

Technical Report No. 41
Revised 2008
Virus Filtration



2008

Virus Filtration Task Force

Technical Report Authors

Kurt Brorson, U.S. Food and Drug Administration

Jennifer Campbell, Millipore Corporation

Jeffrey Carter, GE Healthcare

Sherri Dolan, Sartorius Stedim Biotech S.A.

Mani Krishnan, Millipore Corporation

Scott Lute, U.S. Food and Drug Administration

Jerold Martin, Pall Corporation

Mohammed Haque, Pall Corporation

Michael Morgan, Asahi Kasei, Planova Division

Terry Sato, Asahi Kasei, Planova Division

Gail Sofer, SofeWare Associates

Srikanth Sundaram, Generamedix Inc.

Klaus Tarrach, Sartorius Stedim Biotech S.A.

Technical Report Contributors

Amin Abujoub, Biogen Idec Inc.

Hazel Aranha, GAEA Resources Inc.

Damon Asher, Millipore Corporation

Mark Bailey, Eli Lilly and Company

Thierry Burnouf, Human Plasma Product Service

Qi Chen, Genentech, Inc.

Mark Etzel, University of Wisconsin

Chris Dowd, Genentech, Inc.

Charles Felice, Johnson & Johnson

David Jen, Centocor, Inc.

Paul Genest, Millipore Corporation

Uwe E. Jocham, CSL Behring AG

Maik Jornitz, Sartorius Stedim Biotech S.A.

Stanley Kidd, Pall Corporation

Marina Korneyeva, Talecris Biotherapeutics, Inc.

Rich Levy, PDA

Carol Marcus-Sekura, BASI

Ichiro Moroe, Asahi Kasei, Planova Division

Leonard Pease, National Institute of Standards and Technology, U.S. Dept. of Commerce

Mahesh Prashad, Sartorius Stedim Biotech S.A.

Ted Meltzer, Capitola Consultants

Kathryn Remington, Cardinal Health

Cynthia Romero-Arroyo, Ortho Biologics Inc.

Mike Rubino, Eli Lilly and Company

Sakae Satoh, Asahi Kasei, Planova Division (retired)

Michael Shanks, Wellstat Biologics Corp

Ailsa Shepherd, BioReliance Corporation

Thomas Smith, GlaxoSmithKline

Michael Tarlov, National Institute of Standards and Technology, U.S. Dept. of Commerce

William Riordan, University of Wisconsin-Madison

Frank Van Engelenburg, Sanquin Blood Supply Found.

Hannelore Willkommen, Regulatory Affairs & Biological Safety Consulting

Peter Wojciechowski, Johnson and Johnson

Kaoru Yoshinari, Sepa-Sigma, Inc.

The content and views expressed in this technical report are the result of a consensus achieved by the authoring task force and are not necessarily views of the organizations they represent or the U.S. government.

Virus Filtration

Technical Report No. 41 (Revised 2008)

