Buffer Preparation for Plasma Processes:

Process Efficiency

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

Millipore®

Preparation, Separation, Filtration & Monitoring Products

Buffer Preparation for Plasma Processes: Process Efficiency

Solution preparation in plasma manufacturing is a critical and complicated step yet, due to its perceived simplicity, it is often overlooked during initiatives to improve process efficiency.

Process expansion and resulting facility constraints also often put a strain on buffer preparation and efficient preparation can alleviate these bottlenecks.

One solution to these challenges is a centralized preparation space for preparing in-process buffers to streamline operations. These centralized spaces often rely on single-use technologies and require careful selection of components, equipment and filters for bioburden reduction or sterile filtration.

Centralized preparation space can be particularly helpful in facilities that produce different plasma products such as Factor VIII, IgG and Albumin.

For information about our plasma purification capabilities, visit **MerckMillipore.com/plasma**

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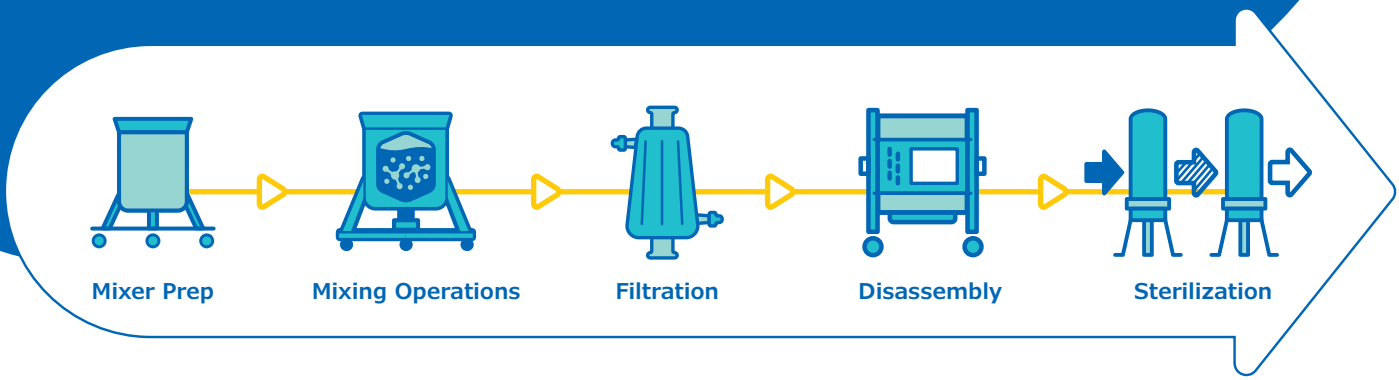
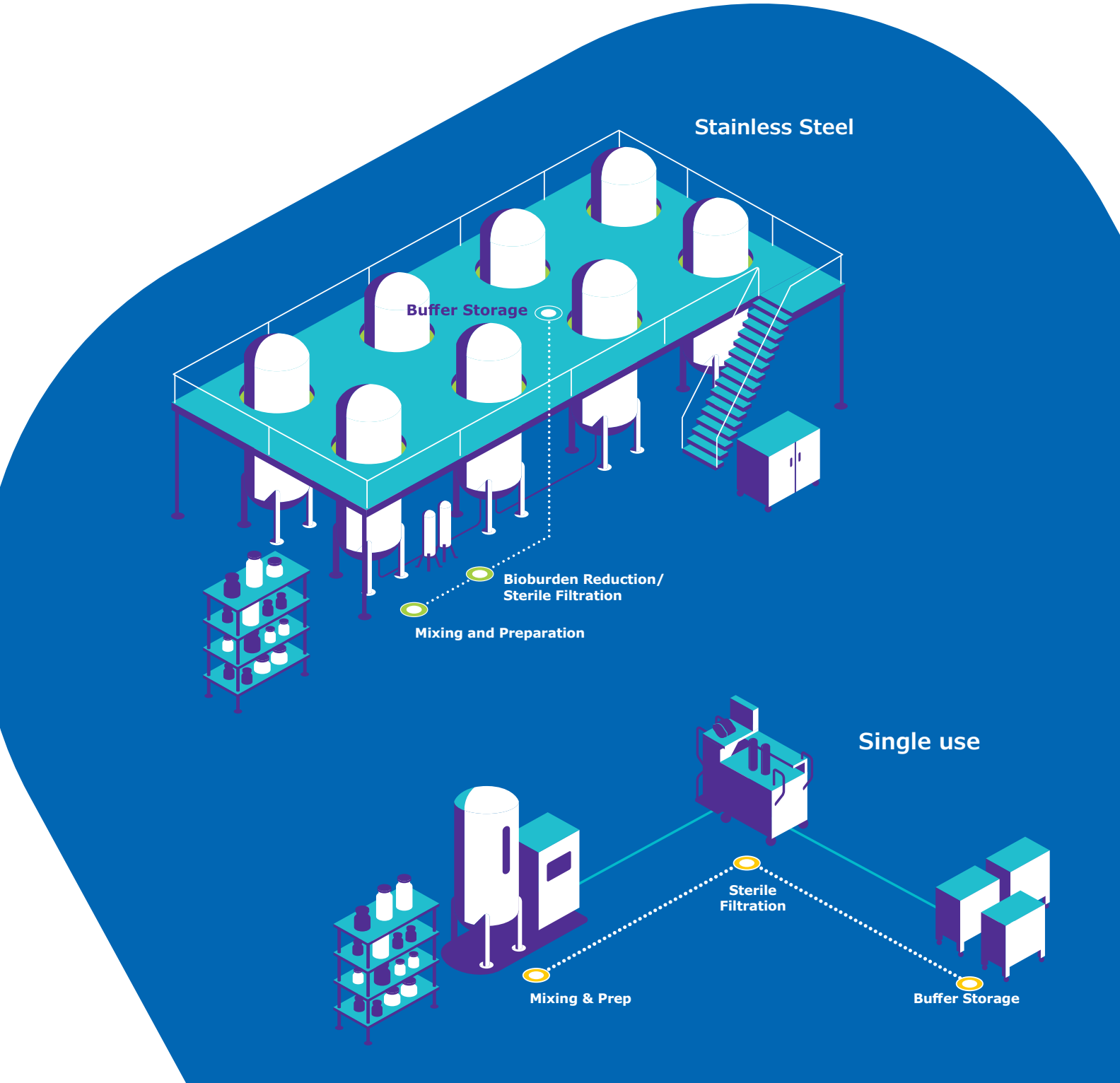
Steps Involved in Buffer Preparation

