

Scalable AAV manufacturing: addressing challenges across the workflow

As the gene therapy field grows and evolves, adeno-associated virus (AAV) has emerged as one of the most significant vectors for its ongoing development. The number of approved therapies and the clinical pipeline continue to grow, making scalable and efficient solutions for AAV production ever more vital. A successful viral vector manufacturing process must be able to deliver a consistent, pure, and high-titer product that exhibits good safety and efficacy. In this article, both upstream and downstream solutions across the AAV production workflow are discussed. Scalable, high-titer AAV production is demonstrated in an insect-cell based Expression System. In addition, the benefits of implementing affinity chromatography in the downstream purification of AAV are also discussed, along with regulatory requirements for safety and purity testing during the AAV production process.

Cell & Gene Therapy Insights 2020; 6(11), 1679–1694

DOI: 10.18609/cgti.2020.185

ACHIEVING SCALABLE, HIGH TITER AAV PRODUCTION IN AN INSECT CELL HOST EXPRESSION SYSTEM

ExpiSf™ Expression System

The ExpiSf™ Expression System (Thermo Fisher Scientific) is the first chemically defined, baculovirus-based insect system for protein and AAV production. ExpiSf™ system enables an average three-fold increase in production when compared to other insect systems. It is

suspension-based, readily scalable, and uses animal origin-free reagents and chemically defined medium which allows for consistent cell growth and high lot-to-lot consistency.

The system also includes a chemically defined expression booster in the form of an enhancer, and an improved transfection reagent, ExpiFectamine Sf™ (Thermo Fisher Scientific), which enables the baculovirus production protocol to be adapted to a suspension format. This allows for high titer production of baculovirus following transfection,

eliminating the need for time consuming amplification steps. Finally, the system includes a Bac-to-Bac cloning kit for construction of baculovirus DNA.

Recombinant AAV (rAAV) production runs were performed using a dual infection approach using two baculoviruses, one containing the Rep and Cap genes, and the other containing the gene of interest flanked by the AAV inverted terminal repeat sequences. The gene of interest for these experiments was green fluorescent protein (GFP).

Shown on the graph on the left of **Figure 1** is the production of AAV for two serotypes, AAV2 and AAV6, using the ExpiSf™ Expression System. For comparison, these runs were performed with and without enhancer to test whether the enhancer boosts AAV production in a similar manner to that previously observed for protein expression. The enhancer boosted rAAV production for both serotypes tested, with high titers achieved 3 days post-infection. For comparison, the same serotypes produced in Sf9 cells in Sf-900 II medium, following a previously published protocol [1], is shown on the right of **Figure 1**. Similar titers to those achieved with the ExpiSf™ Expression System were observed, demonstrating that this system can produce rAAV at levels similar to currently used insect systems.

Tests were performed to demonstrate that rAAV production could be scaled-up to bioreactors. This was done using HyPerforma™ stirred tank bioreactors at the 3L scale. Similar growth kinetics were observed for AAV2 when compared to shake flask controls (**Figure 2**). Additionally, equivalent AAV titers were achieved in stirred tank reactors compared to shake flask controls. To test whether AAV particles produced in the ExpiSf™ Expression System were infectious, HT1080 cells were inoculated with AAV2 crude lysates from both shake flask and bioreactor. Infection was observed as indicated by expression of the AAV gene of interest, GFP.

Finally, an experiment was performed to purify rAAV from an ExpiSf™ production run. 400 ml of clarified lysate from a 1.2L

production run was loaded onto a 1 ml column containing POROS™ CaptureSelect™ AAVX affinity resin to purify the AAV6 particles.

Figure 3 demonstrates that purification of AAV6 particles resulted in a sharp elution peak shown in the UV chromatogram. The elution fractions showed robust purity, and a yield of 62% of recovered particles in the elution fraction. Electron microscopy imaging of purified AAV6 particles contained a consistent mixture of full and empty particles, and purified AAV6 particles were infectious, as shown by HT1080 cells which appear green following infection.

AAV DOWNSTREAM PURIFICATION SOLUTIONS

The key challenges associated with downstream purification of AAV include the high degree of variation from the upstream process, increased impurity burden due to cell lysis and different clarification strategies, and often, challenging analytics associated with AAV characterization. These can all influence the development and robustness of the purification process. It is imperative that the field innovates across the entire workflow in order to achieve highly scalable and productive platform processes with a shortened development timeline.

