viral safety assurance: prevent, detect, remove

Are you doing everything to mitigate your risk?

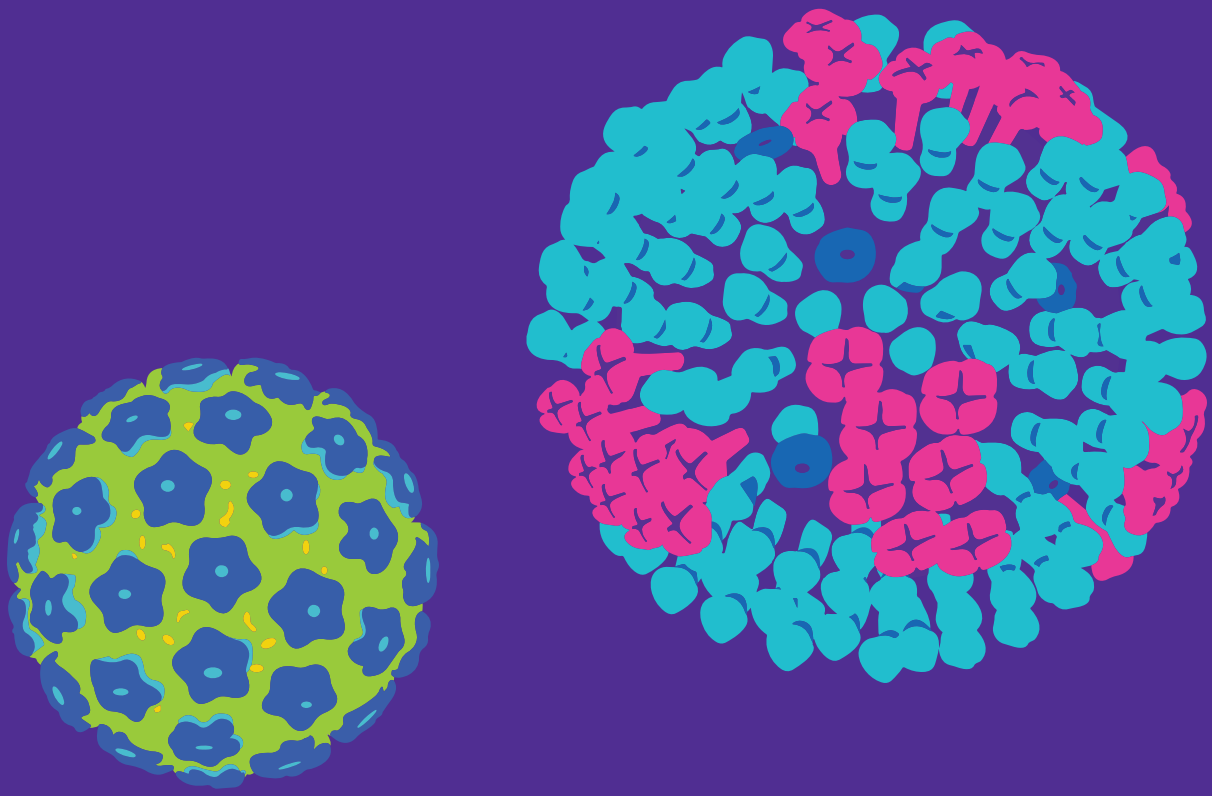
Monoclonal Antibodies

Viral safety relies on the basic tenets of **"Prevent, Detect, Remove"**. This holistic approach involves careful selection and pre-treatment of raw materials to prevent viruses from entering upstream processes, testing for the presence of viruses, and implementing appropriate purification and filtration technologies to remove viruses downstream.

