Enabling solutions for vaccines and viral therapies

Millipore®
Preparation, Separation, Filtration & Monitoring Products

SAFC®
Pharma & Biopharma Raw Material Solutions

BioReliance®
Pharma & Biopharma Manufacturing & Testing Services

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

Our Portfolio of Brands

Millipore®

The Millipore® portfolio offers an ecosystem of industry-leading products and services, spanning preparation, separation, filtration and monitoring – all of which are deeply rooted in quality, reliability and time-tested processes. Our proven products, regulatory and application expertise are a strong foundation you can rely on to consistently perform at the highest level.

Denotes Millipore® Products

SAFC®

The SAFC® portfolio offers customized and ready-to-use raw material solutions, backed by deep regulatory expertise. Our high-quality products and services are supported by an experienced and responsive team of raw material and regulatory experts who are committed to understand your requirements and provide tailored solutions that meet your exact needs.

Denotes SAFC® Products/Services

BioReliance®

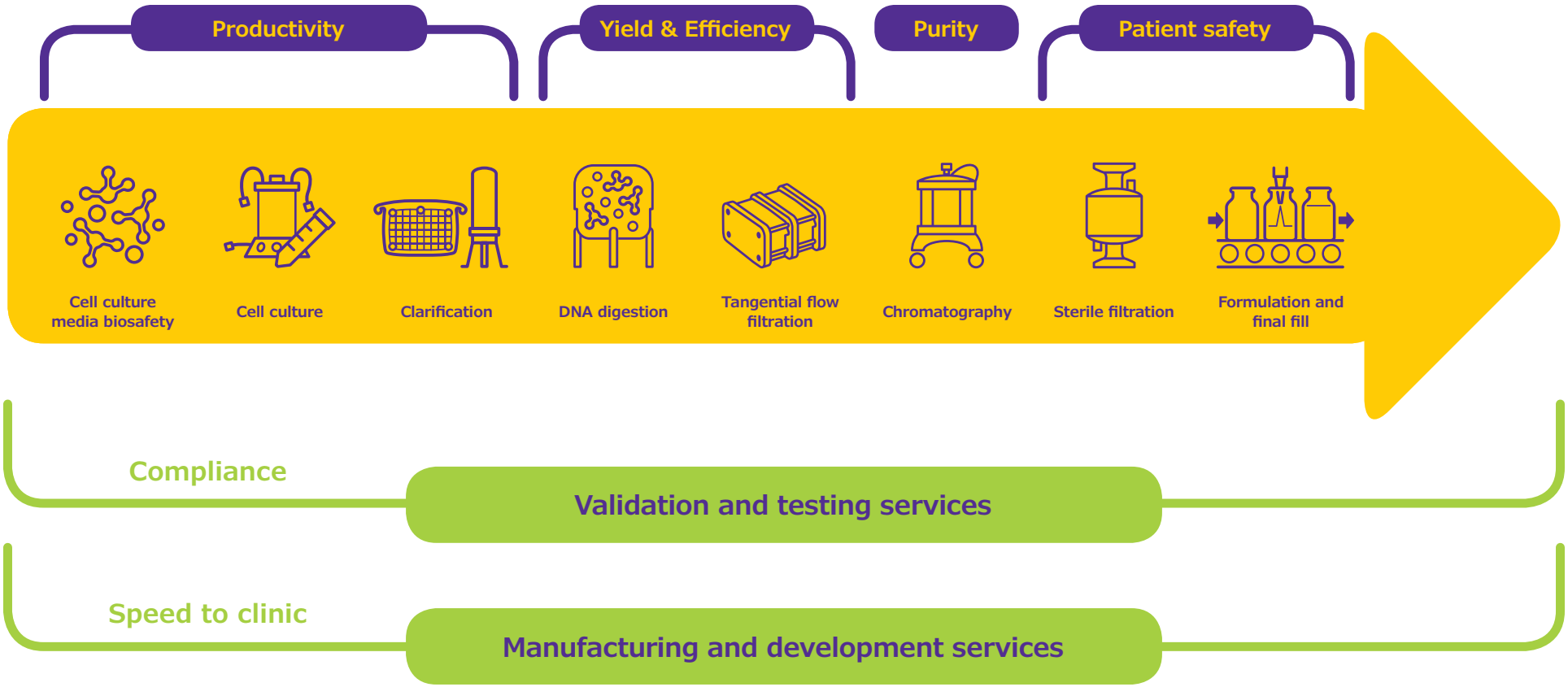
The BioReliance® portfolio encompasses biopharmaceutical characterization, safety testing and process development, as well as clinical and commercial biomanufacturing. Our experienced teams and operational expertise make us the partner who supports you all the way and always has your vital goal in mind.

