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Virus Retentive Filtration

Virus Retentive Filtration Team

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1.0 Introduction

Biological therapeutic products are often manufactured using materials of animal or human origin, including recombinant cells, human blood plasma, cells derived directly from patients or other sources that could conceivably be contaminated by viruses. As some level of contamination risk exists ***(1–6)***, regulatory agencies worldwide require a demonstration of viral safety prior to the clinical use and/or marketing of such biologicals ***(7–10)***.

Risks of contamination are addressed by a combination of donor screening (where necessary) and virus testing of cell banks and raw materials as well as viral clearance steps in downstream purification processes. Virus-retentive filters are specifically designed to remove viruses from the process stream through a size-exclusion mechanism as part of a manufacturer's overarching virus safety strategy. They have been most commonly used in downstream processing as part of the orthogonal clearance strategy of recombinant or plasma-derived products; but in the context of some newer products (e.g., advanced therapy medicinal products (ATMPs) /cell therapies), they can be used to treat reagents and buffers used to manipulate cells for re-infusion or to pre-clear media used to culture or expand cells. They can also be used as barrier technologies for bioreactor media in a biological setting.

PDA *Technical Report No. 41 (Revised): Virus Filtration* addresses how virus-retentive filters work, recommends how to select the best filter for different applications, and describes the physical and biological/safety characterization of filter test methods, as well as strategies for the validation of virus retention.

1.1 Purpose

The biopharmaceutical industry has grown at an unprecedented rate over the past two decades; however, the need for patient safety has not changed. Yet, as part of the orthogonal virus clearance requirements, virus filtration may play a critical role in ensuring biologically derived products have a low risk of adventitious agents.

This technical report explains what virus filters are and where they can be used in current and emerging bioprocesses. Recommendations for selection of a suitable virus filter are included that include information on their physical and biological/safety characterization and guidance on how to incorporate quality by design (QbD) principles into virus filtration applications. Strategies for evaluating and validating virus retention by virus filtration, including defining the worst-case test parameters, are also discussed. Finally, considerations which reflect best practices and current thinking for implementing virus filtration into novel manufacturing technologies, such as barrier filters, continuous bioprocessing modes for filtration, or production of ATMPs are also included. TR-41 provides a summary of best practices for utilization of this technology in process development and manufacturing.

This document should be considered as a guide; it does not establish any mandatory or implied standards.

1.2 Scope

TR-41 provides a framework of the principles of operation, types of configuration, and materials of construction of virus-retentive filters and presents best practices for their design, operation, and validation in various applications; key literature references are noted. A QbD approach to virus safety assurance is described that starts with identification of critical process parameters related to virus filtration and discusses design space and operation within the proven acceptable range and normal acceptable range. Challenges to specific applications, such as large and small virus-retentive filters used for downstream processing of biopharmaceuticals, ATMPs, and plasma-derived products, as barrier technology prior to mammalian bioreactor cell culture, or for treating growth media for production of ATMPs, are also addressed. Additional sections examine critical considerations for evaluation and virus clearance validation studies, integrity testing, and sterilization. The final section focuses on future manufacturing technologies under development, such as the integration of virus filtration into continuous biopro-