Innovative chromatography solutions

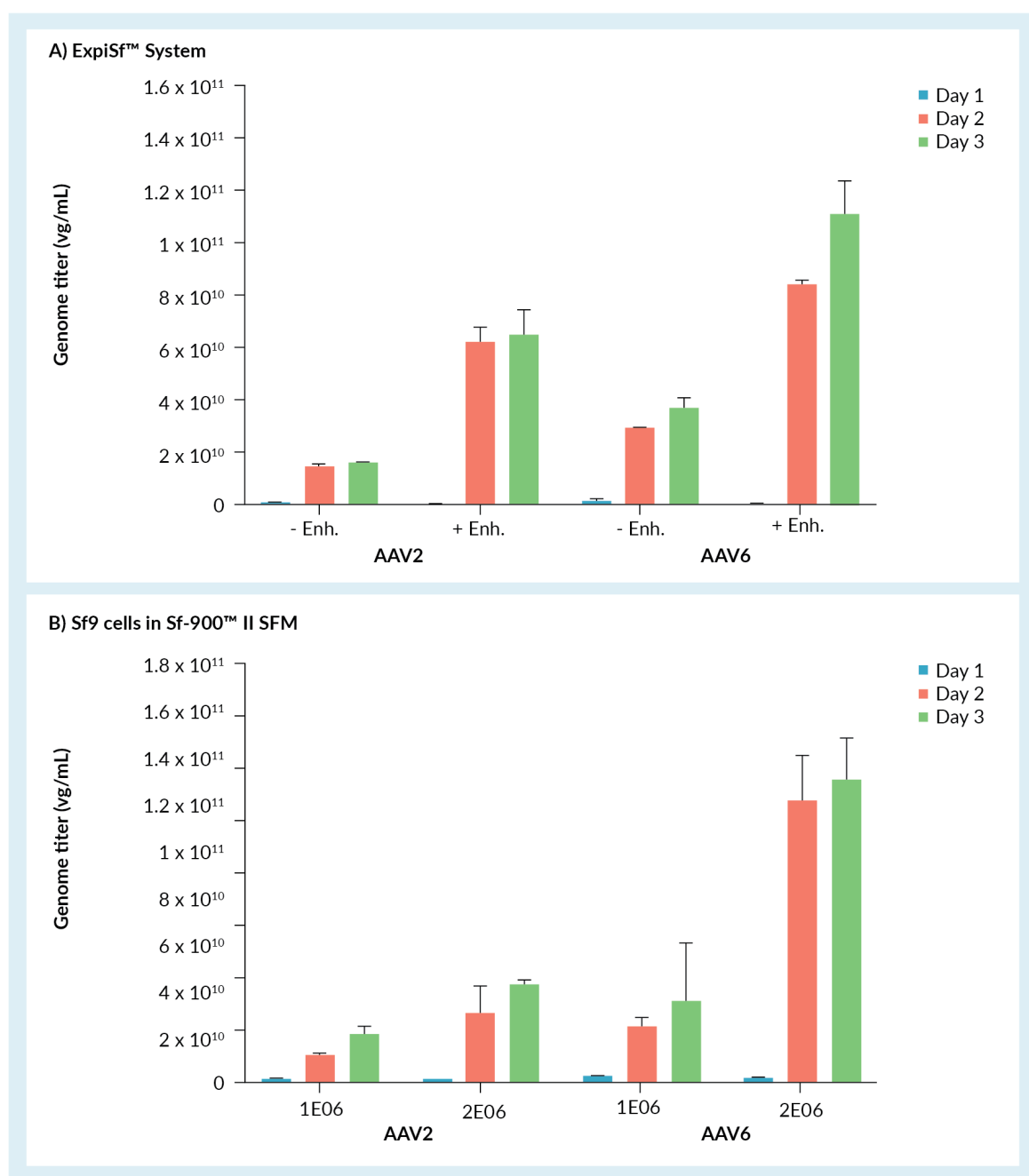
Presently, the evolution of AAV downstream processes has turned to affinity chromatography as the first post-clarification step. The rationale for using this purification approach is that it can accommodate a wide range of upstream processes and at the same time, allow downstream process developers to balance process design with respect to ease of scalability, increasing productivity, and also achieving platformability with a simplified process design.

Thermo Fisher Scientific has developed innovative, best-in-class chromatography solutions to enable the next-gen AAV downstream platform. These consist of the

POROS™ CaptureSelect™ AAV resin family for high-capacity affinity capture, as well as the POROS™ Anion Exchange resin family for high-resolution polishing (Box 1).

FIGURE 1

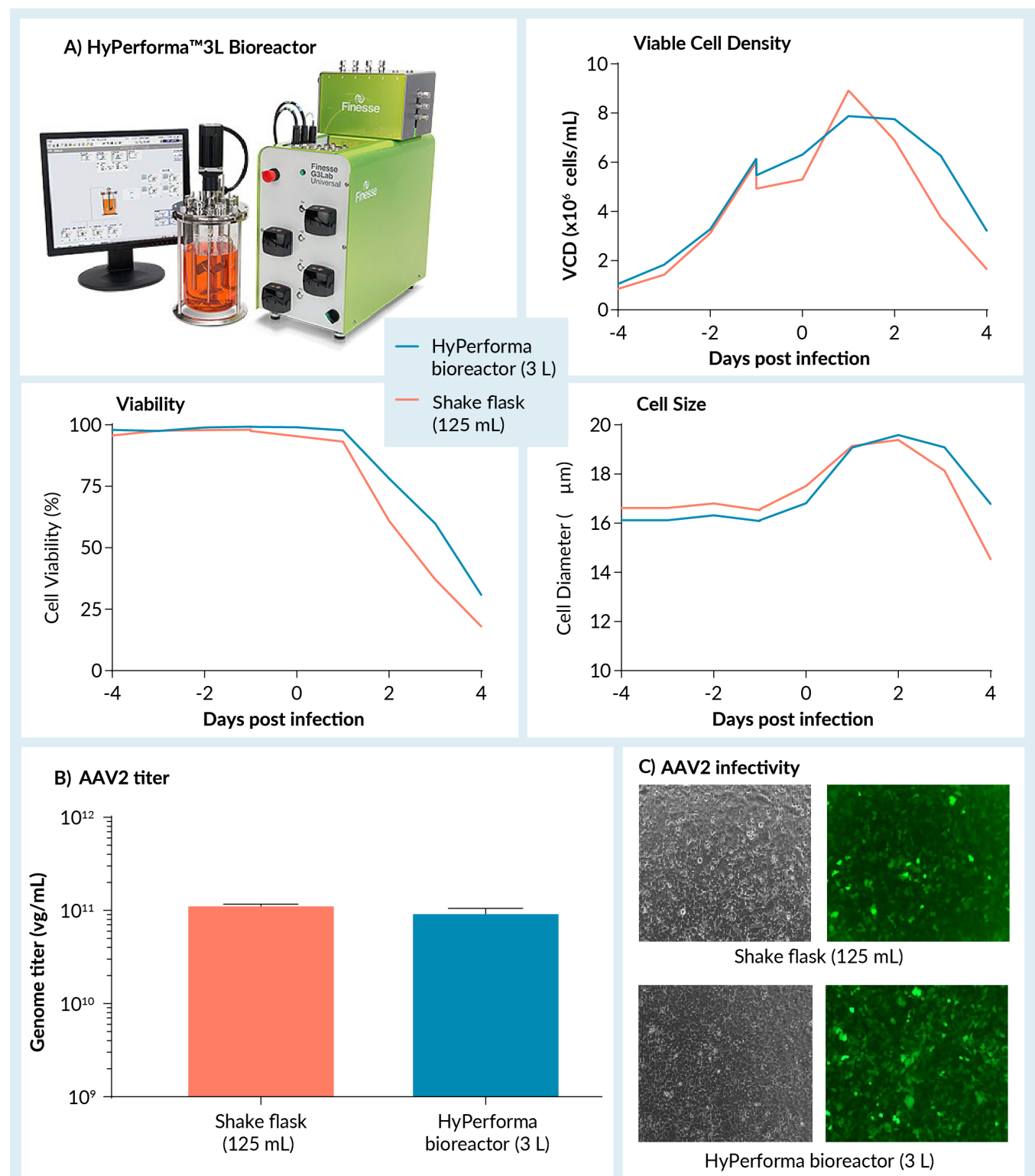
Recombinant adeno-associated virus production in Sf9 cells.