Prevent: Raw material control and barrier technology

Detect: Testing for presence of viruses

Remove: Process's ability to reduce levels of infectious viruses



Various technologies help minimize viral contamination risks throughout the process

	Expression System	Raw Materials	Media Preparation	Cell Culture	Purification
Prevent	• Genetic modification of host cell	• Chemically-defined raw materials • Treatment of high-risk components	• Virus barrier filtration • High Temperature, Short Time (HTST) Treatment		
Detect		• Adventitious virus testing • Next Generation Sequencing (NGS)		• PCR testing • *In vitro* testing • NGS	
Remove					• Low pH/chemical inactivation • Chromatography • Virus filtration

More information: **MerckMillipore.com/Virus-Prevent-Detect-Remove**

PREVENT

Introduction of adventitious agents into the bioreactor

Cell lines used for the production of biotherapeutics need to be extensively characterized before use to determine the level of endogenous retrovirus-like particles, and whether an unexpected adventitious virus is present in the source cells. During expansion, cells are exposed to cell culture media and supplements that offer further opportunity for viral contamination. Although animal-derived materials may present a higher risk than plant-derived or chemically-defined components, no materials should be considered risk-free, as they may have been exposed to viral contaminants at some point during production.

Several approaches can help minimize the risks:

- Using well-characterized cell lines, such as CHO, the preferred expression system for monoclonal antibodies
- Making your CHO cell line resistant to MVM infection with gene editing technology
- Adopting high quality animal-component free or chemically-defined raw materials
- Using filtration technologies designed for cell culture media
- Treating sensitive raw materials to inactivate virus without affecting the properties of the material

More information:
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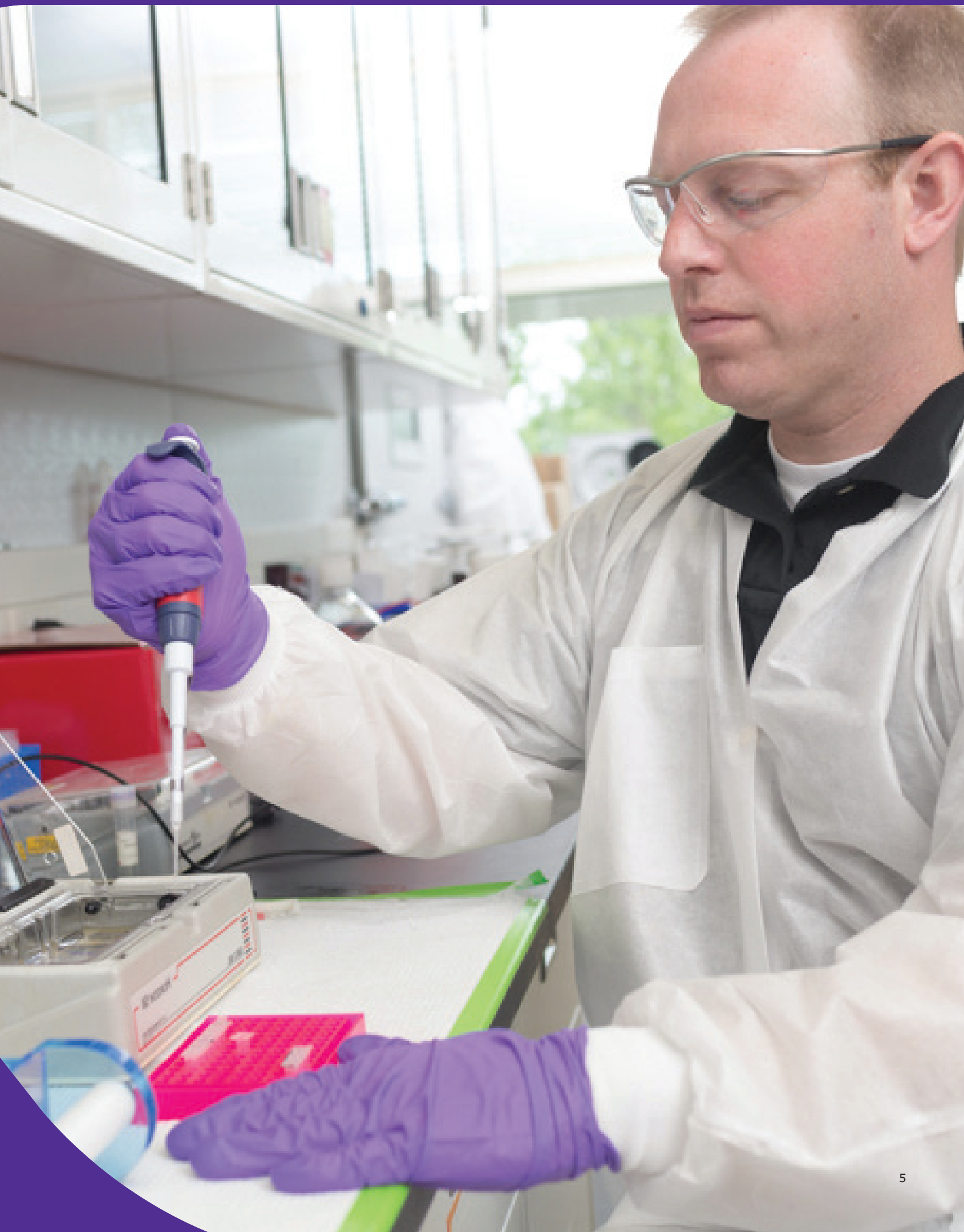
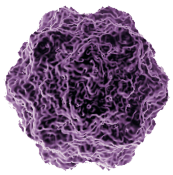


