Simplifying Progress

Hybrid Solutions for the Implementation and Operation of Fully Single-Use Virus Filters in Stainless Steel Manufacturing Facilities

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1. Introduction

Biopharmaceutical manufacturing processes for monoclonal antibodies (mAbs) and other recombinant proteins have reached a high degree of standardization, allowing companies to work with proven technology platforms. For most of these process platforms, a parvovirus-grade virus filter will be an integral part and a mandatory prerequisite for process approval by regulatory authorities. However, some legacy processes may still utilize virus filters with larger pore sizes in commercial manufacturing.

Most biotechnology companies will revise and diversify their manufacturing concepts to follow industry trends. This has led to the construction of smaller and more flexible manufacturing sites based on single-use equipment and state-of-the-art virus filtration technologies. Nevertheless, recent COVID-19-related events have changed our collective view on the security of supply, highlighting the need for more flexibility in critical production processes and interchangeability of key raw materials like virus filters. This led to expedited efforts to diversify production platforms and urged manufacturers to integrate up-to-date single-use technologies into existing stainless steel facilities to create promising new hybrid solutions within commercial manufacturing.

This poster is intended to provide insight and practical guidance for the implementation of hybrid solutions for virus filtration steps in commercial manufacturing.

2. Virus Filtration of mAbs and Recombinant Proteins

Medicinal products manufactured from biological sources (e. g., blood plasma) or utilizing components of animal or human origin (e. g., cell lines or fetal bovine serum) require a virus clearance concept and a virus clearance strategy. Virus clearance during commercial production can be achieved by chromatographic purification steps as well as by adding accessory manufacturing steps like inactivation by chemical treatments or virus retention by normal flow filtration.
Virus filtration plays a critical role during biopharmaceutical production and is regarded as one of the most reliable virus removal steps, significantly contributing to the overall virus clearance strategy. Logarithmic reduction values (LRV) of more than 6 $\log_{10}$ for enveloped viruses and more than 4 $\log_{10}$ for small, non-enveloped viruses can be easily achieved with virus filtration. Confidence in this essential virus clearance technology requires a high degree of robustness towards variable operating conditions and diverse product matrix compositions, true for most second-generation virus filters.

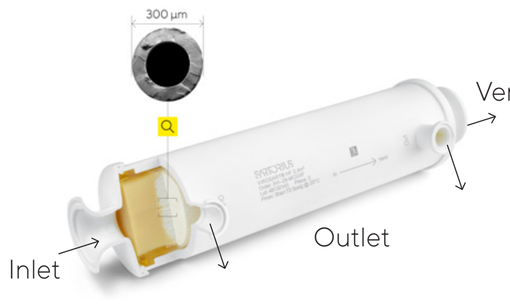

Figure 1: *The Virosart® HF Virus Filter Hollow Fiber Design.*

Virosart® HF represents a new generation of high-speed virus filter for the production of monoclonal antibodies and small recombinant proteins. It combines reliable virus retention with high flow rates and excellent capacity in a smart, low footprint capsule design. The PES hollow fiber allows high packing densities leading to reduced hold-up volumes and low flushing volumes, and the pre-sterilized, ready-to-use assemblies allow easy implementation in fully single-use virus filtration processes.

3. Fully Single-Use Virus Filtration

In recent years, fully single-use technologies have become viable options for clinical and commercial manufacturing. The advantages of single-use equipment are diverse and cover economic as well as operational- and performance-related aspects.
Within multipurpose facilities, fully single-use technologies provide flexibility and therefore facilitate the fast and easy switch between various products. Companies with different molecules in clinical phases benefit from short transition times between two products, significantly reducing the time-to-market. During commercial manufacturing, lower upfront investment costs, more flexible production schedules, and optimal scalability are only a few advantages compared to stainless steel applications.
Additionally, fully single-use processes using pre-assembled and pre-sterilized equipment dramatically reduce the risk of biological- and process-related cross-contamination during manufacturing.

