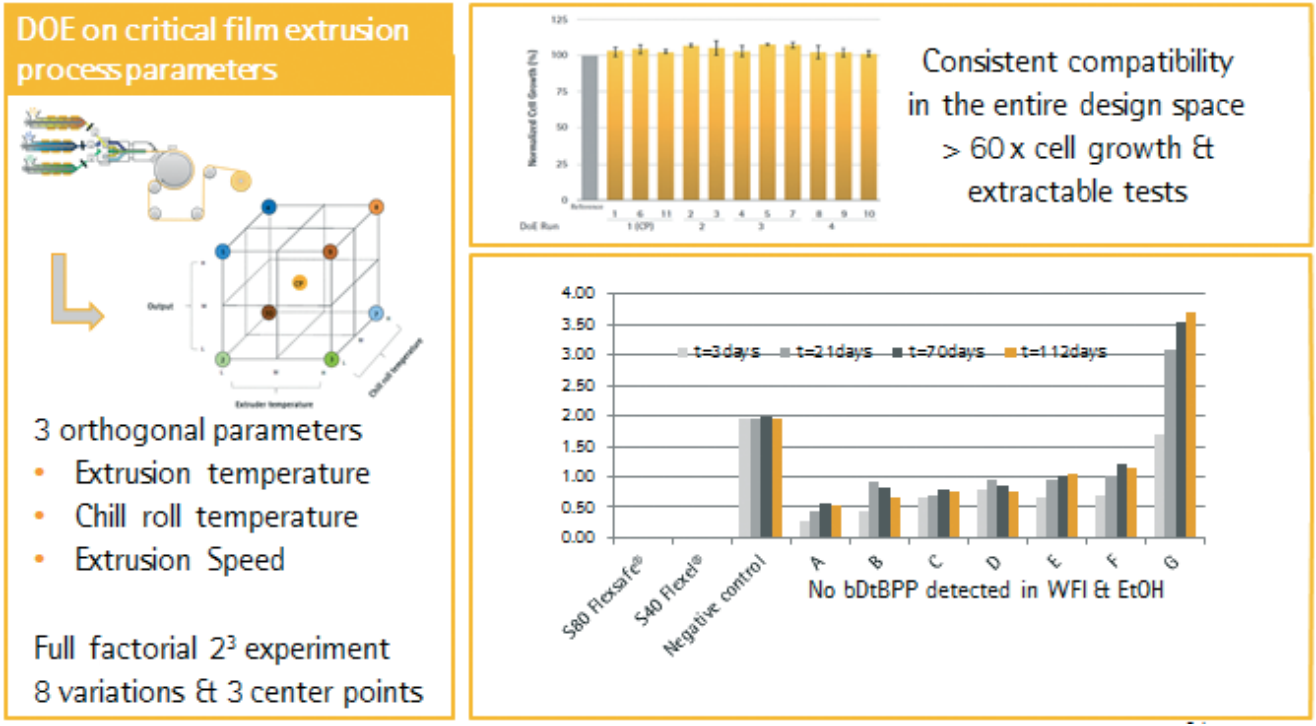


Figure 2: An integrated lifecycle concept speeds up drug development to IND and BLA