Denotes BioReliance® Services

MilliporeSigma

Comprehensive Product & Services Portfolio

Accelerating development of vaccines and viral therapies



Upstream

Cell culture media and single-use bioreactor

Our upstream portfolio includes single-use bioreactors, cell culture media, media supplements, critical raw materials, buffers, mixers and a full range of filtration technologies to prevent microbial contamination and ensure your process meets yield and productivity targets.

The performance of the stirred tank single-use bioreactors scales reliably from the bench to production volumes.

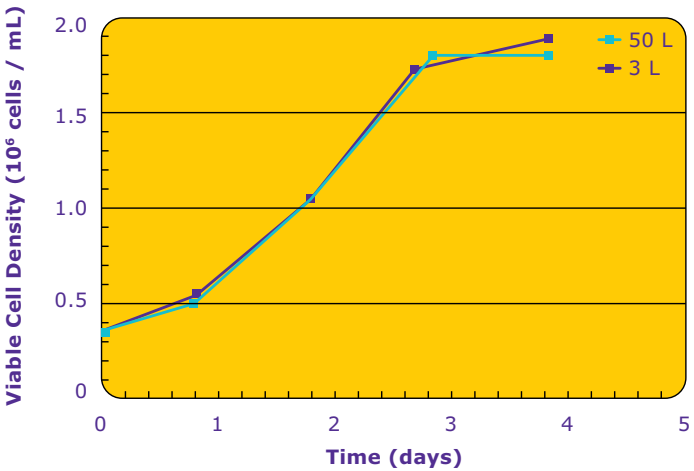


Figure 1. Growth kinetics of MDCK cells in the Mobius® 3L and 50L bioreactors.

Learn more about scalable and efficient Virus-like particles production

Millipore® Products SAFC® Products


Single-Use Bioreactor


Cell Culture Media


Supplements


Media Filtration


Sterile Sampling

Nucleic Acid Digestion, Clarification and TFF

Yield and efficiency

Nucleic Acid Digestion

Benzonase® endonuclease provides an efficient enzymatic tool for nucleic acid digestion and delivers pure viral product complying with all FDA regulations. Our GMP manufactured Benzonase® endonuclease purity grade I (≥99%) is supported by an Emprove® bio dossier and a DMF type II file.

Ultrafiltration and Microfiltration

Our industry-leading Pellicon® cassettes and UF/DF systems consistently and reliably deliver purity assurance at every stage of your development and manufacturing process.

Clarification

With more than 40 years of clarification experience, we are committed to introducing innovative, easy-to-use technologies, like Millistak+® Pod and Clarisolve® disposable depth filters, to help you improve your productivity and process efficiency.

Table 1. Virus recovery obtained during Adenovirus clinical batch manufacturing using Millistak+® COHC depth filter followed by Polysep® II 1.0 µm/0.5 µm filters

Sample description	Virus titer (PU/mL)	Virus recovery (%)
Current process filtrate	2.17e10	92
COHC filtrate	1.98e10	84
30CE filtrate	2.28e10	97
30DE filtrate	2.07e10	88

Learn more about vaccine clarification practices

Millipore® Products SAFC® Products


Depth Filtration


Microfiltration


Ultrafiltration


DNA Digestion


Bioprocessing Systems

Chromatography

Purity and efficiency

Chromatography

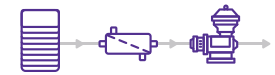
To meet your purification and process efficiency needs we provide scalable single-use chromatography systems and a full portfolio of resins. Our comprehensive selection of chromatography resins feature Eshmuno® and Fractogel® media, which are enabled by tentacle bead technology that is suited well for virus purification.

The NatriFlo® HD-Q Membrane features an advanced material with a three-dimensional macroporous hydrogel structure that provides a high density of binding sites and rapid mass transfer. The single-use, plug-and-play NatriFlo® HD-Q Membranes Adsorbers deliver binding capacity that exceeds resin-based columns with fast flow-rates typical of membrane adsorbers.

Table 1. Comparison of recovery, purity and competitive anion-exchange resin for adenovirus vector purification.

Chromatography adsorbent	Total infectious output (pfu)	Total virus output (vp)	Recovery (%)	Purity by HPLC
Competitor Resin A	0.64×10^{10}	1.3×10^{11}	53	75
Fractogel® TMAE	0.9×10^{10}	1.7×10^{11}	75	91
Fractogel® DMAE	0.4×10^{10}	0.7×10^{11}	33	76
Fractogel® DEAE	0.81×10^{10}	1.6×10^{11}	68	74

Table 2. Comparison of traditional versus new methods of Newcastle disease virus (NDV) purification for use in oncolytic virotherapies. TTF is tangential flow filtration. UC is ultracentrifugation. AEX is anion exchange.