Regardless of the choice of stainless steel or single-use, buffer preparation generally follows similar steps from mixer preparation, mixing, filtration, disassembly and sterilization (if required).



Single-use technologies streamline the buffer preparation process by reducing the time associated with mixer preparation, disassembly and tank sterilization.

Additionally, process footprint size is greatly reduced, saving you valuable facility space.



Common Buffers Used in Plasma Production

Buffer quality is vital for the success of plasma processes as buffers maintain pH and conductivity conditions to stabilize your process intermediates during purification.

Steps in Plasma Processing

Below are the most common types of buffers employed by plasma fractionators all of which we offer to solve our customer's purification needs.

Phosphates

- Sodium dihydrogen phosphate dihydrate
- Di-Sodium hydrogen phosphate dihydrate
- Potassium dihydrogen phosphate
- Di-Potassium hydrogen phosphate anhydrous

Acetates

- Sodium acetate anhydrous
- Sodium acetate trihydrate
- Acetic acid (glacial) 100%
- Acetic acid 30%

Citrates

- Citric acid anhydrous
- Citric acid monohydrate
- Tri-Sodium citrate dihydate

Amino acid buffers

- L-Histidine
- L-Histidine monohydrochloride monohydrate
- Glycine

pH adjustment agents

- Hydrochloric acid fuming 37%
- Hydrochloric acid 1 mol/L
- Acetic acid 1 mol/L
- Sodium hydroxide
- Sodium hydroxide 1 mol/L
- Potassium hydroxide

