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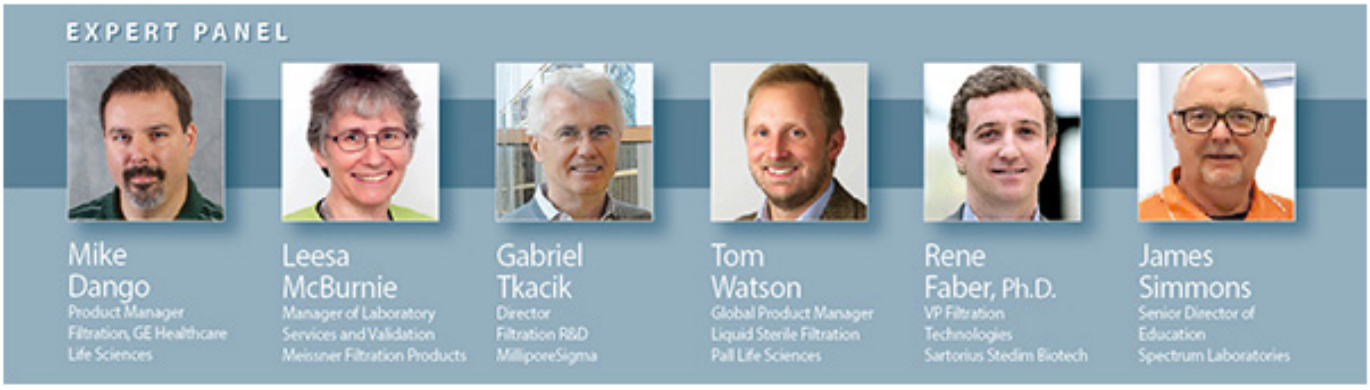
GEN Roundup: Filters' Future Focuses on Functionality

GEN's Expert Panel Reviews Filtration's Triumphs, Tradeoffs, And Trials to Come



One of the most critical activities in downstream biopharmaceutical production is filtration. Other activities—discovery, R&D, cell-line development, cell-line optimization, small-scale production, and upstream manufacturing—precede filtration and represent a great deal of effort, all of it intended to result in a commercial biotherapeutic product. But if the production stream admits an adventitious virus or some other cell-line contaminant that cannot be removed during the filtration process, all that previous work can literally go down the drain.

GEN recently asked bioprocess purification specialists to discuss key advances in virus filtration over the past 10 years and to give us their thoughts on what's absolutely necessary for successful and economic large-scale filtration.

GEN: What have been the major advances in bioprocess filtration over the past decade for improving virus removal?

Ms. McBurnie: Let's go back even further. We have come a long way from 1892 when Dimitri Ivanovsky discovered filterable viruses, that is, disease-causing agents that could not be removed by bacterially retentive filters.

Regulatory guidance for viral removal studies has made it easier to validate viral removal filtration. This guidance began with PDA TR41 Virus Filtration in 2008; was followed by PDA TR47 Preparation of Virus Spike used for Viral Clearance Studies in 2010; and now includes PDA TR71 Emerging Methods for Virus Detection in 2015, which describes some of the newer viral genomic detection tools.

Current guidance assists in the development of viral removal membranes because it provides clear goals and methods with which viral removal filters can be rated. It also assists in viral removal process validation for the same reasons.

Mr. Tkacik: Virus filtration in bioprocessing is standardized on a minimum of 4-log parvovirus removal. New products introduced in the past decade offer an exceptional speed and economy of the unit operation. The best products on the market often allow users to validate very high levels of parvovirus clearance in excess of the 4-log minimum while assuring robustness in the process, including no adverse effect of process interruption on log reduction values. Prefilters, designed to work seamlessly with the virus filter, are optimized for specific ranges of stream pH and ionic strength, further improving the filtration economy.

Perhaps the most significant new trend is the development of specialized, economical virus barrier filters upstream of the bioreactor, simplifying the task of reducing the risk of bioreactor viral contamination.

Dr. Faber: For many years, virus filtration has been a key technology in bioprocessing for virus removal. It is a proven and robust process step, but today's concentration of product and different scaffolds are posing a challenge to standard virus filters.

Processing time has emerged as a critical factor for effective manufacturing. So the current trend is that there are virus filters that are either tailored to high flow rates or high retention. Additionally, new technologies that apply different modes of action (including ultraviolet-based technologies) are beginning to show success in processes where standard technologies such as filtration and pH treatment are not suitable. These technologies offer the opportunity to support new molecule trends in the market.

