

A holistic buffer management overview

Buffer preparation is a core operation of all biologics production processes. Buffers are used throughout processing from media preparation to final filtration, and although reliable buffer preparation is critical, the operation is often considered low added value. In a standard bioprocess, typical consumption is in a range between 5 and 10 liters of total buffer volume per liter of bioreactor, and even higher when bioreactor titer increases. For a 1,000 L bioreactor, the downstream process will require between 5,000 L and 10,000 L of buffers, with on average 15 different buffer solutions per process. Thus, supply of the right volume of buffer at the right time can be a process bottleneck. This document will discuss optimization of buffer preparation in-house and the various considerations for outsourcing. Depending on the process requirements, the ideal solution may be a combination of more than one option.

Optimizing your in-house preparation

In-house buffer preparation remains the most common method for managing buffer supply. Users have equipment onsite to perform powder hydration and will source multiple raw materials and consumables needed for the preparation. By keeping preparation onsite, a manufacturer can optimize and debottleneck the process in different ways: with enhanced raw material handling, adoption of single-use technologies for hydration and storage, as well as adapting filtration to the level of risk.

Sourcing and handling raw materials

Chemical raw materials are the core of buffer preparation. The choice of the right chemical grade is fundamental from a quality, purity, and supply chain point of view. Supplier documentation is key during the qualification of a new component. Our M-Clarity™ Program simplifies this process, making it easier to select the right product for the intended use with six clearly defined levels of quality attributes, documentation, and services. Structured dossiers from suppliers, such as those available from the Emprove® program, help end-users perform robust risk assessments.

Beyond qualification, handling of chemicals can be another major challenge in buffer preparation. A typical preparation requires sampling, accurate weighing and dispensing of multiple components. This is time-consuming, requires precision and is a common source of error, employee risk and contamination. In addition, certain chemicals have the tendency to cake, creating solid blocks that operators need to break before handling. All these operations – especially when performed at multi-ton scale – can represent safety risks for operators, e.g. by lifting heavy loads, hammering caked material or being exposed to volatile powders.

Powder handling technologies can mitigate these risks. Moisture-driven caking can be addressed by packaging technologies regulating moisture content such as Drypour® packaging. Currently, urea, glycine, and selected cell culture media are commercially available as granulated grades.

Considerations for Powdered Raw Materials

- **Product selection:** product testing and manufacturing documentation
- **Handling:** minimize handling and caking to reduce operator risk
- **Right size packaging** for optimized preparation

In addition, delivery of chemicals in optimized packaging such as powder transfer bags, will simplify sampling, weighing and dispensing, lowering workload as well as risk of contamination and dust formation.

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Filtration

Most biomanufacturers routinely process buffers through bioburden reduction or sterilizing grade filters to control bioburden and minimize the risk of microbial contamination.

These filters are available with different membrane composition, structure, pore size and microbial retention specifications to meet different process needs. For typical buffer filtration operations, these include high flow and capacity with minimal filter footprint. Our Millipore Express® PHF and Milligard® PES membrane filters are ideal for buffer filtration and include options for both sterile filtration and bioburden reduction. For more plugging buffers that require high capacity sterilizing-grade filters, our Millipore Express® SHC filters are the preferred solution.

Buffer preparation

Mixing of buffers (sinking powders) and media (floating powders) presents substantial challenges in achieving adequate dispersion and dissolution of particles, especially at high volumes. The creation of a strong vortex is key to success. The Mobius® Power MIX system provides high performance mixing based on proven technology. Floating powders are efficiently drawn into the vortex, wet and then distributed throughout the volume in the vessel.

The Mobius® Power MIX system is designed to meet the needs of single-use manufacturing from small to large scale. Leveraging the proven technology of magnetically coupled NovAseptic® mixers, traditionally used with stainless steel tanks, the Mobius® Power MIX system offers solutions for a wide range of mixing applications, including high concentration buffers and hard-to-mix cell culture media. The Mobius® Power MIX system also comes with a jacketed carrier which allows for temperature elevation during the mixing process to improve the dissolution of difficult to dissolve powders.



Transfer and storage

Depending on the buffer delivery strategy and shelf life, buffers are often prepared days or weeks in advance of being used in process. After preparation and filtration, buffers will be stored in sterile storage bags. Small volumes can be stored in Mobius® 2D standard assemblies, which can be easily transported in container carts. Larger volumes can be transferred in Mobius® 3D storage bags which can be stored either in stainless steel bin or in polyethylene drums and collapsible bins. Mobius® assemblies, as well as storage and transportation systems are designed to reduce operator error and improve process efficiency.