(A) AAV genome titers of crude lysates from ExpiSf9 cells cultured in ExiSf CD medium. As a control, AAV production runs in the absence of enhancer were performed. (B) AAV genome titers of crude lysates from Sf9 cells cultured in Sf900 II medium. Production runs in (A) and (B) at 25-mL scale in 125-mL shake flasks. Bars in (A) and (B) represent AAV genome titers 1-, 2- and 3-days post-infection. "- Enh." Indicates no addition of ExpiSf enhancer; "+ Enh." denotes addition of ExpiSf Enhancer 18-24h prior to cell infection.

FIGURE 2

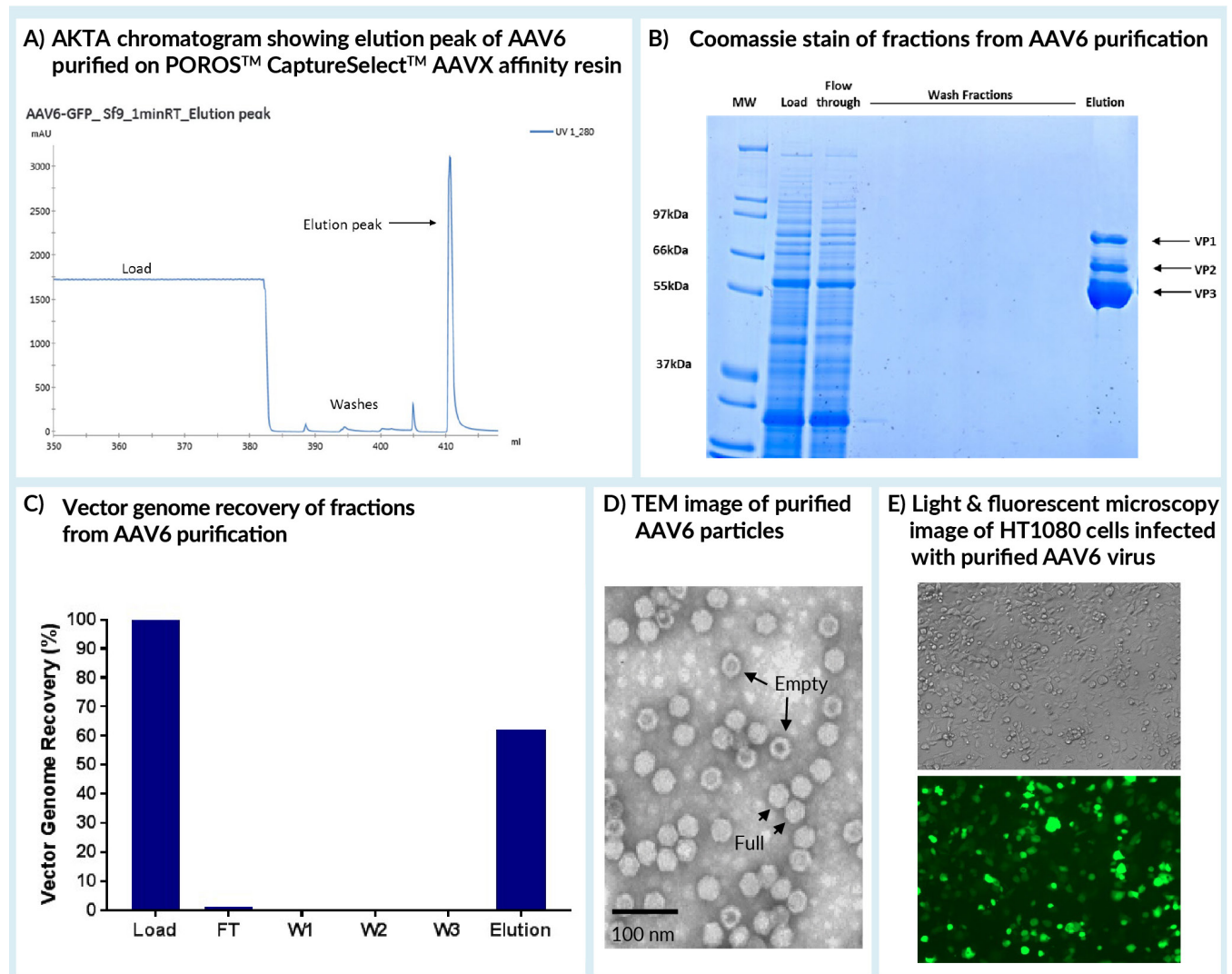
Scalable production of infectious recombinant adeno-associated virus in ExpiSf9 cells.