GEN: What are the keys to successful, efficient, and economic large-scale filtration?

Mr. Dango: The success of a full-scale process is established at the bench scale by using scalable filter formats. For example, when work is carried out with hollow fiber cartridges, the fiber length, diameter, and material is kept constant to provide scalability to cell harvest/clarification and ultrafiltration/diafiltration steps.

Aside from the basics of ensuring as linear a scale-up process as possible, anticipating and designing for potential disruptions (volume, concentration, or purity variability) at process scale is wise. More important, however, is thinking about the scale-up process as early as possible.

Operations such as cleaning and sterilization, or process monitoring and control strategies, may take a back seat to maximizing yield and purity during bench-scale trials, but a process that is not robust or is very complex to implement may require costly and time-consuming changes to be successful.

Ms. McBurnie: In addition to optimizing the filtration schema, efforts should include analysis of process variables that can potentially impact the feed stream. They should also incorporate deployment considerations (such as single-use filtration versus conventional cartridge/housings). Post-use operations, such as integrity testing, should also be considered. Scalability of the filtration step is another key consideration, as this can change over the life cycle of a given operation, especially in single-use batch operations where flexibility should be preserved.

Proper prefiltration selection is crucial, as small-scale inefficiencies may not be uncovered until the process is scaled up. Thoroughly characterized filterability trials provide the necessary data for determining an appropriately sized, economical, and efficient process step. Putting all this together enables us to establish and implement a successful, scalable, robust solution.

Mr. Tkacik: Two key areas determine success of large-scale filtration process steps: availability of economical, high-capacity filters and extensive expertise in factors affecting scaling. Both areas have seen new advances in recent years. More effective, easy-to-use clarification filters are available, including the latest products developed specifically for dealing with pretreated (flocculated) cell cultures with very high cell density.

High-capacity sterilizing filters in large-area devices are now widely available. New understanding of stream-specific scaling methodologies for sterilizing grade filters was developed to provide firm guidance for process developers. Reliable tangential flow filtration (TFF) systems can be built to all needed scales, including systems with specialized TFF devices for handling very high viscosity product formulations. All of this leads to easy process development and economical, robust processing at full scale.

Mr. Watson: For sterilizing grade filters designed for liquid service, more efficient filtration has been achieved with filters using polyethersulfone (PES) membranes with a pore structure optimized for high flow rates and high-throughput capacity. Furthermore, by using novel membrane pleating, some suppliers have been able to increase the amount of PES membrane area in the widely used, industry-standard, 10 inch filter element. This has resulted in devices incorporating >1 square meter of filter membrane per 10 inch element, compared with 0.5–0.7 square meters typical of predecessor products.

By using "high area" filters with a PES membrane, the drug manufacturer can benefit from filter systems that are several-fold smaller than those based on more traditional technology. Smaller systems don't just mean reduced filtration costs, but also the lowering of expenses linked to product loss, inventory management, and filter flushing.

Dr. Faber: Among others, robustness and cost efficiency are two key factors for running large-scale filtration processes successfully. Proper filter selection and sizing during process development are instrumental to robust large-scale filtration processes. Cost efficiency is achieved by screening of different filter materials and combinations of prefilters and final filters with minimal product volume using small-scale flat-filter devices such as Sartorius Stedim Biotech's SartoScale units.

These trials serve to identify the filter configuration with the highest total throughput performance for a given feed stream, assuring cost-efficient processing in large scale, especially for applications such as media preparation, sterilizing grade filtration after cell harvest, and early downstream processing filtration steps. The scale-up of such initial trials is confirmed with small-scale pleated devices, which are better than flat filters at mimicking the process-scale elements. This assures optimal robustness of the large-scale filtration process, preventing premature blocking and potential product losses.

Mr. Simmons: The key to being successful at the large scale is to do the right work at the small scale to optimize the process. A series of experiments must be performed on a small volume of the sample. These experiments will determine allowable shear, achievable concentration factor, number of diavolumes required (if the process includes diafiltration), and the loading factor (volume in liters divided by membrane surface area in square meters) required for the process to be completed on large scale within the allotted amount of time.

Data must be carefully collected from these experiments to ensure that the final, defined process is robust. If this work is performed correctly, it is a relatively simple matter to scale up to the larger volumes.