	Traditional process	NatriFlo® HD-Q Membrane Adsorber
Purfication Process		
Process duration	9 hours	0.5 hours
Product recovery	65-70%	>90%
Scalability	⊗ UC difficult and expensive to scale up	✓ Depth filter and AEX easily scalable

Learn more on how to use advanced tools to achieve process intensification in virus purification

Millipore® Products

Chromatography Resins

Chromatography Columns

Membrane Chromatography

Chromatography Systems

Flexible manufacturing

Single-use assemblies and systems

Single-use manufacturing strategies using Mobius® assemblies and systems can enable flexible manufacturing facilities, reducing capital expenditures, time to market and changeover time.

Mobius® single-use manufacturing solutions provide you the flexibility to run any individual unit operation or build an entire single-use process train. The scalable portfolio of single-use systems are designed for use with pre-sterilized and pre-qualified, ready-to-use Flexware assemblies.

Designed to provide intuitive and ergonomic operator interactions that simplify workflows and reduce cleaning requirements, these solutions enable rapid turnaround and reduce bottlenecks. Convenient Lynx® connector and NovaSeal™ disconnect technologies enable closed processing, help assure operator safety and reduce contamination risks.

Table 1: Comparing traditional and Mobius® fill-finish processes at a vaccine manufacturer

	Traditional Fill-Finish	Single-Use Solution
Cleaning and set-up	14 hours	< 1 hour
Cleaning validation	Extensive	Zero
Filling time	24 hours	10 hour
Average vials/hour	3,000	10,000
Aseptic connections	50	0
Rate-limiting factor	Facility	Materials
Time for filling campaign	36 hours	12 hours

Single-Use Assemblies

Single-Use Mixing

Single-Use Systems

Sterile Sampling

Learn how partnerships lead to improved speed and efficiency

Millipore® Products

Sterile Filtration

Maximizing safety of your viral therapies

Trusted for the most critical applications, our single-use final fill assemblies reduce risk of cross-contamination and deliver process flexibility and productivity, without compromising product sterility.

Opticap® Capsule Filters with Durapore® Membranes

- Contain our industry leading Durapore® membranes, which deliver reliable performance and the highest levels of sterility assurance
- These membranes are available in multiple pore sizes, delivering flexibility to meet your specific process needs

Millipak® Capsule Filters

- Unique stacked disk design minimizes product hold-up and binding — ideal for high value applications such as final filling
- Contains our industry leading Durapore® membranes which deliver reliable performance and the highest levels of sterility assurance

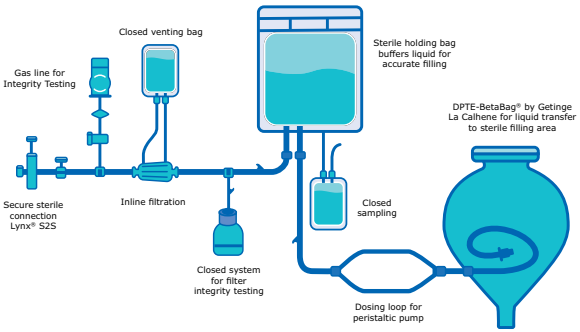
Mobius® Single-Use Final Fill Assemblies

A complete and comprehensive library of pre-qualified components, including tubing, filters, sterile connectors, single-use pumps and needles.

- Flexibility and increased filling productivity
- Reduced upfront capital investment
- Increased speed to market
- Reduced risk of cross contamination and enhanced operator safety
- Integrates with Milipak® Barrier filters, which simplify in-line pre-use integrity testing of sterilizing-grade filters without the use of a flush bag

Durapore® Capsule Filters

Millipak® Capsules Filters



Sterile filtration product selection guide

Millipore® Products BioReliance® Services

Formulation and Fill Assemblies

Barrier Filter

Filter Validation

Boosting Vaccine Formulations

Excipients and Adjuvants

Our extensive portfolio of process chemicals, excipients and lipids are designed for high-risk applications like vaccine formulation.

Innovative polymers and lipidic drug delivery excipients featuring superior characteristics that ease formulation processes, including squalene and customized lipids manufacturing.

- Very high purity
- Consistent quality from Non-GMP to GMP
- Improved characteristics
- Paper-free packaging to minimize risk during production

Emprove®

Process chemicals and excipients, including buffers, stabilizers, mineral salts, preservatives and adjuvants are part of our Emprove® Program, which provides comprehensive regulatory documentation to simplify and speed up regulatory filings.

Table 1: Exemplary specification parameters of two of our stabilizers show superior values.