(A) Viable cell densities, cell viabilities and cell diameters of ExpiSf AAV production runs for AAV2 in 125 mL shake flasks and Finesse 3 L stir-tank bioreactors (picture upper left). (B) AAV genome titers of ExpiSf cell lysates from 125 mL shake flasks and 3 L stir tank bioreactors. Samples were collected three days post-infection. (C) Light and fluorescent images of HT1080 cells inoculated with AAV2 crude lysates from 125 ml shake flask and 3 L stir-tank bioreactor runs.

FIGURE 3

Purification of rAAV6 from ExpiSf™ production run.



(A) Chromatogram showing elution peak of rAAV6 purified on POROS™ CaptureSelect™ AAVX affinity resin. (B) Fractions from AAV6 purification run on a Coomassie stained gel. The capsid proteins VP1, VP2, and VP3 are indicated. (C) Vector genome recovery, relative to the load, in flow-through (FT), wash (W1–W3), and elution fractions of rAAV6 purification run. (D) Transmission electron microscope image of purified rAAV6 particles. Empty and full particles are indicated in the image. (E) Light and fluorescence microscopy images of HT1080 cells infected with purified rAAV6 virus.

POROS™ CaptureSelect™ AAVX Resin performance

As published previously, the AAVX affinity resin is specifically developed for the purification of a broad range of serotypes [2,3]. To date, AAVX has demonstrated binding to almost all serotypes tested. Importantly the pan-serotype binding property of AAVX provides a key building block for an AAV downstream platform and could address the rapid process development needs of different

serotypes and capsid engineering, as well as transgene combinations.

Figure 4 shows a simple static binding experiment to demonstrate binding between the AAVX resin and various naturally occurring and recombinant AAV vectors. It clearly shows binding of the resin to a large variety of AAV serotypes.

In a further set of experiments designed to demonstrate the scalability of the POROS™ CaptureSelect™ AAVX Resin (and therefore not focused on optimization of purification),

► BOX 1

POROS™ CaptureSelect™ AAV resins.

CaptureSelect affinity resins are used in commercial purification processes globally, for a wide range of therapeutic molecules such as antibody-based derivatives, recombinant proteins and enzymes, biosimilars, plasma proteins, and of course, viral vectors.

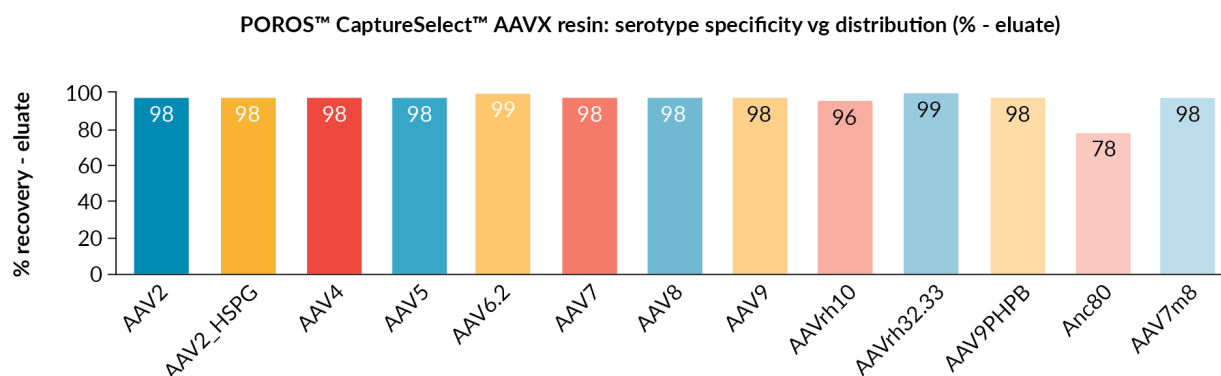
CaptureSelect affinity ligand technology is based on the unique properties of a sub-class of camelid antibodies that contain heavy chains only and no light chains. This technology retains the antigen binding capabilities of a conventional antibody, via a unique VHH domain with 3 CDR regions. The affinity ligands are produced at scale in yeast using an animal-origin free process and then coupled to a resin backbone to create the final affinity resin.

The POROS resin backbone is made of polystyrene-divinylbenzene, which results in highly stable packed beds, as well as a linear and scalable pressure flow performance during scale-up. For AAV affinity resins in particular, the base bead was designed to be 50 microns, with a larger interparticle pore structure, ensuring POROS resins are fully scalable and easily packed from developmental to commercial scales. Due to the open pore structure and resulting reduced mass transfer, both capacity and resolution are well maintained as linear velocity is increased, resulting in more efficient purification.

By combining POROS with CaptureSelect, three high-capacity affinity resins were created: AAV8 and AAV9 resins that specifically bind AAV8 and 9, respectively and AAVX, which is pan-serotype affinity resin.

► FIGURE 4

AAVX resin serotype specificity.



Recovery using the AAVX resin was determined for various AAV serotypes. Binding is performed in static mode. The % of recovery (VG) was determined by qPCR. This data was kindly provided by Massachusetts Eye and Ear.

a team from Thermo Fisher's viral vector services group used the AAVX resin in dynamic mode for the purification of two different serotypes (blinded as A and C). Performance of the resin was tested at various production scales and demonstrated that yields are comparable at various scales, up to the multi-100L (Figure 5).

Several more collaborative and in-house case studies were performed with AAVX. Purification of AAV6 with GFP as a transgene was successfully purified with both high purity and yields, for both insect and mammalian-produced vectors.