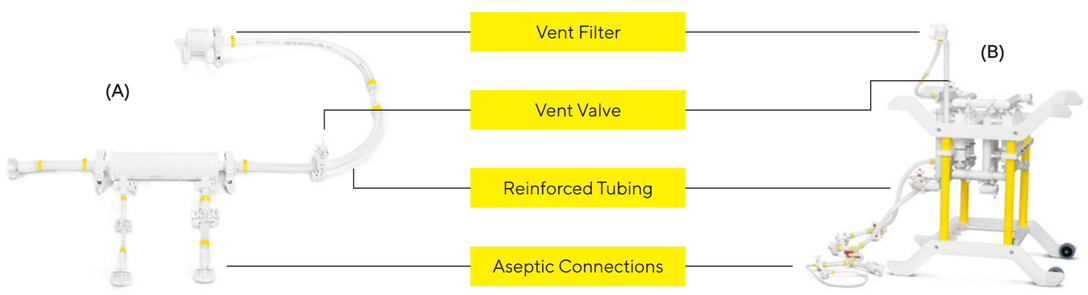

Figure 2: (A) *Sterile Single-Use Filter Transfer Units for the Virosart® HF.* **(B)** *Sterile, Large-Scale Maxicaps MR® Format for Virosart® HF.*

Process scalability is a key consideration when implementing single-use solutions, determining whether a particular virus filtration device will also be a viable and easy-to-use application solution in commercial manufacturing. The adaptation to the required process scale can be achieved by using varying capsule sizes, and therefore, the quantity of built-in virus filter membrane. Small to medium-sized processes can, for example, often be carried out with individual capsules that can be pre-assembled to contain all process-relevant connections and pre-sterilized by the supplier prior to delivery. These so-called Virus Filter Transfer Units (Figure 2A) enable plug-and-play operations in a sterile manner.
Larger manufacturing processes with bioreactor volumes up to 20,000 L or the filtration of challenging molecules may require effective membrane areas that exceed the capacity of individual capsules. In such cases, up-scaling technologies like the Maxicaps® MR devices provide the necessary flexibility in commercial production (Figure 2B). These pre-sterilized, large-scale virus filtration devices incorporate the filtration performance of multiple capsules within one functional unit. Thus, the efforts to establish connections and install the filter, as well as potential handling failures and risks of faulty connections, are reduced to an absolute minimum. Furthermore, all relevant operational steps like venting, flushing, and pre- and post-use integrity testing can be conducted in parallel for all capsules.
In this respect, such a setup can be seen as a functional equivalent of multi-use filter housings in stainless steel applications but with the additional benefits and advantages that come with single-use technologies.

4. Realizing Hybrid Approaches

The successful implementation of fully single-use technology within a stainless steel facility will depend on the available filtration technology, plant layout, and the associated process conditions. Consequently, creating an effective hybrid solution will require an understanding of the filtration technology, the process steps and associated parameters, as well as process control and regulatory requirements.
To assess the compatibility of the technology and to understand in more detail if an implementation is feasible, the following steps can be used as high-level guidance:

Status Quo
- Identify key similarities and differences between old and new technology | devices and the consequences that may arise from that evaluation (e. g., membrane format, pressure resistance, chemical stability, size | scaling, connectors, etc.)

Process Steps and Parameters
- Collect all individual steps necessary to run the virus filtration from installation to post-use integrity test and identify potential conflicts with facility layout or equipment (e. g., range of pumps, availability of lines | piping, valves and sensors, pressure profile of the system etc.)
- Translate small-scale and virus clearance data into manufacturing scale to determine the required membrane area
- Understand the fixed process targets (e. g., target pressure) and parameters in the process or setup that can be modified to support the implementation

Automation and Process Control
- Determine the current level of automation and the desired level of automation in the future
- Consider whether existing valves and sensors support fully automated operations or if manual input is required

Process Closure
- Verify the planned bioburden control strategy and confirm device compatibility (e. g., "sterile" with steaming in place vs. "bioburden reduced" by sanitization in place using caustic solution)

The latter point, in particular, can result in significant challenges. Sterilization in a stainless steel environment is usually achieved via steaming in place, whereas self-contained single-use equipment is optimized for gamma-irradiation and may not withstand such harsh pre-treatments. Furthermore, when changes to existing commercial processes are applied, internal regulatory requirements regarding bioburden control are often elevated. Therefore, sterile operations may be preferred over setups featuring only bioburden-reduced operations. This point may require some additional attention during process conception to avoid unexpected project and timeline risks during the actual implementation.