SAFC®

Pharma & Biopharma Raw Material Solutions

BioContinuum™ Buffer Delivery Platform

The BioContinuum™ Buffer Delivery Platform is a configurable offering of buffer concentrates, buffer dilution system, single-use assemblies, and services tailored to provide the highest level of accuracy and precision for absolute certainty in buffer preparation and management. Whether designing a new, low-overhead facility or expanding capacity at an existing facility, the BioContinuum™ Buffer Delivery Platform delivers a competitive edge by reliably supplying your process buffers from point-of-manufacturing to point-of-use utilizing a fraction of the resources and facility space.

- Simplify buffer preparation and management with an integrated offering of buffer concentrates, buffer delivery system, Mobius® MyWay Select single-use assemblies and services
- Reduced manufacturing footprint devoted to buffer preparation and management
- Increase speed and flexibility in buffer preparation to meet the needs of evolving manufacturing demands
- Increase operator safety by reduced handling of dry powders
- Integrated quality using Emprove® raw materials, Mobius® MyWay Select single-use assemblies and robust volumetric dilution control

Emprove® Chemicals Portfolio

Tailored to your risk management needs, our Emprove® portfolio of approximately 400 raw and starting materials is divided into three categories.

These categories address the risks of different operations and simplify chemical selection.

Emprove® Essential

Designed for moderate risk applications, Emprove® Essential products offer GMP compendial compliance, supply chain transparency and regulatory support designed to assist drug manutacturers' formalized risk assessments. They are produced according to controlled manufacturing processes. Critical parameters such as elemental impurities and residual solvents are characterized by using validated analytical techniques.

Emprove® Expert

Addresses higher risk applications where the lowest microbiological and endotoxion levels are of utmost importance. Along with risk management, the features of the Emprove® Expert line go even further: the cGMP manufacturing processes are designed to yield products with specified low microbiological and endotoxin levels, thus supporting the overall risk mitigation strategy.

Emprove® Buffers

We offer a complete range of GMP buffers for your purification and formulation steps with full traceability of our sourced raw materials to ensure the quality and consistency of your product. We can provide a comprehensive regulatory documentation package for our Emprove® program to simplify your regulatory filing.

SAFC®

Pharma & Biopharma Raw Material Solutions

Emprove®: Regulatory-Ready Dossiers

Complementing our product portfolio, the Emprove® Program provides three types of dossiers to support different stages of development and manufacturing operations such as qualification, risk assessment and process optimization. The dossiers consolidate comprehensive product-specific testing data, quality statements and regulatory information in a readily-available format to simplify your compliance needs.

Our Emprove® Program Simplifies and Speeds Regulatory Filing by:

Supporting risk assessment, management and mitigation

Increasing supply chain transparency

Expediting approval preparation and extending compliance

We offer three types of dossiers to support your operations:

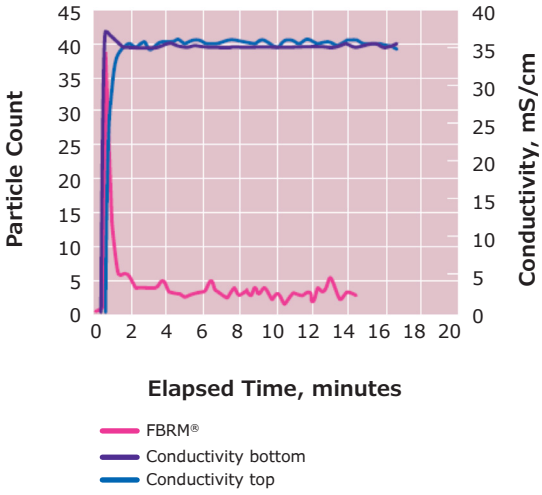
1. **Material Qualification Dossier**
   Provides the fundamental information for the qualification process.
2. **Quality Management Dossier**
   Provides information needed for your formalized risk assessment.
3. **Operational Excellence Dossier**
   Provides detailed data you need to qualify and ensure consistent and predictable drug quality.