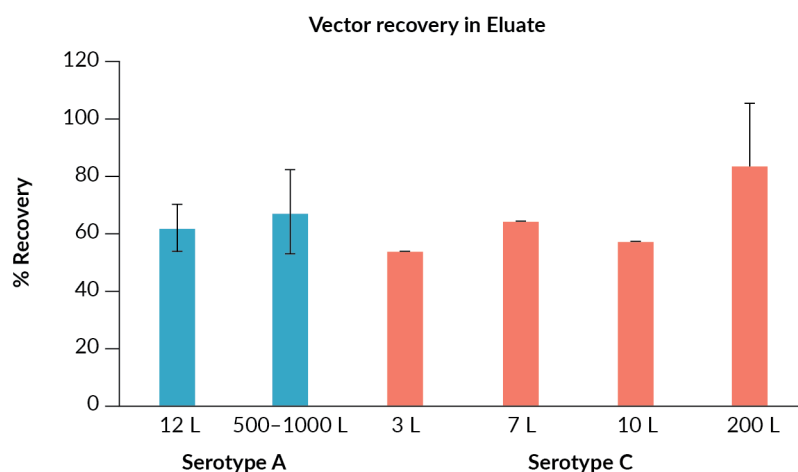
Dynamic binding capacity on the AAVX resin using AAV 6 GFP was also investigated

– either Sf9 or HEK293 lysate containing AAV6 was loaded onto the resin, and capsid breakthrough and flowthrough were monitored. In both cases, high capacity of the AAVX resin was observed as expected, but some differences in breakthrough were seen (Figure 6).

For the Sf9 system, the cells were lysed and the nucleus treated and filtered, and then directly loaded. For this feed stream, no breakthrough was seen during the entire loading process, up to 4×10^{14} capsid per mL resin. In contrast, for the HEK293 system the entire bioreactor volume (cells plus supernatants) was lysed, filtered, and tangential flow filtration (TFF) was performed

► **FIGURE 5**

Performance of the AAVX resin at various AAV production scales.



Recovery of two serotypes was tested using small and large production scales (up to >500L). Purification was performed in dynamic mode.

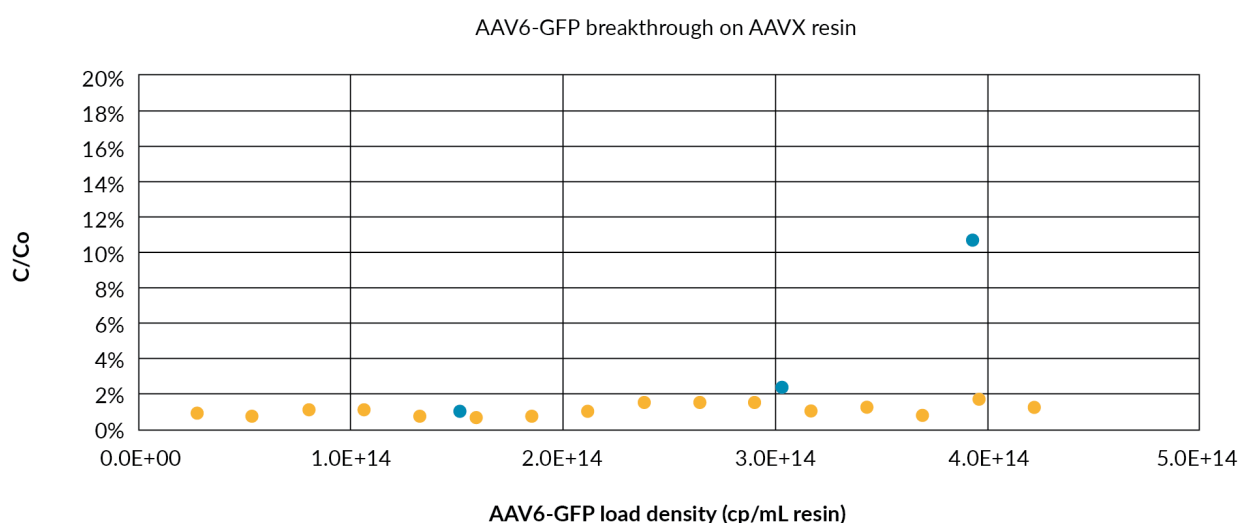
before loading. In this case, ~10% breakthrough was recorded at $4E.0+14$ capsid per mL.

As similar amounts of total capsids were loaded for these two parallel runs, this experiment clearly illustrates that feed strain can influence AAVX capacity, since in both

cases residence time, capsid serotype, and transgenes were identical. In general, for any kind of affinity chromatography, a cleaner starting material should always be preferred as this will benefit process recovery, as well as cleaning by minimizing nonspecific binding from the increased impurity burden.

► **FIGURE 6**

Breakthrough analysis of AAV6 in produced in different expression systems (HEK293 and Sf9).



The AAVX resin shows high dynamic binding capacity for both AAV6 feedstreams.

Downstream process development is critical for resin performance

Unlike in the monoclonal antibody field, where a standard downstream platform has been created through years of development and process knowledge accumulation, AAV platform process conditions have yet to be well established. Due to accelerated clinical timelines, process flow can be rushed, and early materials limited.

As mentioned above, some customers reported low yield in early purification attempts for AAV6. However, by taking a systematic approach to optimization, the yield can be dramatically increased, as shown in **Figure 7**. It is crucial to understand the effects of the following key parameters:

- ▶ Elution pH and excipients
- ▶ Load purity and concentration
- ▶ Residence time
- ▶ Intermediate wash
- ▶ Analytics

Through accumulation of process knowledge over time, it will be possible to move

to platform conditions for standardized AAV purification using AAVX resin, which will be crucial in achieving optimal process performance.