PREVENT
Introduction of adventitious agents into the bioreactor



Making your CHO cell line resistant to MVM infection with gene editing technology

Centinel Intelligent Virus Defense™ technology

Elimination of a specific gene target (Slc35A1), resulted in a CHO cell line that is resistant to infection by Minute Virus of Mice (MVM), a common contaminant of biopharmaceutical manufacturing operations. Using this cell line enables you to:

- Drive value by reducing the risk of viral contamination
- Defend valuable product investment from potential harm
- Deliver advanced virus resistance, supporting process efficiency and consumer safety

Adopting high quality animal-component free or chemically-defined raw materials

Emprove® chemicals

- More than 400 high quality GMP manufactured Emprove® chemicals
- Contain comprehensive product information and documentation you need for qualification and regulatory approval

Emprove® portfolio now includes sterile and virus filters in addition to single-use components.

EX-CELL® Advanced™ and Cellvento® CHO chemically-defined cell culture media and feeds

- Chemically-defined, animal-component free media to reduce adventitious viral contamination risk
- Enable superior cell growth and productivity in batch, fed-batch mode or perfusion applications
- Available in powder, compacted powder, and liquid forms

We also offer animal-component free media and supplements including: **CellPrime® rTrypsin, CellPrime® rAlbumin, CellPrime® rTransferrin, and CellPrime® rInsulin.**

Using filtration technologies designed for cell culture media

Viresolve® Barrier filter

Prevent viruses, mycoplasma and bacteria from reaching your bioreactor. Specifically designed to filter chemically-defined cell culture media, Viresolve® Barrier filters are easy to implement and use, making them an ideal technology to minimize the risk of upstream viral contamination.