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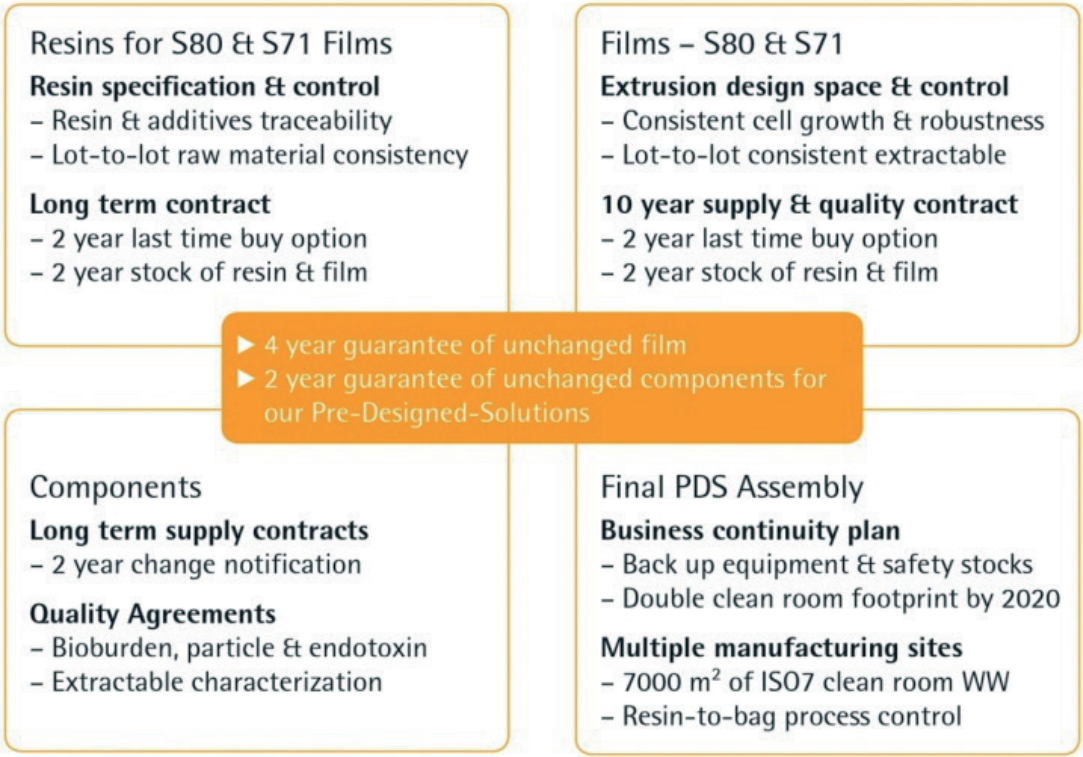

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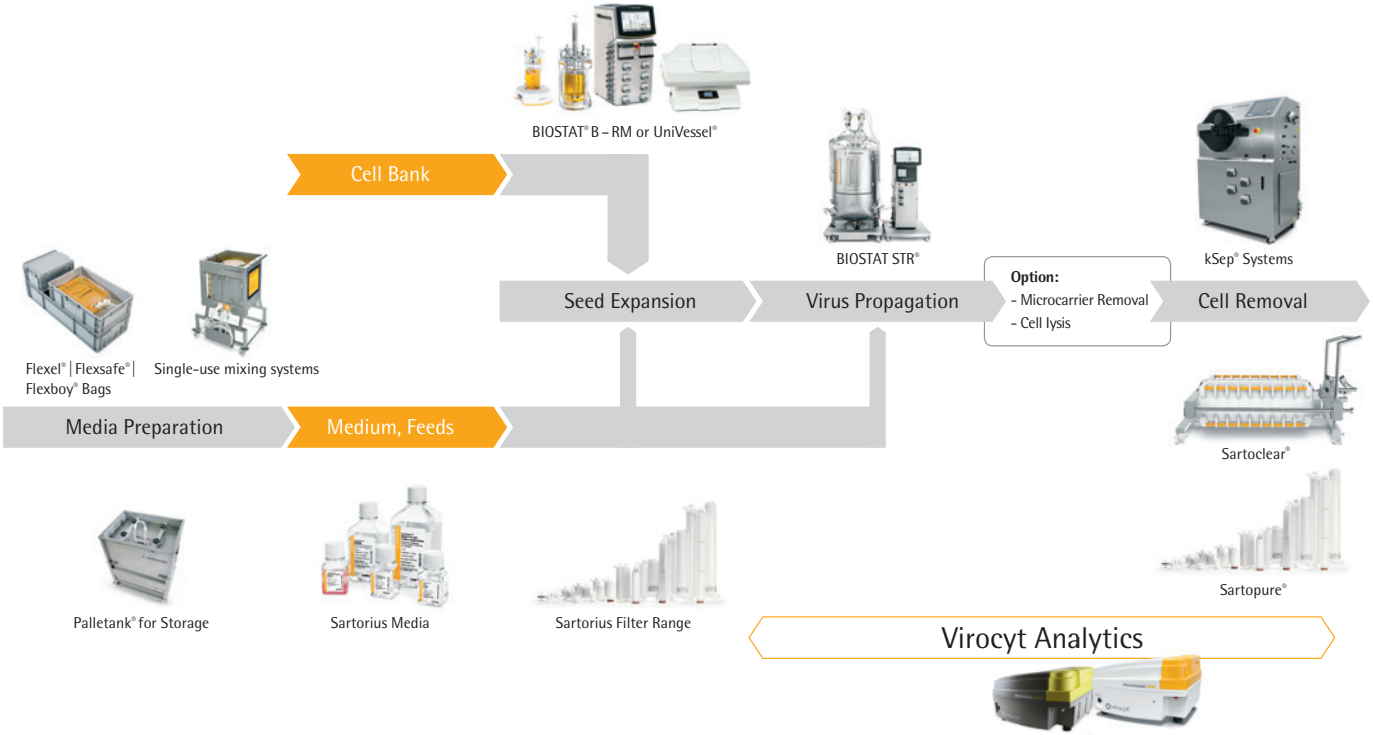