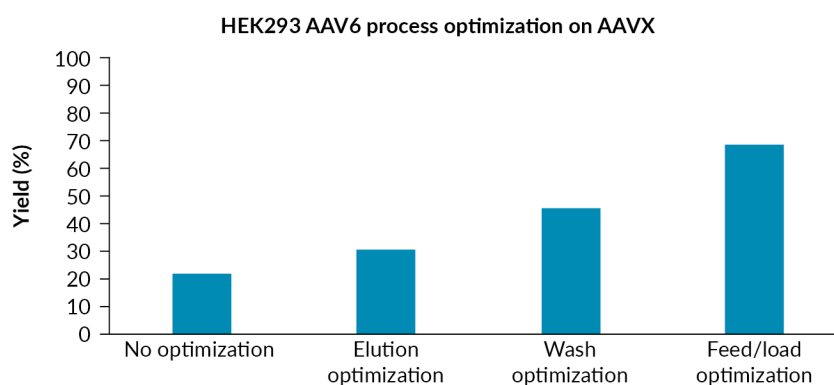
Demonstration of effective viral clearance

According to guidance from the FDA (ICH Q5A), the risk of potential viral contamination for viral therapeutics derived from cell lines should be addressed with a three-pronged approach: prevent, test, and remove. In the case of AAV, the upstream process itself can sometimes include helper viruses, and presents a scenario where both the product and the process contaminant may be viruses. To assure the final product is free from viruses, multiple viral clearance steps throughout the downstream process are implemented. Effective virus removal during chromatography steps will benefit overall viral clearance of the process. To illustrate the viral clearance potential of the AAVX resin, a scaled-down model virus spiking experiment was performed using a clinically relevant purification process for AAV8.

A wide range of model viruses of different sizes, molecular makeups, and physical chemical properties was selected. As expected,

► FIGURE 7

Process optimization of AAV6 purification using the AAVX resin.



Final yield was improved by optimizing elution conditions, wash steps and load concentration. Thorough optimization clearly leads to a significant increase in yield.

model viruses were effectively removed in elution with greater than 4 log clearance, with the exception of Reo-3 and HSV-1 (Figure 8). Interestingly, similar clearance results were obtained when comparing the manufacturing center point conditions to the worst-case scenario process conditions of increased load and residence time.

In summary, POROS™ AAV CaptureSelect™ affinity resins are ideal tools for AAV downstream purification. With increasing demand in the AAV field these resins hold great potential for helping the AAV field move towards standardized platform purification tools.

Regulatory requirements exist globally for mycoplasma testing for a variety of therapeutics made in cell cultures, including rAAV. To maximize the sensitivity of safety testing, regulators call for testing at specific points in the cell culture where a contaminant would be most detectable. For AAV manufacturing, it is recommended that mycoplasma testing is performed at the end of the cell culture process, at the bioreactor harvest, and prior to purification of the recombinant AAV.

Regulators describe use of rapid mycoplasma tests, including PCR-based tests, as an acceptable alternative to extended period or 28-day culture-based testing for mycoplasma.

MANAGING REGULATORY EXPECTATIONS: CONTAMINANT & IMPURITY TESTING

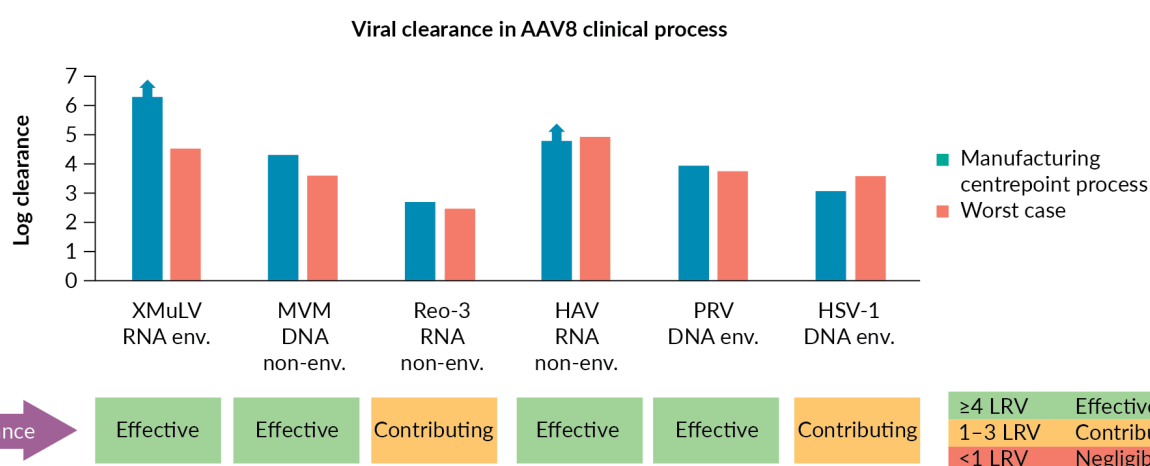
Finally, when considering the production of AAV, regulatory expectations around contaminant impurity must be considered. For the purposes of this article, the focus will be on mycoplasma detection and quantitation of DNA residuals.

MycoSEQ™ mycoplasma detection system

The PCR-based MycoSEQ™ mycoplasma detection system is specifically designed for lot-release testing in cGMP applications. It was designed to meet or exceed the guidance in the European pharmacopeia 2.6.7,

FIGURE 8

Demonstrating the viral clearance potential of the AAVX affinity resin.



A viral clearance study, using six different model viruses was conducted. Robust clearance was demonstrated for xMuLV, MVM, HAV and PRV (>4 LRV). In addition, a contributing clearance was shown for the viruses Reo-3 and HSV-1. Manufacturing centerpoint process: representative manufacturing process parameters. Worst case: a combination of high load and high residence time; conditions with the highest probability of virus co-purifying with the product.

2007, on mycoplasma testing with nucleic acid-based detection methods.

The fully integrated system includes sample preparation kits and protocols, qPCR-based detection, instrumentation and software. The system is also supported with training and guidance on implementation and validation.

