Biotech

Technical Regulatory Topic

Points to Consider When Performing Virus Filtration Validation Studies

Document Number:	USTR3438
Revision Number:	1.0
Date:	01-FEB-21
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1 Introduction

Virus filtration is widely accepted as a robust mechanism to ensure virus safety of biotherapeutic manufacturing processes. However, as virus safety of the product cannot be determined by testing alone, there is a regulatory expectation that for a virus filtration step which contributes to the overall amount of virus removal being claimed for a manufacturing process, this step must be validated [1]. Virus clearance studies are performed prior to a product entering Phase 1 of clinical trials, and again at Phase 3. Although virus filtration validation trials are typically conducted at contract laboratories with significant expertise in performing virus clearance, there are many points to consider to ensure a successful trial that meets expectations, and these are described below.

2 Which Viruses Should I Include?

The choice of viruses depends on what clinical phase the drug is in. For Phase 1 products, traditionally, two types of viruses were included:

- Parvovirus: Porcine Parvovirus (PPV) or Minute Virus of Mice (MVM)
- Retrovirus: Murine Leukemia Virus (MuLV)

However, to reflect the increased experience and understanding of virus filtration based on size exclusion, there is growing acceptance to test parvovirus only, based on its small size as a worst-case model [2].

For products in Phase 3, the requirement is to include the following:

- Relevant viruses (those which could potentially be present in the product)
- Specific model viruses (viruses closely related to known or suspected viruses with similar physico-chemical properties)
- Non-specific model viruses (a combination of viruses with different properties to demonstrate robustness of the filtration step)

The ability to grow the virus to a sufficiently high titer, availability of assay, and biosafety considerations will also contribute to the choice of viruses used. ICH Q5A provides details of regulatory expectations for selection of viruses for validation testing.

3 Selection of Worst-Case Test Parameters

Consideration must be given to test under worst-case simulated processing conditions. For some cases, bracketing studies may be required to determine the impact of the physical properties of the product (e.g., pH, conductivity, protein concentration) on virus removal. Typically, virus filtration studies have been performed at the expected differential pressure or flow rate that will be used in the full-scale process. However, there has increasingly been a regulatory expectation that virus filtration validation studies include at least one depressurization (sometimes referred to as stop/start) during the test. The duration of the depressurization should be based on a risk assessment of what could reasonably be expected in the controlled, full-scale process. The virus filters must be tested to a defined end point, usually based on volume throughput or % flux decay across the filter. In addition, care should be taken to ensure appropriate scale down of the process filter to the laboratory scale device.

4 Process Fluid

For products that are supplied frozen for virus filter validation testing, it is advisable to provide the product as two frozen shipments and allow time for a filterability study of the thawed product, ideally with the viruses of interest spiked into the fluid. This additional step can be helpful to ensure the actual validation trial proceeds as expected, and neither the thawing nor virus spiking of the product leads to premature filter plugging.

5 Prefiltration Needs

Prefiltration of the process fluid, typically using a 0.1 µm or 0.2 µm sterilizing grade filter, is commonly performed prior to virus filtration studies; this helps to remove any product aggregates, as well as any debris introduced by the virus spike, although virus contract laboratories endeavor to use the highest purity virus spikes available.

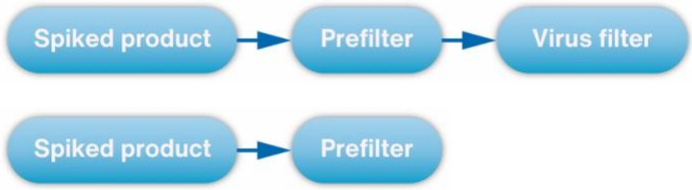
For virus clearance studies performed with a prefilter specified in the manufacturing process, it is critical that any virus clearance is attributed to the virus reduction filter only. This requirement can be achieved by including the prefiltration in one of three ways, as outlined below.

5.1 Decoupled (Off-Line) Prefiltration

This approach prevents loss of larger viruses through the prefilter, but care should be exercised during prefiltration to avoid excessive manipulation, which could contribute to further aggregation. Testing is performed in the following manner:

5.2 Coupled (In-Line) Prefiltration

This approach is only suitable when using small parvoviruses and viruses that are not removed to any significant extent by the prefilter. It requires two separate tests performed in parallel and under identical test conditions, as depicted below.



The log reduction values of the viruses are compared between both set-ups, such that the virus retention capabilities of only the virus filter can be determined.

5.3 In-Line Spiking

This approach is recommended if product re-aggregation occurs over time after the prefiltration step and overcomes removal of larger viruses through the prefilter.

Further details of prefiltration considerations are provided in more depth elsewhere [3].

6 Virus Assay

Prior to performing the virus filtration spiking studies, cytotoxicity and interference testing must be performed to consider any inhibitory effects on the virus assay caused by the process fluid. Once this has been evaluated, the end-user should discuss with the contract laboratory the amount of clearance they want to claim, so the appropriate level of virus can be spiked. A spiked product control hold accounts for any loss of virus due to factors other than the virus filtration. In addition, considerations should be given to performing large volume sampling, which can enable higher log reduction values (LRV) to be obtained (~2 LRV higher than conventional plating) if required (e.g., to increase total amount of virus clearance being claimed).

As reviewed here, virus filtration validation depends on a number of factors, but thoughtful advanced planning with the contract laboratory and the filter supplier can maximize the opportunity for a successful validation test. Pall is available for technical consultation on all aspects of virus safety throughout the product lifecycle.

7 References

[1] ICH Q5A, *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnological Products Derived from Cell Lines of Human or Animal Origin*, 1999.

[2] *Joint BWP/QWP Workshop with Stakeholders in Relation to Prior knowledge and its Use in Regulatory Applications, EMA, London,* Nov 2017.

[3] Pall USD3302. *Validating Pegasus™ Prime virus removal membrane filters: How do I incorporate a prefilter in my virus clearance study?*

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