Figure 1: Upstream Viral Vaccine Platform

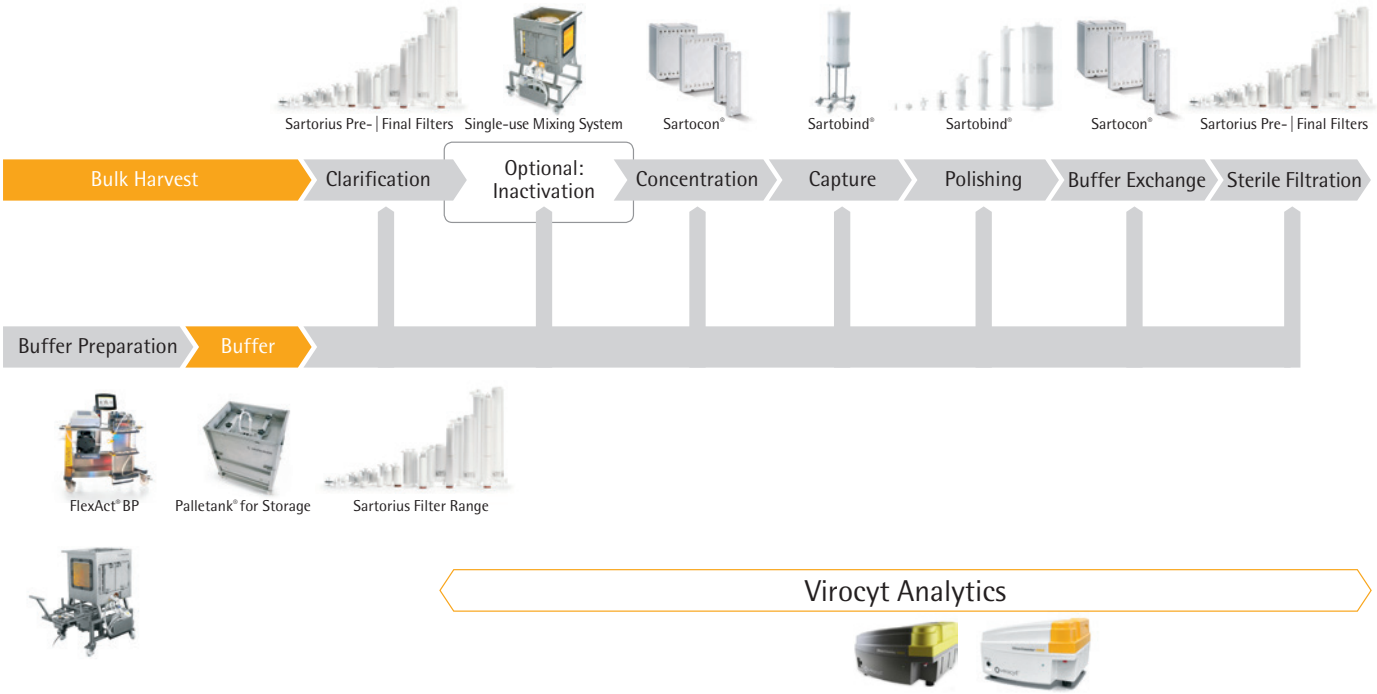


Figure 2: Downstream