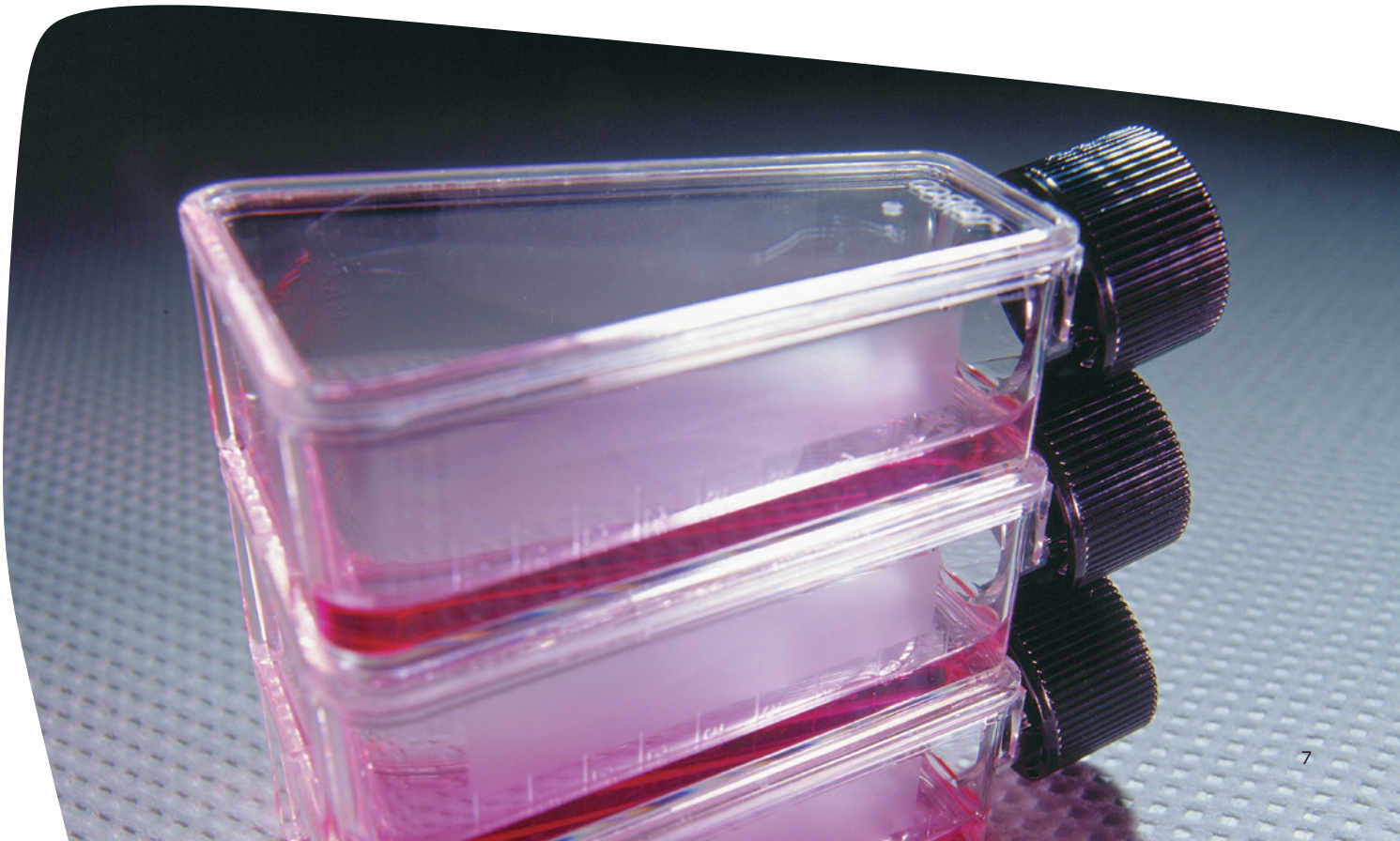
- Maintains equivalent protein quality attributes
- High-flux viral filtration for rapid processing
- Scalable from lab to commercial manufacturing

Treating sensitive raw materials

High Temperature, Short Time (HTST) Treatment

- Pasteurization-based technology to significantly reduce the possible number of infectious agents by 4-6 logs in liquid media products
- Applicable for most chemically-defined media, buffers and feeds/supplements such as glucose

Our GMP-compliant Sterile Liquid Centers can help you design and validate a process to manufacture your cell culture media, buffers, water for injection, and upstream process chemicals, and deliver them to you as ready-to-use.



DETECT

Viral contamination

FDA and EMA guidance documents and reflection papers outline virus testing strategies and recommendations; their expectation is that no virus should be detected in production processes. Traditional tests for adventitious viruses offer opportunities for broad detection of diverse viruses however these are time consuming and have limited sensitivity. New testing technologies such as Next Generation Sequencing (NGS) complement traditional methods, opening doors for more rapid, sensitive detection of viral contaminants. Both traditional and new testing technologies require technical expertise and outsourcing these activities to a specialist in these areas can be a cost-effective and efficient solution.