Mobius® 3D Large Liquid Transportation Systems are fluid management solutions that enable biopharmaceutical manufacturers to safely move via road or air large liquid volumes like buffers, between different global sites, different regional sites, or even within the same facility.

To ensure safety, our Mobius® storage and transport solutions have been validated according to International Safe Transit Association (ISTA). These tests validate package strength and integrity therefore ensuring real world transfer conditions. Mobius® containers have been tested against ISTA 3 series tests, assuring the package and product can withstand any transport threats.



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The prepared buffer can then be transferred aseptically to the point of use, using Lynx® S2S (Sterile to Sterile) connectors for single buffer transfer, or Lynx® CDR (Connect – Disconnect – Reconnect) connectors for multiple connections.



QC testing

Meeting the specifications of the various buffers in a manufacturing process is critical. Before being released to the process, buffers need to be tested to control parameters like sterility, pH, conductivity and endotoxins. An imprecise measurement can delay use by repeat analysis while a contaminated sample can result in the buffer being discarded. Sampling should be robust and safe both for the product and for the operator. NovaSeptum® GO sampling units ensure a safe and representative sampling of the process fluid. A sample is taken from the tank with a needle through a silicon septum and collected in a sterile bag, bottle or syringe. The sample is isolated from point of collect to analysis, eliminating the risk of process and sample contamination.



Outsourcing buffer preparation

To minimize resources, many biopharmaceutical companies outsource buffer preparation. Several reasons can justify this shift: allocation of employees to core manufacturing activities with more added value, time savings, reduction of floor space dedicated to the weighing and hydration of buffers, debottlenecking of equipment, reduction of operator safety risk and preparation error.

Ready-to-use sterile filtered liquid solutions

Biopharmaceutical manufacturers may outsource their buffer preparation preferring to buy as ready-to-use solutions. These sterile-filtered liquid buffers are typically customized solutions, packed in single-use bags, and shipped in drums and returnable outer containers to the end-user in configurations that have been tested according to ISTA 3H guidelines.

Sterile liquid buffers are available in batch sizes ranging from 50 L to 10,000 L, and are produced according to ISO 9001:2008 in our locations in the U.S., Europe, and Asia. Formulations and specifications are tailored to the user's requirements and produced with high quality raw materials (e.g. Emprove® chemicals) hydrated in Water For Injection. Buffers are sterile filtered and aseptically filled either in bottles, in standard, or in custom bags, from 1 L to 1,000 L. For sustainability, bags can be transported in returnable outer containers that are cleaned and recycled under a controlled fleet management program. A Certificate of Analysis provides standard and custom testing information on the buffer, and satellite samples can be shipped for quality control.



Cleaning in place solutions

Every biomanufacturing process involves cleaning to protect equipment and prevent cross-contamination. Cleaning In Place (CIP) solutions are used to clean stainless steel tanks and piping systems, to wash and store chromatography resins, and to regenerate membranes. CIP solutions typically used include highly concentrated caustics (e.g. sodium hydroxide), acids (e.g. hydrochloric acid, phosphoric acid) or solvents (e.g. ethanol). These solutions are considered as Dangerous Goods, and their transport packaging is qualified to the according UN rating. Our CIP portfolio contains a lot of catalog products, which are available in bottles, drums or intermediate bulk containers. To support large scale manufacturing, CIP solutions can be supplied in ISOtainers up to 20,000 L, with a controlled and trackable fleet management program.



To continuously increase quality and safety, pre-installed, encoded dip-tubes are available for 200 L and 950 L packaging. The dip tube and quick connector provide a closed system by using a dry-coupling technology and the sophisticated encoding system avoids product mix-up.



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Deciding the best option for your process

To determine the best approach for buffer preparation, operational efficiency needs to be balanced with capital investment, raw materials, consumable and other operating costs. There are many potential options between full in-house preparation and a complete outsourcing model.

Buffer cost modeling tools can help evaluate costs of different buffer preparation approaches, to support data-driven decision making. Traditional cost models compare the economics of made in-house buffer preparation from powders with buffer outsourcing using either ready-to-use liquid buffers or buffer concentrates. In many cases, the preferred option is often a hybrid with a mix of different buffer preparation methods due to certain constraints, such as footprint limitations, warehousing, labor, or buffer availability in each buffer preparation format.

We have developed a tool to help biomanufacturers determine the preferred option of buffer preparation methods within the respective facility constraints to optimize buffer costs. A software-driven approach quickly evaluates the parameters and identifies the preferred option based on process and facility information. Contact your representative if interested in evaluating the best suited option.

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The Millipore® portfolio of Merck 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 timetested processes. Our proven products, regulatory and application expertise are a strong foundation you can rely on to consistently perform at the highest level.

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Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