Viral Vaccine Platform

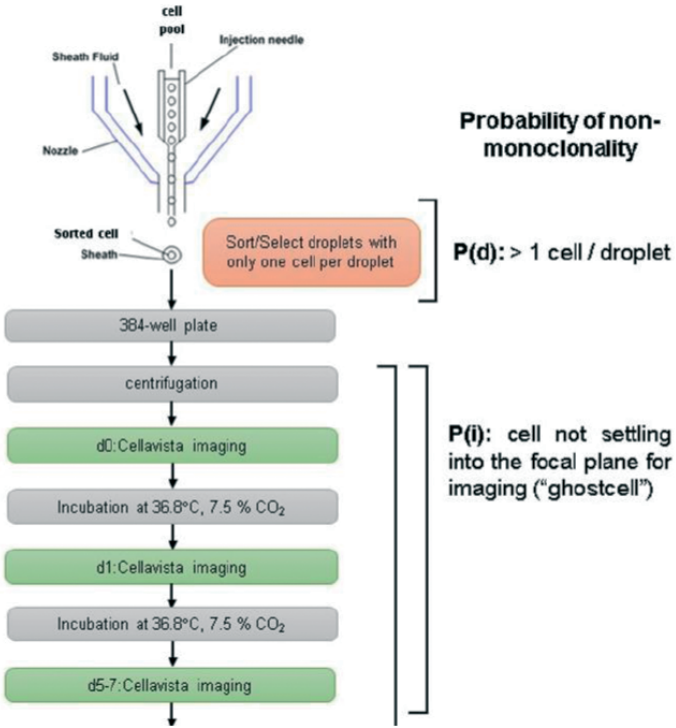
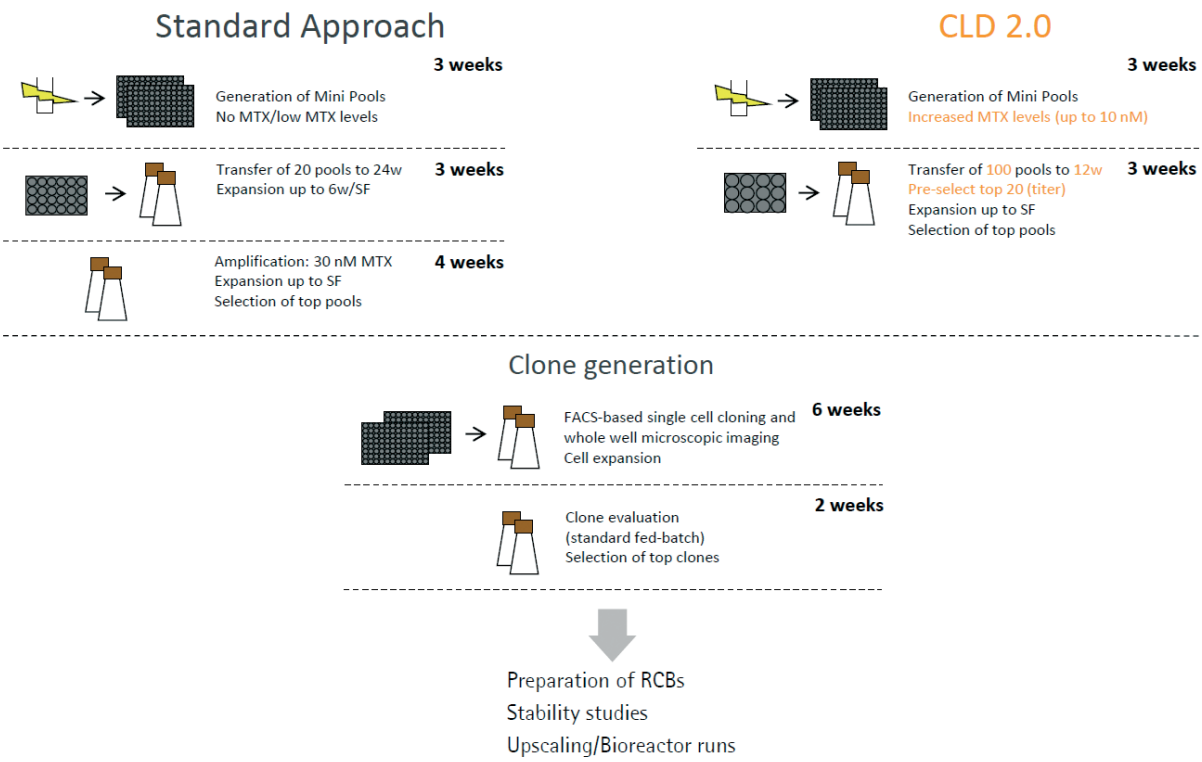