Buffer Mixing Solutions

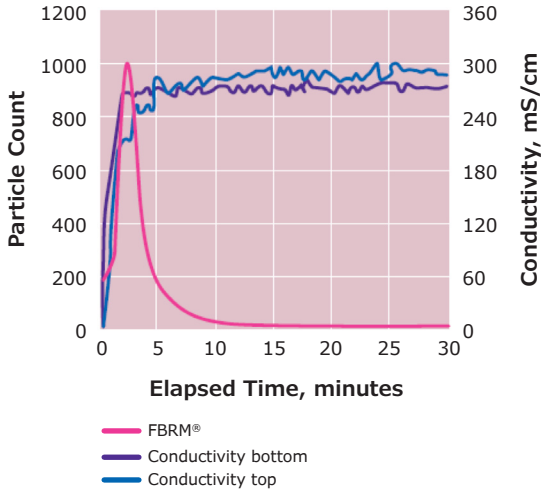
Mixing of buffers (sinking powders) and media (floating powders), especially at high volume, presents challenges in dispersion and dissolution of particles. The creation of a vortex and abundant surface movement in our Mobius® Power MIX system is key to success in this process.

The axial and radial flow patterns generated in the mixing system allow for quick distribution of sinking powders, minimizing settling at the bottom of the vessel. Floating powders are drawn into the vortex, enabling effective wetting distribution and dissolution throughout the entire vessel volume.

Mixing 1X PBS in Mobius® Power MIX 2000



Mixing 1.5X NaCl in Mobius® Power MIX 2000



Mobius® Single-Use Mixing Solutions

Integrated powder delivery, mixing and filtration delivers economical and flexible processing.

Benefits

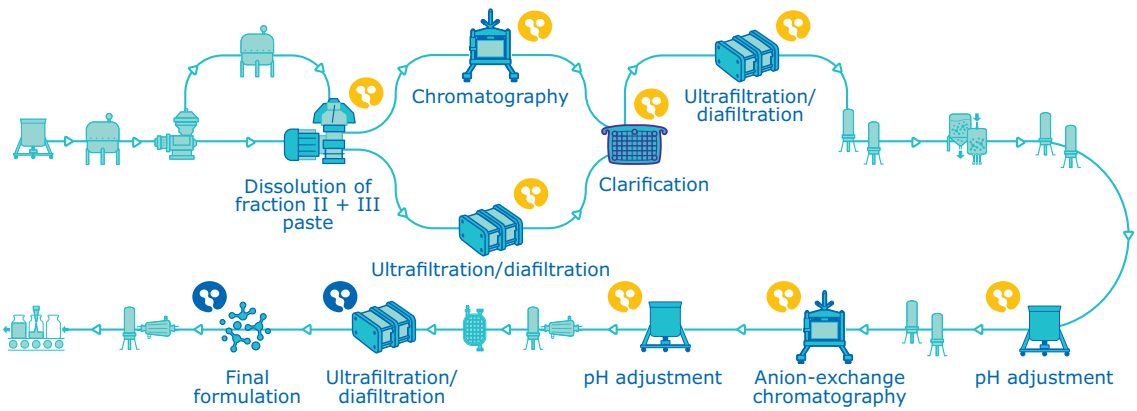
- Single-use technology for increased production capacity in multi-product facilities
- Easy setup, use and transportation
- Powerful magnetically coupled impeller designed to efficiently mix the most challenging buffer, media and biopharmaceutical ingredients
- Broad working volumes that range from 15% of the total volume (size dependent) to 10% above for processing flexibility
- Stainless steel units have doors that open to one half the mixer's diameter for easy bag loading
- 100 L, 200 L and 500 L models are available in plastic or jacketed stainless steel
- Optional hoist for powder delivery minimizes operator exposure to powders and improves handling
- Integrated load cells and temperature sensor
- Compatible with in-process pH measurement options
- Closed, sterile, and zero deadleg sampling directly from the mixing bag