More information:
MerckMillipore.com/Virus-Prevent-Detect-Remove


Fisherbrand
Finnpipette

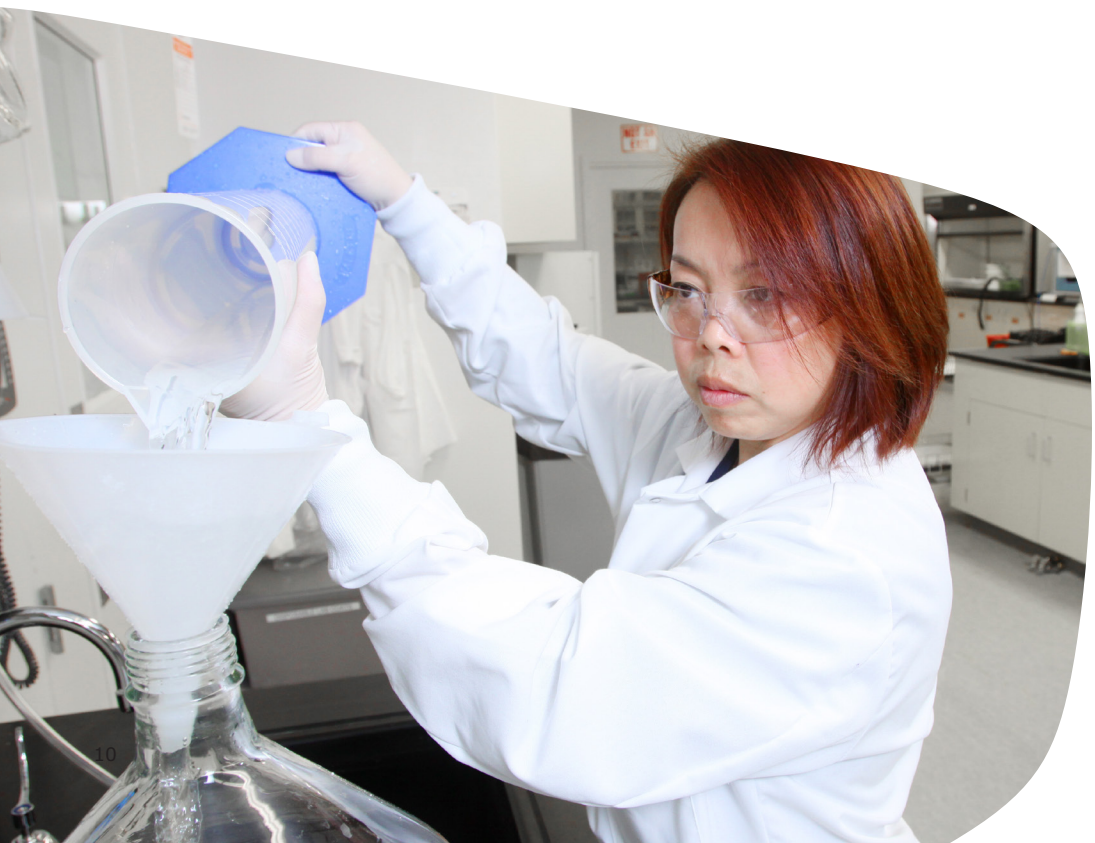
DETECT
Viral contamination

Virus detection with BioReliance® biosafety testing services

- Cell line characterization
- Virus bank characterization
- Next Generation Sequencing
- Raw material testing
- Bulk lot and final product release testing

BioReliance® biosafety testing services include assays for the detection of a broad range of adventitious agents in the raw materials used for the production of biopharmaceutical products. A full panel of these assays has been specifically designed for the detection of viruses in raw materials, cell banks, viral stocks, bulk and final products:

- Adventitious virus assays (in vivo, in vitro, retrovirus detection, TEM and PCR/RT-PCR)
- Porcine and bovine adventitious virus assay as described in the 9 CFR
- Next generation sequencing (NGS) to detect and identify adventitious agents
- A range of assays addressing specific contamination risks is also available



Next Generation Sequencing (NGS)

The use of NGS safety testing for adventitious agents enables the detection of any nucleic acid contaminant that may be present. NGS provides an additional level of biosafety assurance that can support traditional testing methods such as in vitro and PCR-based assays.

- Can detect and identify viral, bacterial and fungal contaminants present in a sample
- Testing can be performed on raw materials, cell banks, virus banks, culture media and bulk harvests
- Speeds the investigation and remediation of biomanufacturing biological contamination events

REMOVE

Virus from the downstream process

Downstream unit operations help reduce the levels of infectious virus in the bulk material. Downstream viral clearance is accomplished by a combination of operations that either remove or inactivate virus. Multiple operations, each with an orthogonal or complementary mechanism for virus reduction, are needed to meet the viral safety targets. Such operations might include:

- Chromatography – removal by binding affinity, charge or hydrophobicity. Most downstream processes include at least two chromatography operations, and although their primary objective is purification, they are critical to reaching viral clearance targets.
- Chemical treatment – reduction by inactivation. Chemicals used for viral inactivation must meet the same high quality standards as the other raw materials in your process.
- Filtration – removal by size. Removal of virus by filtration is based on size, and high levels of both enveloped and non-enveloped virus can generally be expected to be removed.