© 2008 PDA



Table of Contents

1.0 INTRODUCTION	2	6.0 VIRUS FILTER VALIDATION/ EVALUATION STUDIES	19
1.1 Purpose/Scope	2	6.1 Filter Properties	19
2.0 GLOSSARY OF TERMS	3	6.2 Test Virus	20
3.0 VIRUS-RETENTIVE FILTERS	7	6.2.1 Virus Selection.....	20
3.1 Size Exclusion.....	8	6.2.2 Virus Stock Preparation and Maintenance.....	20
3.2 Other Retention Mechanisms	8	6.2.3 Virus Spike.....	21
3.3 Virus Retention Probability of Reduction Factor	9	6.3 Scaled-Down Models	23
3.4 Virus Size/Retention Rating	9	6.4 Operating Conditions for Validation, Revalidation and Number of Runs	23
3.5 Protein Size/Sieving/Passage Rating.....	10	6.5 Raw Materials and Equipment.....	24
4.0 VIRUS FILTER SELECTION AND CHARACTERIZATION	11	6.5.1 Virus Filtration Devices and Configurations	24
4.1 Filter Construction	11	6.5.2 Integrity Testing During Development	24
4.2 Filter System Configurations	11	6.5.3 Membrane Lot Selection.....	25
4.3 Particulates and Extractables	13	6.5.4 Feedstream	25
4.4 Filter Compatibility	14	6.5.5 Filtration Conditions.....	25
4.5 Protein Recovery (Adsorption/ Retention/Biocompatibility)	15	6.6 Virus Assays and Assay Validation.....	25
4.6 Thermal Stress Resistance.....	16	6.6.1 Assay Method Validation.....	26
4.7 Hydraulic Stress Resistance.....	16	6.7 Establishing Representative Worst-Case Process Conditions	27
4.8 Toxicity Testing.....	16	7.0 INTEGRITY TESTING	29
4.9 Viral/Phage Challenge Testing.....	17	7.1 Manufacturer’s Checklist	30
4.10 Cleaning/Sanitization/Sterilization.....	17	7.2 Virus Retention Integrity Tests.....	32
5.0 PHYSICAL AND MECHANICAL CHARACTERIZATION	18	7.2.1 Dextran Retention.....	32
5.1 Filtration Rate and Clogging (Throughput).....	18	7.2.2 Gold Particle Retention	32
5.2 Fluid/Piping.....	18	7.2.3 Gas-Liquid Porosimetry.....	33
5.3 Fluid/Filter	18	7.2.4 Manual Bubble Point or Leak Testing	33
5.4 Physical and Structural Limitations	18	7.2.5 Manual Forward/Diffusive Flow	33
5.5 Miscellaneous	18	7.2.6 Manual Pressure Hold/Decay.....	35
		7.2.7 Automated Integrity Test Instruments for Gas Porosimetry-Based Test Methods.....	36
		7.2.8 Liquid and Liquid-Liquid Porosimetry	36
		7.3 Relationship between Integrity Tests and Virus/Phage Retention	37
		7.4 Failure Analysis/Troubleshooting	37

Table of Contents

8.0 STERILIZATION	38
8.1 Steam Sterilization	38
8.2 Autoclave Sterilization	38
8.3 Sterilize-in-Place	39
8.4 Irradiation Sterilization	39
8.5 Gas Sterilization	39
9.0 APPENDICES	41
APPENDIX I: Virus Retention and Protein Passage Nomenclature Classification	41
APPENDIX II.a: Large Virus-Retentive Filter Test Protocol	41
APPENDIX II.b: PR772 Preparation Procedures	45
APPENDIX II.c: Procedure for Enumeration of PR772 Bacteriophage	48
APPENDIX III.a: Small Virus-Retentive Filter Test Protocol	49
APPENDIX III.b: PP7 Preparation Procedures	53
APPENDIX III.c: Procedure for the Enumeration of PP7 Bacteriophage	56
APPENDIX IV: Filter Validation Recommendations	57
10.0 REFERENCES	58

1.0 Introduction

1.1 Purpose/Scope

Biotechnological and biological therapeutic products are often manufactured using materials of animal or human origin, including cultured primary or transformed cells, milk or other components from transgenic animals, natural extracts and human or animal blood plasma. These products are usually proteins that are manufactured by complex manufacturing processes. Although approved recombinant biotherapeutics have an excellent safety record, the risk of contamination by known or unknown pathogens exists, (1–6) and regulatory agencies worldwide require a demonstration of viral safety prior to clinical use and/or marketing of biopharmaceuticals. (3, 7–10)

The risk of transmission of certain infectious pathogens cannot be completely mitigated by donor screening, vaccination of patients, a single virus inactivation step, or virus testing of cell banks and raw materials. It is desirable to introduce additional robust viral clearance steps in the biotherapeutic purification processes to help reduce or eliminate viruses without compromising the molecular integrity of the products. Virus-removal filters (often incorrectly termed “nanofilters”) are specifically designed to remove viruses and other biomolecules from the product (protein) solution through a size-exclusion mechanism.

Virus filtration is performed as part of a manufacturer’s overarching virus safety strategy. In this context, virus filtration (size-based removal) is a complement to virus inactivation, both of which contribute to virus clearance. (11–21) Implementation of virus clearance complements additional measures, such as control over raw materials and testing of cell culture or plasma feedstock. Collectively, these measures form the framework of a virus safety strategy.

This PDA Technical Report addresses virus-removal filters that retain viruses by a size-exclusion mechanism. It explains how they work, recommends how to elect the best filter for various applications, and describes physical and biological/safety characterization of filters test methods, and validation of virus removal. This document should be considered as a guide; it is not intended to establish any mandatory or implied standards.