Protecting Your Process

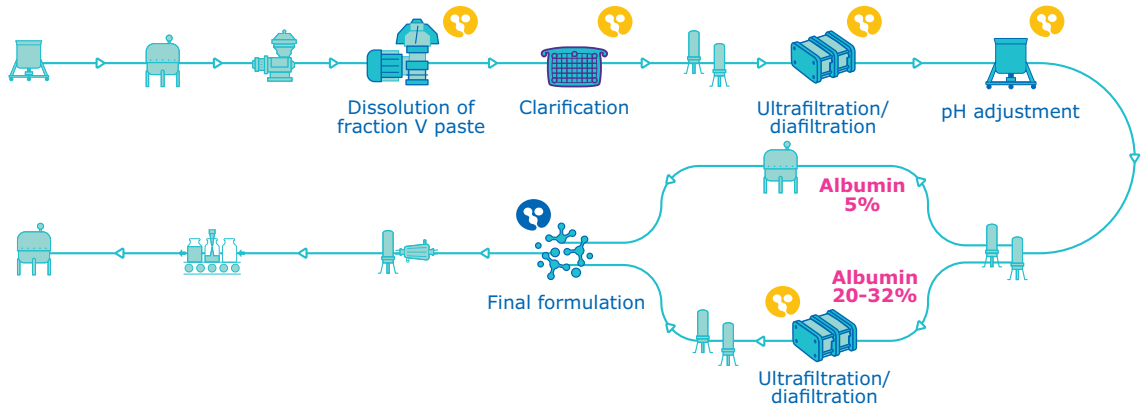
Buffer filtration is an important operation in every process and high flux filters that enable rapid processing are generally the preferred choice for efficient operations. Assuming the filters are compatible with the buffer stream, the most important consideration is the level of microbial protection required.

Filters for processing buffers used in downstream processing may be bioburden reduction rather than sterilizing-grade filters as these intermediate processing steps are typically low bioburden rather than truly aseptic. By contrast, sterilizing-grade filters might be preferred for processing formulation buffers as these are closer to the end of the process and the final filling operation.

Immunoglobulin Processing

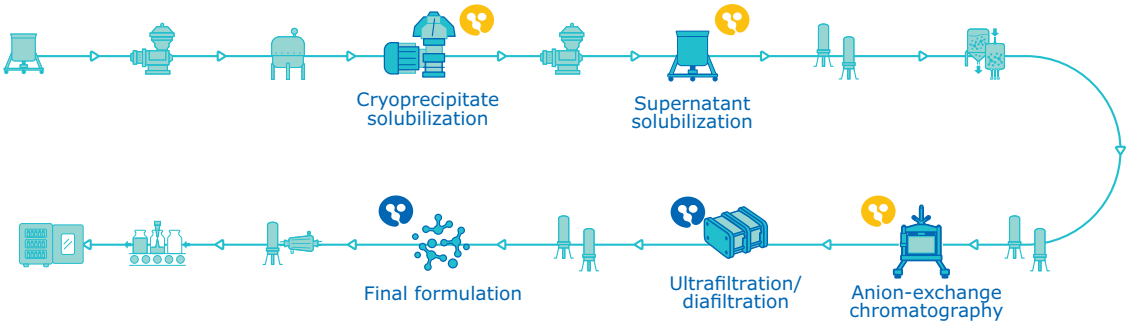


Albumin Processing



Bioburden reduction filters Sterilizing-grade filters

Factor VIII Processing



Millipore Express® PHF (Process High Flow) Filters

- Designed for filtration that does not require validation of sterility assurance
- Sterilizing-grade membrane
- Broad chemical compatibility
- High flow rates

Millipore Express® SHF (Sterile High Flow) Filters

- Designed for steps that require high flow, sterile filtration
- Sterilizing-grade membrane
- Broad chemical compatibility
- High flow rates