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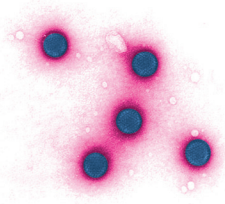
REMOVE
Virus from the downstream process

Chromatography – removal by binding affinity, charge or hydrophobicity

Affinity Chromatography	Ion Exchange Chromatography
Protein A affinity chromatography resins can make an important contribution to virus reduction targets for both endogenous retrovirus as well as adventitious virus such as MVM.	Excellent viral clearance across Fractogel® and Eshmuno® tentacle IEX resins has been demonstrated in many studies.
 **Eshmuno® A Protein A chromatography resin**	 **The Eshmuno® IEX family of resins**
A rigid, high capacity, acid and alkaline-resistant affinity chromatography resin for the purification of Fc-containing proteins, including monoclonal antibodies.	A unique family of ion exchangers designed for highly productive downstream purification of diverse biomolecules. Its strong anion exchange resin, Eshmuno® Q, combines the tentacle structure with an innovative hydrophilic polyvinyl ether base matrix for more effective binding of the target molecules, offering you outstanding virus removal capabilities.
 **ProSep® Protein A family of resins**	 **Fractogel® IEX family of resins**
This family of protein A based affinity chromatography media is designed for large-scale, cost-effective purification of high-titer therapeutic antibodies.	A synthetic polymer media that ensures high protein binding capacity, fast mass transport and sharp elution profiles resulting in high throughput and selectivity.



Chemical treatment – reduction by inactivation

Chemicals that are used for virus inactivation must meet the same quality standards as the other raw materials in your process. All of our products are manufactured or purified according to GMP standards from high purity raw materials. What's more, they bear the Emprove® trademark and come with comprehensive regulatory documentation that contributes to the quality of your registration dossier. The result: greater productivity and lower costs.

Emprove® high-quality products for virus inactivation:

- Solvent and detergent treatment
- Protein stabilizers for pasteurization
- Reagents for low pH treatment

Filtration – removal by size exclusion

The Viresolve® Pro device contains an innovative, dual-layer patented asymmetric polyethersulfone (PES) membrane designed to simultaneously deliver high parvovirus LRV (log reduction value), capacity and flux.

The addition of a prefilter such as the Viresolve® Pro Shield/Shield H or Viresolve® Prefilter removes protein aggregates and impurities that can foul virus filters, enhancing the Viresolve® Pro device capacity and flux.

DEVELOP AND DEMONSTRATE

The effectiveness of your viral clearance steps

The manufacturer is required to demonstrate the effectiveness of viral clearance steps and document adequacy of the manufacturing process to achieve an appropriate level of viral safety. Our BioReliance® biosafety services offer a broad range of consulting services, well-characterized BioPure Virus™ stocks, and viral assays to help meet your clearance validation requirements.

More information:
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DEVELOP AND DEMONSTRATE

The effectiveness of your viral clearance steps

Viral filtration process development and services

From Upstream to Downstream and through Final Fill, our M Lab™ Collaboration Centers (non-GMP facilities) are resource hubs for your process development, scale up and optimization.