5. Hybrid Setup Using Virus Filter Transfer Units

A flexible and easily scalable hybrid setup can be realized using Virus Filter Transfer Units. These pre-assembled and pre-sterilized units can be considered independent and closed building blocks in such a virus filtration setup. Each unit will provide all necessary components like tubing, connectors, and accessories, for example, clamps or even an air filter (Figure 2A). The transfer unit can be connected directly to the facility piping or to a manifold if more individual connection options are required (Figure 3). After connecting the single-use transfer units to the stainless-steel part, steam-resistant connectors will allow sterilization of the piping, including the established connection to the single-use parts. The following process steps, including pre-use integrity testing, can now be conducted in a sterile manner. Depending on the piping layout, simultaneous integrity testing of parallel filter elements pre-use and post-use can also be achieved by utilizing a central vent line, including an air filter as an additional sterile barrier.

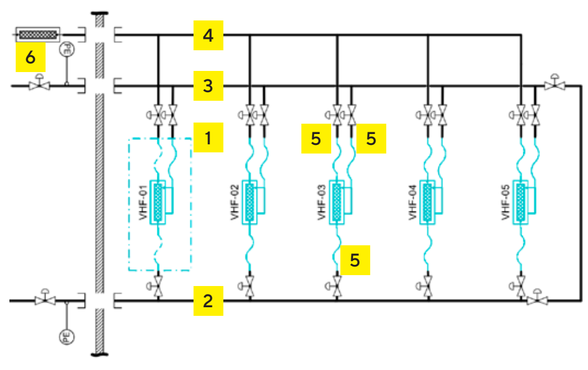

Figure 3: *Example of the incorporation of Virosart® HF single-use Virus Filter Transfer Units into a stainless-steel skid. The depicted piping lay-out combined with the valve infrastructure allows for fully automated process execution and individual control of each filter unit. Semi-automated approaches using a less sophisticated system archi-tecture are also feasible and can reduce the number of valves and process control complexity.*

The gamma-sterilized transfer unit **(1)** is connected to the inlet line **(2)**, outlet line **(3)**, and the central vent line **(4)** via steam-through connectors **(5)**. The piping, including connectors, is then steam-sterilized, allowing for sterile process operations. The central air filter **(6)** facilitates sterile pre-use integrity testing, which can be executed simultaneously or individually based on the availability of valves.

6. Discussion and Conclusion

Single-use virus filtration technologies represent a potential tool to diversify existing stainless steel bioprocessing platforms. Depending on the piping structure, automation strategy, and the general process framework, one-size-fits-all solutions may be challenging, and customized concepts will be required to realize efficient hybrid application solutions.
These hybrid approaches allow manufacturers to benefit from single-use technologies in stainless steel facilities. During the concept phase, manufacturers will have to decide to what extent they will implement single-use solutions. As shown in Figure 3, Virus Filter Transfer Units represent small, flexible, and easy-to-scale building blocks that can be seamlessly integrated and connected to the plant using, for example, a stainless steel manifold. Large-scale virus filtration devices like the Maxicaps® MR System will not require additional stainless steel parts to facilitate integration. They directly combine multiple capsules in a fully single-use setup, allowing simultaneous operation (including pre- and post-use integrity testing) and reducing the overall necessary connections down to four individual connectors.
Sterile process execution using such hybrid approaches can, in some cases, represent an additional challenge. However, this can be solved by defining the right connection strategy by combining gamma-irradiatable equipment with those that can be steam-sterilized.