Efficient Filter Sizing

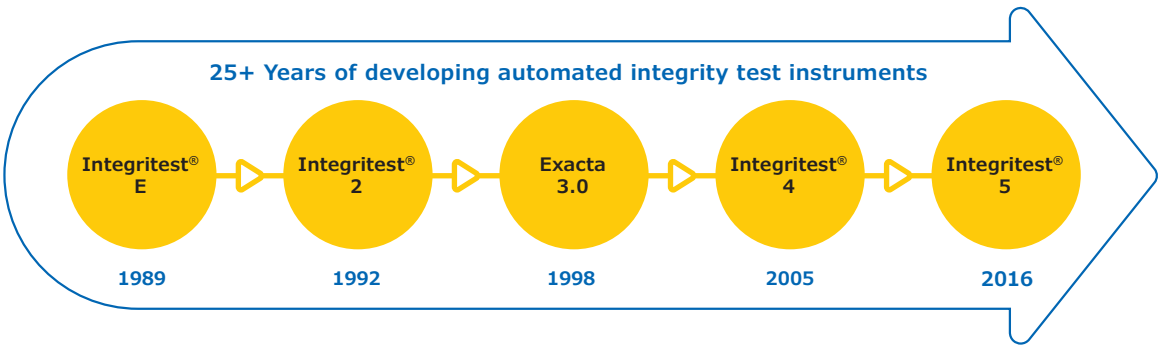
Many buffer solutions have low concentrations of particulates and are typically non-plugging with water-like viscosities at room temperature. Filter sizing for these solutions is generally dominated by permeability. The table below shows examples of recommended device filtration areas and processing times for processing buffer batches of different sizes through Millipore Express® PHF filters. Filter sizing of any buffer solution is dependent on the throughput of the solution on the selected filter, the operating conditions and the filter connections. Estimated filtration area requirements should be confirmed before large-scale processing.

Batch Volume (L)	Filtration Time (hr)	Calculated Amin (m^2)	Device	Device area (m^2)
50	0.5	0.03	Opticap® XL300	0.048
100	0.5	0.06	Opticap® XL600	0.097
500	2	0.08	Opticap® XL600	0.097
1000	2	0.15	Opticap® XL5	0.17
2000	2	0.30	Opticap® XL10	0.57
3000	2.5	0.36	Opticap® XL10	0.57

Integrity Testing

A risk assessment is generally used to determine if integrity testing of a buffer filter is required following filtration. When implemented, it is usually off-line due to the low risk operation and ease of reprocessing if necessary. Integrity testing can be streamlined by using an automated filter integrity tester.

Supported by a Knowledgeable, Responsive, Global Partner



History and experience matter. We introduced the first commercial automated integrity tester over 25 years ago. We were the first to automate sizing, and we developed the first water intrusion test – HydroCorr™. We know filters. We know integrity testing.

Integritest® 5: Integrity Assurance with Ease and Confidence

Accurately and reliably verify the integrity of your filters and processing equipment with the portable, easy to implement, and automated Integritest® 5 instrument. The Integritest® 5 instrument delivers a simple intuitive user experience, while providing optional depth of flexibility to fit your process.

Benefits

- Robust unit protects against water and dust entry, and automatically checks calibration
- Improved test algorithm reduces test time and simplifies test creation
- Intuitive software includes help screens available for every step
- Flexible displays, run information, and test collections to suit your process
- Standard model offers all networking functions, including multi-unit management and synchronization

Safe and Efficient Fluid Management

Mobius® 2D and 3D assemblies, storage and transportation solutions are key components for efficient, ergonomic and scalable fluid management, from media and buffer prep to final fill applications.

Choose from a variety of container options, including polyethylene drums, stainless steel bins for storage or transportation, collapsible plastic containers and carts, ranging from 10L to 1000L. Our assemblies and solutions are designed to reduce operator error, process risks and improve efficiency. With a full spectrum of systems to choose from, at varying scales and levels of certification, you get greater flexibility, mobility and support for your single-use technologies.