Perhaps the most important aspect of a mycoplasma detection test is the level of confidence in the results obtained. MycoSEQ™ enables validation at levels of 10 genome copies or 10 colony forming units per ml of test sample and does not detect any off-target microorganisms. Objective multi-parameter results interpretation is used and there are full workflow controls, including a patented discriminatory positive control for confidence in either negative or positive test results.

Following validation regulatory filing and review, MycoSEQ™ has received regulatory acceptance for use in lot-release testing applications across multiple therapeutic modalities, including cell culture manufacturing, cellular therapy, vaccines, tissue therapy, and AAV manufacturing processes.

Residual host cell DNA testing

Residual host cell DNA quantities contained in final dosage forms must follow guidelines established by major regional and global regulatory agencies, including the FDA, EMA, and World Health Organization, as well as local regulatory jurisdictions.

For AAV, a particular challenge which has developed is that some vectors can also package (i.e., inside the viral capsid) fragments of host cell DNA and/or DNA from vectors used in the rAAV process. In general, the regulatory guidance is that residual DNA levels for continuous non-tumorigenic cells in final products should be limited to less than 10 nanograms per dose. In cases where DNA levels are approaching that specification, the DNA size should be below approximately 200 base pairs.

Testing for residual host cell and vector DNA occurs across the purification process, from the beginning until the end. Testing at each step of the purification process enables understanding of the capability for clearance of host cell and associated vector DNA components.

Multiple AAV manufacturing systems are available – but whether 293, HeLa cell, Sf9, or baculovirus-based systems are used, each of these contribute host cell DNA components, as well as the associated vectors or helper viruses that are used to generate the recombinant AAV. It is important to account for all of these residual DNA components when understanding and measuring the capability of a purification process.

Thermo Fisher Scientific has developed two residual host cell DNA assays focusing on AAV manufacturing workflows. The first is a HEK293 quantitative host cell DNA kit. This is a qPCR-based assay for quantitation of host cell DNA from human embryonic kidney 293 cell lines used in the development of gene therapy, cell-based vaccines, and similar biological therapeutics. It includes precisely quantified, highly purified genomic DNA from an established human embryonic kidney 293 cell line and provides a comprehensive solution which includes all standards and reagents required for quantitation of host cell DNA. The workflow is rapid, with time to results of <5 hours. It is also highly sensitive with a demonstrated Limit of Quantitation (LOQ) of 0.3 picograms of DNA/qPCR reaction in samples extracted from HEK293 processes, resulting in a full workflow LOQ of 15 pg DNA/mL test sample. The sample preparation is proven to be insensitive to the components found in typical purification buffers and salts across the complete workflow for purification of recombinant virus.

Secondly, there is a more recent residual DNASEQ assay; a quantitative Sf9 and baculovirus DNA kit. This kit is unique in that it is a duplex quantitative PCR assay for quantitation of both baculoviral vector and Sf9 host cell DNA. It shares a similar workflow

to the HEK293 assay and again, comes as an all-inclusive kit with all genomic DNA standards and reagents. The workflow is rapid and streamlined, with a time to results of <5 hours.

Sample prep for residual DNA assays

Sample preparation for a residual DNA-SEQ assay can be done either with a manual workflow, or an automated 96 well plate sample-based method for high-throughput sample testing needs.

Detection is performed using the Applied Biosystems QuantStudio™ 5, or 7500 Fast Real-time PCR system, and data analysis with AccuSEQ™ Real-Time PCR Detection Software, which is specifically developed to execute the calculations typical of residual host

cell DNA quantitation, and helps enable the user to comply with 21 CFR Pt 11 guidance.

Thermo Fisher Scientific offers a range of residual host cell DNA quantitation kits, including Chinese hamster ovary, *E. coli*, HEK293, human, Sf9 and baculovirus, Vero, *Pichia pastoris*, MDCK, and NS0 (mouse) kits (Box 2).

CONCLUSION

Reliable and integrated solutions are needed in order to provide robust and scalable AAV manufacture, and overcome the challenges associated with both upstream and downstream processing. Thermo Fisher Scientific can offer a range of technological solutions along with guidance and support, in order to achieve high-quality viral vector production in compliance with relevant regulatory guidance.

► BOX 2

The important role of regulatory support in AAV manufacture

Thermo Fisher Scientific is able to provide qualification and validation support for its entire bioproduction portfolio, with field application scientists providing detailed and rigorous on-site training in the use of all bioproduction solutions. Guidance is provided on method qualification and validation study design to accelerate implementation, along with systems validation services.

Company representatives can also attend Type C meetings and provide detailed responses to regulatory queries during reviews. Drug master files are in place for relevant products in jurisdictions that utilize these. For jurisdictions that do not use these processes, regulatory support packages can be provided to answer specific questions that regulators may have regarding the use of Thermo Fisher Scientific bioproduction solutions in commercial manufacturing processes.

When providing innovative technologies, it is important to drive regulatory understanding and expectations. Thermo Fisher Scientific team members are actively engaged with industry organizations, providing education on our technologies and the capabilities of our solutions. In addition, ThermoFisher participates in industry guidance groups on standards used in the type of tests the company supplies

Q & A



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Q How is ExpiSf™ different to competitor insect systems?

KT: Firstly, this was the first chemically-defined medium for insect cells to come to market. Another important aspect is that Sf9 cells in this medium are able to grow to higher cell densities than in the counterpart Yeastolate medium. We are able to infect these cells at higher cell densities, which translates to a higher yield.

Another benefit compared to other systems is that we developed an enhancer that helps boost both protein expression as well as AAV titers.

Q Is there a difference in protocols for protein expression and AAV production with the ExpiSf™ system?