	Endotoxins (I.U./g)		Reducing sugars (%)	
	MilliporeSigma	Ph Eur, USP	MilliporeSigma	Ph Eur, USP
Sorbitol	≤ 1	≤ 2.5	≤ 0.11	≤ 0.2, 0.3
Mannitol	≤ 1	≤ 2.5	≤ 0.05	≤ 0.2

Our sample kits include 3 different batches of 1kg packaging for customer's qualification process

Learn how partnerships lead to improved speed and efficiency

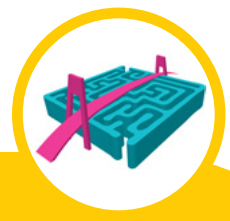
SAFC® Products

Excipients

Buffers

Lipids (Standard and Customized)

PLA/PLGA Biodegradable Polymers



Emprove® Program

BioReliance® Biosafety Testing Services

Patient safety and compliance

For vaccine and viral therapies, BioReliance® biosafety testing services provide a comprehensive range of assays and services to support every stage of your biologics development and manufacturing process. From cell banking and cell line characterization, through lot release testing and product characterization, GMP testing is offered with leading turn-around times and scientific expertise.

BioReliance® upstream services include:

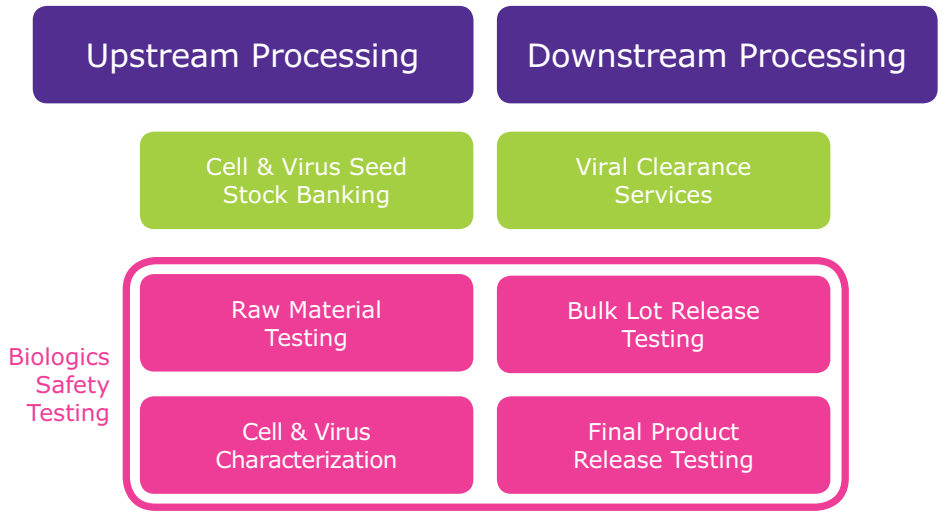
- MCB/WCB bank manufacturing
- MCB/WCB bank characterization
- Biorepository services
- Virus bank manufacturing
- Virus bank characterization
- Next Generation Sequencing
- Raw material testing

BioReliance® downstream services include:

- Analytical services for biologics
- Viral clearance studies
- Bulk lot release testing
- Final product release testing

BioReliance® Upstream services include:

BioReliance® Downstream services include:



Learn more about holistic total virus strategy for bioprocessing

BioReliance® Services

BioReliance® Viral and Gene Therapy Manufacturing

Your trusted partner

World-class process development and manufacturing for virus-based therapeutic products. From small scale toxicology and Phase I material to commercial-scale manufacturing and fill finish, our flexible facilities and expert staff are leaders in viral product manufacturing.

Manufacturing Areas Feature:

- Completed FDA/EMA pre-licensure inspections
- Separate facility areas for scale-up, process validation, Phase III trials and commercial launch
- 16 client-dedicated Class 10000 (ISO® 7) clean room production suites
- Two dedicated Class 1000 (ISO® 6) fill suites; one designed for small commercial fills
- Biosafety release testing assurance via BioReliance® services
- Highly qualified process development teams focused on early-stage process optimization and scale up

20 years
of experience working with a broad range of platforms and vector systems

>500
Clinical production lots for Phase 1 – Phase 3

LENTIVIRUS, AAV, ADENOVIRUS, RETROVIRUS

Global Quality System

>1m → vials filled

Take a video tour of our viral product manufacturing facility in Carlsbad

SAFC® Services

BioReliance® Services

Viral Product Manufacturing

ImMEDIAte Advantage™

Liquid Buffer Services

M Lab™ Collaboration Centers

Better, Faster, Together

Visit our M Lab™ Collaboration Centers:

M Lab™ Collaboration Centers provide a global network of vibrant collaboration spaces where you can explore ideas, learn innovative techniques and work side by side with experts to solve critical process development challenges.

Global Process Development Network

With 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 200 scientists, engineers and technicians including process development scientists, biomanufacturing engineers and systems process engineers.

- > 25 years of experience in vaccine and viral product process development.
- Our technical experts have solved over **5,000 customer problems** and **saved customers 13,000+ hours annually** in process troubleshooting and deviation investigations.

M Lab™ Collaboration Center

Vaccine Learning Center

Webinars

EMDMillipore.com/vaccines

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