Mobius® 2D and 3D Assemblies and Storage Systems

Applications

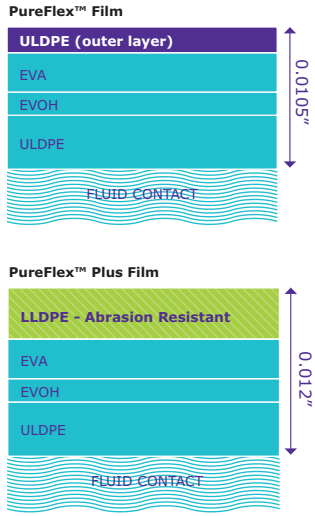
- Sterile filtration and transfer
- Storage of buffers, media and bulk intermediates

Single-Use Film Technology

PureFlex™ and PureFlex™ Plus Film

PureFlex™ and PureFlex™ Plus films are used in Mobius® single-use assemblies and NovaSeptum® sterile sampling products, and are safe, robust and chemically resistant.

- Fluid contact material: Ultra low-density polyethylene (ULDPE)
- Gas barrier: Polyethylene vinyl alcohol-copolymers (EVOH)
- Outer layer:
  - PureFlex™ film: Ethylene vinyl acetate (EVA) and ULDPE
  - PureFlex™ Plus film: EVA and linear low density polyethylene (LLDPE) which increases the film's resistance to abrasion, puncture, stretching and tearing



Single-Use Sterile Connectors

Reliable and easy-to-use, Lynx® connectors enable risk-free, sterile fluid transfer, and are available in a wide range of types, sizes and configurations.

Lynx® S2S (Sterile to Sterile) Connector

- Designed to integrate single-use systems
- Gamma and autoclave-compatible


Lynx® S2S Connector

Lynx® CDR (Connect, Disconnect, Reconnect) Connector

- Industry's first disposable connector enabling multiple aseptic connections
- Validated for up to six sterile connections and disconnections with wet and pressurized flow path


Lynx® CDR Connector

Lynx® ST (Steam-To) Connector

- Connects steamable hard-piped processing systems to a single use flow path


Lynx® ST Connector

Sterile Sampling Solutions

Sterile, closed, disposable systems for process sampling.

Accurate, sterile sampling of your product is critical. An imprecise or false positive result can lead to time-consuming investigations and costly delays. With our NovaSeptum® sampling system, you can sample with confidence.

NovaSeptum® Sterile Sampling System

From buffer and media preparation to final formulation and filling, the closed NovaSeptum® sterile sampling system gives you the freedom and security to sample processes wherever you need. Available in a wide variety of formats and volumes, NovaSeptum® sampling systems are easily integrated into your process for robust, reliable process monitoring.

- Flexible, pre-sterilized, disposable sampling options
- Ensures the security of the process, the operator and the sample
- Zero risk of cross-contamination
- Compliant with the most stringent regulatory and quality requirements
- Allows for accurate samples: 1 mL to 1000 mL

NovaSeptic® Connectors

- NovAseptic® connectors improve the efficiency and robustness of your aseptic process
- Proven, innovative flush-mounted design for low hold-up volume
- Flexible aseptic design; available tank-connected or in-line
- Provides ease of access to critical areas for sampling prior to product release
- Adaptable to a wide range of equipment; easily and securely fitted to ensure system sterility

Process Chemicals for Storage and Cleaning

You can order our GMP grade products in the volumes and concentrations you require. We can provide comprehensive Emprove® dossiers to simplify and speed your regulatory filings.

Explore, Learn and Collaborate at Our Worldwide M Lab™ Collaboration Centers

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. These nine non-GMP labs offer you the flexibility to troubleshoot and test without impacting your production line. Staffed by a network of technical experts, these labs are where we solve your toughest problems — together.

