CONTINUOUS VIRUS FILTRATION: AN EXISTING TECHNOLOGY WITH A PROMISING FUTURE

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The accelerated rate of advancement in downstream bioprocessing is largely driven by the increased need for improved mAbs, vaccines and other therapeutic modalities. The goal for these endeavors is to achieve the capability to provide affordable and accessible therapeutics. Continuous bioprocessing, specifically, is becoming more widely adopted in biomanufacturing, and companies are exploring the various ways that implementation of this technology can help to increase productivity and produce high quality products while saving resources and time. Although much progress has been achieved in upstream processes and downstream chromatography and viral inactivation steps, there is little published data on continuous virus filtration (VF). Moreover, little is known about how virus filters can withstand the expected low flux conditions and potential pressure interruptions that can occur during continuous operation. It may be reassuring to know that an already established technology, one that has been used to ensure the safety of biologic products for years, can be tailored to fit into and function within continuous downstream processes.

Here we present a case study where we evaluated the impact of low flux and pressure interruptions on small-scale hollow fiber virus filters with hydrophilic modified polyvinylidene fluoride (PVDF) membrane. Long-term filtrations of four representative mAbs were conducted to a target throughput of 1000 L/m^2 with a low flux of 7 LMH. These conditions are certainly challenging for any virus filtration operation and ensuring robust viral clearance under such conditions is critical to the design and implementation of continuous VF. Minute virus of mice (MVM) stability was confirmed prior to conducting spiked runs, and creative methods were implemented to ensure stability of MVM in the feed stock and avoid pump-driven pressure fluctuations throughout the long runs. Filters were shown to effectively remove MVM (>4 log) when run continuously for up to 6 days. Interestingly, the gradual pressure increase that can occur over the duration of long-term filtration runs due to filter fouling was shown to be reflective of load material variability. Pressure interruptions, however, were shown to have minimal impact on overall MVM LRV. Effective virus removal was achieved with pressure increases being largely product-specific, which demonstrates the capability of the virus filters to remove virus independent of pressure increases that are expected to occur with increased protein load.

These experiments demonstrate that virus filters, an existing technology that was originally designed to operate in batch mode under constant pressure, can be implemented in ways that overcome the challenges specific to continuous virus filtration and fit well into the “facilities of the future”. Based on small-scale filtration data, decisions can be made as to the number of filter changeouts needed during a continuous operation, as well as filter loading capacity. These decisions will tend to be both product- and process-specific. Equipped with knowledge about material stability and analytical characteristics and the findings presented here, issues encountered in continuous operations can be overcome by tailoring the process design. Thus, an existing technology combined with an understanding of optimal process design as well as newer process analytical technologies (PATs) can help companies increase operational flexibility while achieving desired product throughputs.