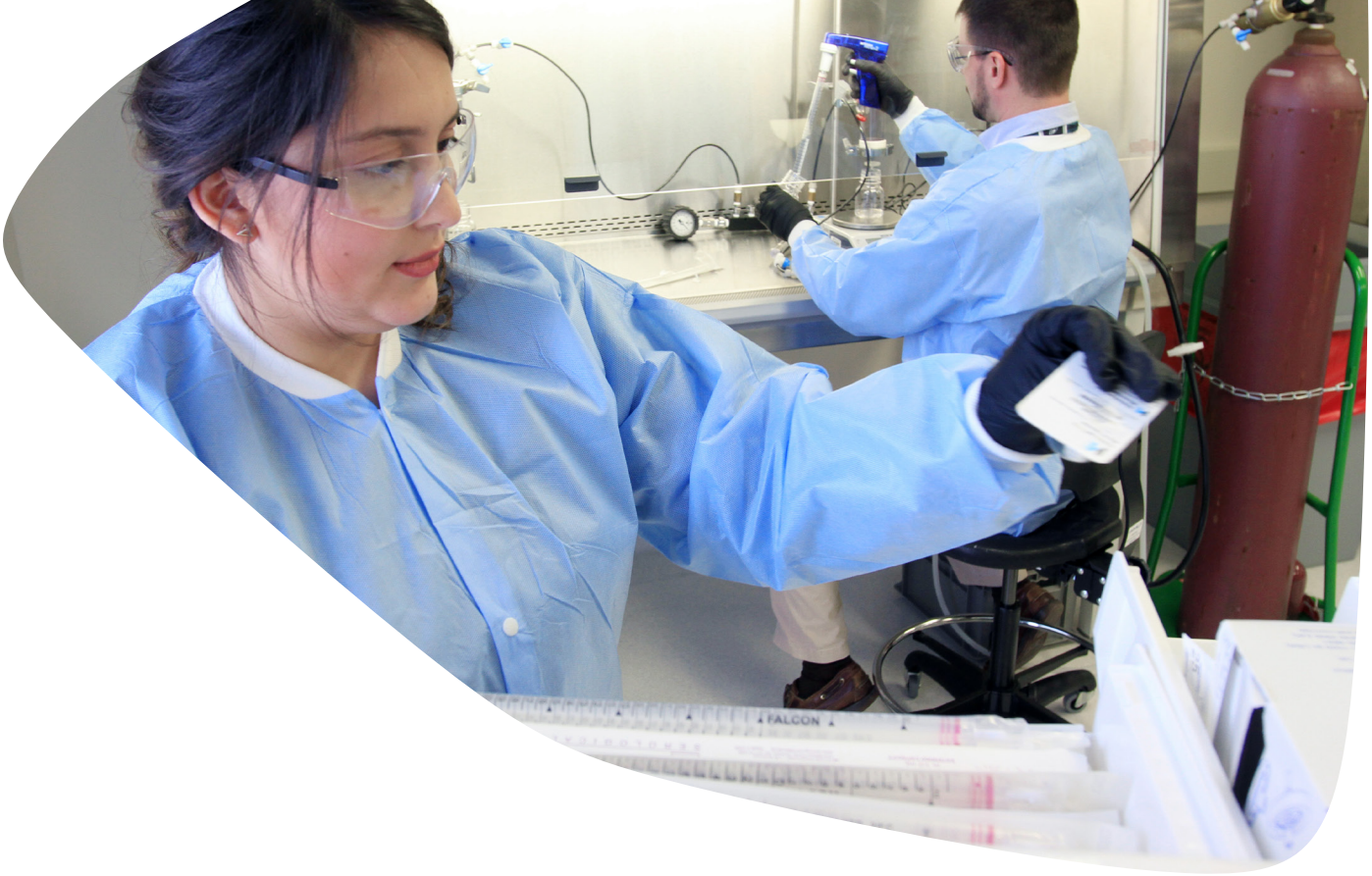
Viral filtration process development is supported by:

- Design, technology selection, filter sizing and protocol development
- Process scaling, optimization and yield improvements
- Process validation and engineering
- Process monitoring, quality control and technical support
- Training: hands-on and theory

M Lab™ Collaboration Centers, a global network

With 9 sites around the world, we can quickly accommodate your evolving needs at a time and a place that works for you.

Access the support of our global network of more than 100 scientists, engineers and technicians including process development scientists, biomanufacturing engineers and systems process engineers.



Viral clearance study consulting services

- Consultation on viral clearance strategy through different stages of clinical development
- Expert guidance in regulatory requirements and guidelines interpretation

BioReliance® viral clearance and viral safety

- Evaluates the potential of your process to remove infectious viral particles
- Offers well-characterized BioPure Virus™ stocks
- Operates in state-of-the-art facilities with fully-equipped laboratory suites in both the US and the UK
- Dedicated teams of highly trained and experienced personnel
- The industry's largest historical study database
- Performed thousands of viral clearance studies for clients, covering a broad range of biologic products and purification and virus inactivation methods

For additional information, please visit
www.**MerckMillipore.com**

To place an order or receive technical assistance, please visit
www.**MerckMillipore.com/contactPS**

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