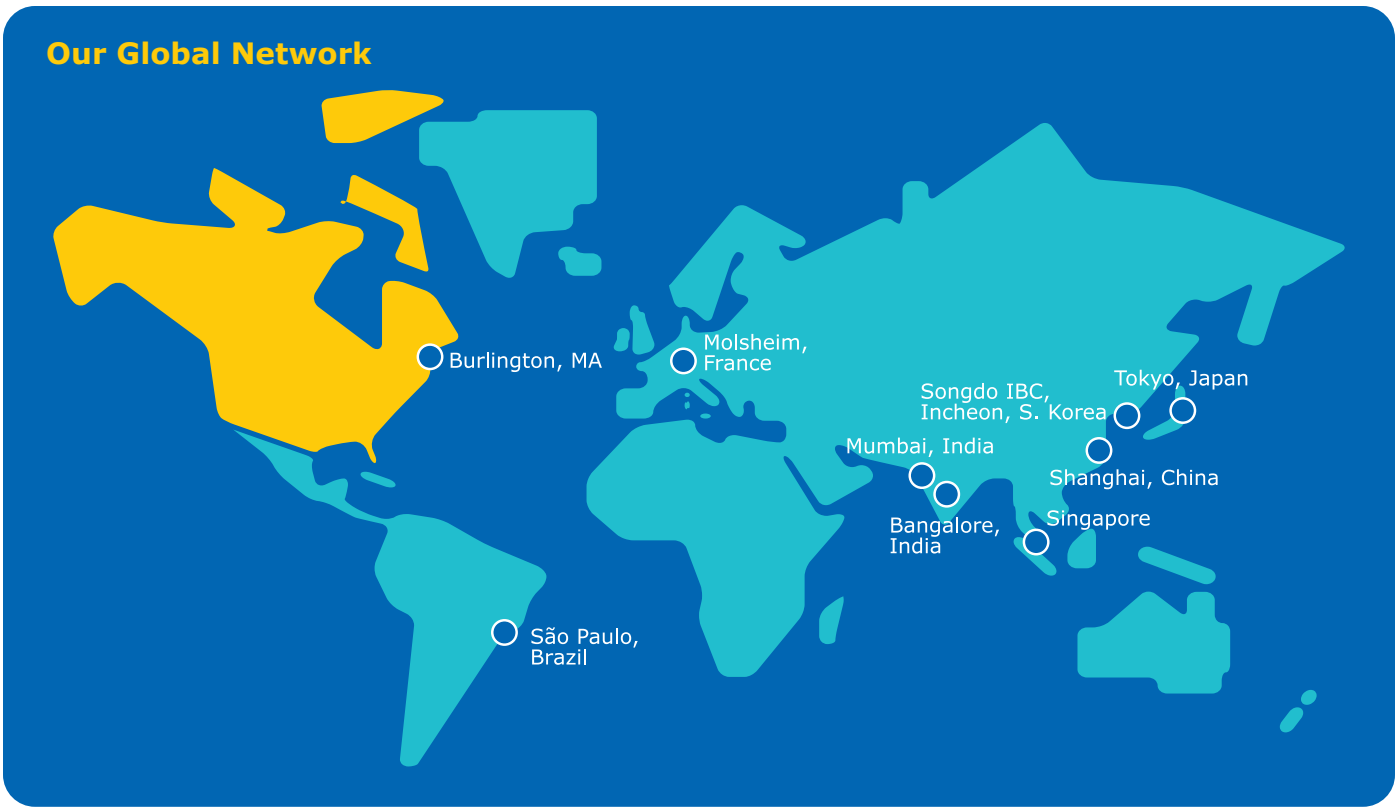
Global Process Development Network

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.

Why Visit an M Lab™ Collaboration Center?

At the M Lab™ Collaboration Centers, no challenge is too great. Our technical expertise spans all aspects of the process train. Areas of support we offer include, but are not limited to:

- Overcome barriers to single-use implementation
- Receive guidance for process development and scale up
- Troubleshoot existing processes
- Gain technical knowledge required prior to new product adoption
- Acquire new skills and expertise in bioprocessing and formulation development
- Discover best practices and techniques for adopting next generation bioprocessing
- Develop and test new procedures prior to implementation



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Preparation, Separation,
Filtration & Monitoring Products

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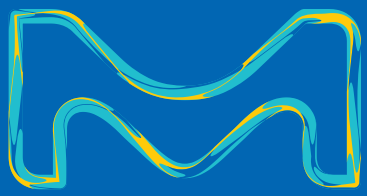

Cover Image:
This material image was produced before the Covid19 crisis started.
We take our responsibility seriously and fully comply with all protection rules.

MerckMillipore.com/plasma

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