KT: Interestingly, there is. For protein expression we determined that seeding at 5 million cells/ml, and infecting with a multiplicity of infection (MOI) of 5 seemed to land us on top performance. When we started testing AAV, we took a Design of Experiments (DoE) approach and looked at different cell densities and MOIs for high production. We found that slightly lower seeding densities of 3 million cells/ml for insect cells, and a slightly lower MOI for a dual infection, worked better. It is also worth noting that in both systems, the enhancer does boost expression.

Q How do you separate regular viral particles from empty capsids?

JL: The affinity resin will bind both empty and full capsids. You require a polishing step following capture, typically anion exchange is used. For our resins we have the POROS

HQ and XQ, as strong anion exchangers, and the D and PI as weak anion exchangers. The HQ seems to be very popular and is able to resolve empty versus full separation.

Q Could you elaborate on the capacity of the resin as it pertains to process development parameters such as residence time? Does feed concentration matter?

JL: Based on our experience, the capacity of CaptureSelect™ resins, in general, should be in the 10s of mg protein/ml of resin.

To do a rough calculation, that translates to the lower 10^{15} range of capsids per ml. As you can imagine, a lot of things can affect that number. In our AAV6 experiments, for example, we have comfortably seen 10^{14} capsids/ml range at a 1-minute residence time.

With POROS™ being highly rigid and a bit more open in pore structure, you can run at higher flow rates without significantly compromising the capacity.

With regards to feed, clearly optimization is required to maximize the binding. In general, the cleaner the feed the better. You also want to keep the concentration of the titer of the AAV fairly high. If you move to very low titers you may potentially run into problems, as you will be getting closer to that linear part of the binding experiment, which impacts the capacity.

Q Are the mycoplasma ResDNA and host cell protein detection kits regulatory compliant?

MB: Yes, and these were specifically developed to meet or exceed the most rigorous regulatory expectations globally. We have had these on the market for over ten years now, and they have been validated for use in multiple commercial manufacturing processes across a variety of therapeutic modalities.

Q Can the residual host cell DNA assay recognize and quantitate DNA fragments of different sizes?

MB: Yes, and our R&D team has generated data to demonstrate that. Importantly, as I mentioned earlier, the assay amplicon is in the 100 base range, so we are able to quantitate DNA that has been reduced down below the regulatory guidance of 200 base pairs.

We have already generated data showing that the quantitation is accurate, whether the DNA is intact – or as intact as possible for purified genomic DNA – or has been enzymatically or mechanically using sonication, reduced in size.

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BIOGRAPHIES

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Kenneth Thompson, PhD, is a Manager of Cell Biology R&D in the Life Sciences Solutions Group at Thermo Fisher Scientific in Frederick, MD (USA). Dr. Thompson leads a team of scientists focused on developing new products for cell biology applications including Baculovirus-based insect systems for protein expression and virus production. Dr. Thompson received his PhD in Molecular and Cellular Biology and B.S. in Biological Sciences from the University of Maryland, Baltimore County.

Dr Chao Yan Liu**Senior Manager, R&D, Cell Biology, Thermo Fisher Scientific**

Chao Yan Liu is a R&D Senior Manager, Cell Biology at the Life Sciences Solutions Group based in Frederick (MD, USA). Chao Yan Liu received the M.D. degree from the Hebei Medical University (Hebei, China) and the Master degree in Pathology from the Academy of Medical Sciences in Beijing, China. She got her post-doctoral training at Blood Research Institute, Medical school of Wisconsin and then became research assistant professor at the University of Buffalo, New York. After being very active for more than 10 years in academic research in the field of cellular biology and immunology, in 2005 she joined the Research and Development department of the former Life Technologies. She has made great contributions to more than ten of the GIBCO® brand Cell Culture Essential products including AlgiMatrix™ 3D Culture System, OpTmizer™ CTS™ T-Cell Expansion SFM, TrypLE™ Select Enzyme, ES Cell Qualified FBS, GlutaMAX™ media supplement, FreeStyle™ F17 Expression Medium and CD FortiCHO™ Medium. She has extensive experiences in mammalian cell culture, serum and protein free, chemical defined medium formulation, as well as protein expression. She served as leading scientist to develop two novel transient transfection systems, Expi293™ and ExpiCHO™ Expression Systems. In the past 2 years, she and her team focused on both protein expression and viral production system development.

Dr John Li**Staff Scientist, Downstream Purification, Bioproduction, Thermo Fisher Scientific**

John Li holds a B.S.c. in Biochemistry and a PhD in Structural Biology from the University of Toronto, Canada. Today, John is a Staff Scientist at Thermo Fisher Scientific where he focuses on downstream purification process development for monoclonal antibodies, AAV, and other biotherapeutic modalities. Before joining Thermo Fisher, John was a Process Development Scientist at Immunogen where he evaluated new downstream platform designs for antibody and antibody drug conjugates.

Michael Brewer

Director, Global Principal Consultant, Regulatory for the BioProduction Division (BPD), Thermo Fisher Scientific

Michael Brewer is the Director, Global Principal Consultant, Regulatory for the BioProduction Division (BPD) at Thermo Fisher Scientific. In this role, Michael is responsible for providing global support to BPD customers and serving as the regulatory thought leader and expert across all technology areas within BPD. Prior to moving to this role, he led the team responsible for product applications including microbiology, analytical sciences, and quality control. The products are fully integrated solutions for glycan profiling, bacterial and fungal identification, mycoplasma and viral detection, and host cell DNA and protein quantitation. Michael has over 30 years' experience in the biopharma industry, including Scios, Synergen, and Amgen in a variety of roles including discovery research, analytical sciences, and quality control. Prior to joining Thermo Fisher Scientific, he led a group at Amgen that developed qualified, validated, and implemented molecular methods for host cell DNA quantitation, contaminant (mycoplasma, virus, and bacteria) detection, contaminant identification, strain typing, and genotypic verification of production cell lines.

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Webinar published: Oct 29 2020; Publication date: Jan 15 2020.

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