Figure 1: Validation of Cellca's Single Cell Cloning Approach

- Combination of the probability seeding more than 1 cell per well and the probability of cells out of focus leads to the following overall probability of monoclonality:
- P (monoclonal): **99.9 %**

- Sartorius Stedim Cellca's single cell cloning process is in line with regulatory requirements



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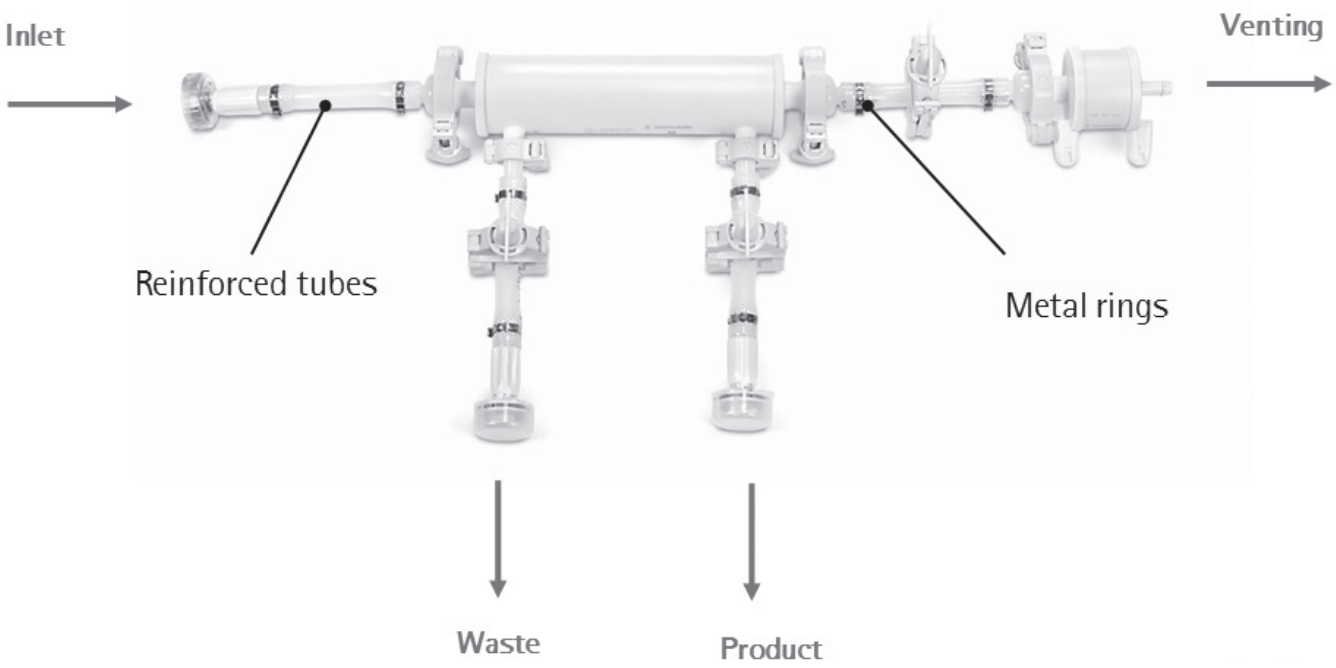

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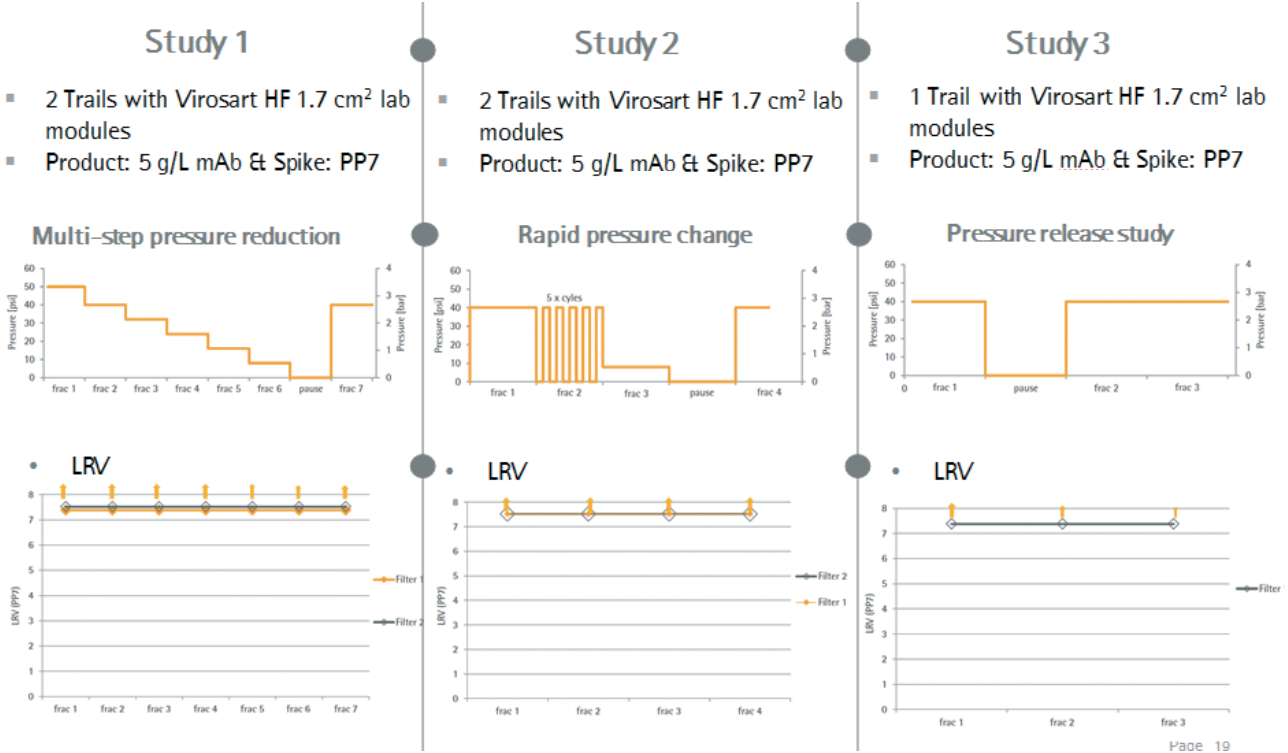

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