Buffer Management: From Central Function to Strategic Advantage

As biomanufacturing processes evolve to support higher titers, tighter timelines and increasing operational complexity, long-standing manufacturing practices are being re-examined. Buffer preparation is one of the most critical yet under-optimized elements of downstream processing. Despite its significant impact on labor, cleanroom footprint, scheduling and manufacturing readiness, buffer preparation strategies in many facilities have remained largely unchanged for decades.

This white paper explores why traditional large-scale buffer preparation models are becoming a constraint in modern biomanufacturing and how intensified approaches, such as optimized raw material handling, inline dilution (ILD), inline conditioning (ILC) and ready-to-use (RTU) solutions, can transform buffer preparation from a bottleneck into a strategic enabler. It outlines how manufacturers can rethink buffer preparation to improve efficiency, flexibility and risk management while positioning facilities for future growth.

THE GROWING STRAIN ON TRADITIONAL BUFFER PREPARATION

Historically, buffer preparation has been treated as a necessary central function that simply needs to perform reliably. For many years, this approach was sufficient. However, the pace and direction of biomanufacturing innovation have fundamentally changed the demands placed on buffer preparation.

Upstream productivity has increased dramatically over the past several decades, with titers rising from micrograms per liter to 8–10 g/L in modern processes. While downstream unit operations have also improved, they have not kept pace with upstream advances. This imbalance has resulted in increased

A J.T.Baker® DispenseRight™ powder delivery system bag in use.

chromatography cycles, longer downstream campaigns and a substantial rise in buffer consumption.

For facilities designed around earlier productivity assumptions, the consequences are significant. Plants originally built to support 2 g/L production may now be operating at 5 g/L or higher, requiring two to three times more buffer than initially planned. This increased demand extends far beyond tank capacity. It affects cleanroom footprint, labor allocation, scheduling complexity and overall campaign readiness. In many facilities, buffer preparation and staging occupy approximately one-third of available cleanroom space.

Compounding these challenges is the fact that buffer preparation often represents a final gate before downstream processing can begin. Even when harvested material is

ready, columns are packed and operators are scheduled, downstream operations cannot proceed unless buffers are released and available at the right time. As a result, buffer preparation has quietly become a significant constraint in commercial biomanufacturing.

AN INFLECTION POINT FOR LEGACY MODELS

Traditional made-in-house (MIH) buffer preparation models are increasingly misaligned with modern manufacturing needs. These models typically rely on receipt, quality release and manual dispensing of dry powders, followed by mixing, testing and staging in large tanks in a dedicated buffer suite or logistics area. While these approaches can be scaled by adding equipment and labor, they struggle to deliver the speed, flexibility and efficiency required in today's environment.

Manual powder dispense and kitting for accurate and precise buffer preparation.

Operational complexity continues to rise as facilities move toward multiproduct manufacturing and more frequent changeovers. Buffer preparation, which depends heavily on fixed infrastructure and manual processes, is inherently difficult to adapt to this level of variability.

The industry is beginning to recognize this mismatch. Much like the early adoption of single-use technologies, manufacturers are reassessing which activities truly need to be performed in house. Just as companies once insisted on performing all cleaning and sterilization internally but now routinely rely on gamma sterilized single-use systems, a similar shift is underway in how buffer preparation and management are viewed. Modernizing buffer preparation is increasingly seen not as a risk but as an opportunity to improve performance and resilience.

WHAT BUFFER PREPARATION INTENSIFICATION MEANS IN PRACTICE

At its core, intensifying buffer preparation is about achieving more with fewer resources, less space, less labor, less time and less risk while improving consistency and control. This can be accomplished through a combination of incremental improvements and more transformative process changes.

One pathway to intensification begins with rethinking traditional dry powder raw material workflows. Improvements in packaging, dispensing and quality release can significantly reduce manual handling and cycle times. Pre-weighed, direct-dispense formats help improve powder flowability and reduce handling errors, while greater reliance on supplier quality systems, consistent with principles outlined in ICH Q7, can shorten the time from material receipt to release.

Individually, these changes may appear incremental. Collectively, however, they can remove days or even weeks from the timeline between raw material receipt and utilization, improving manufacturing readiness and reducing scheduling risk. An additional benefit is the reduction in warehouse space required to accommodate large quantities of raw materials.

More transformative approaches involve shifting away from batch-based buffer preparation altogether. ILD uses concentrated buffer stocks (e.g., 10× or 30×) that are diluted with water for injection at the point of use to achieve final specifications. ILC goes a step further by combining multiple concentrates and adjusting pH inline, enabling on demand generation of a wide range of buffers at the desired composition and concentration.

Aliquoting buffers for facility distribution.

These approaches fundamentally change the role of buffer preparation within the facility. Rather than producing buffers days in advance and staging them in large tanks, buffer generation becomes dynamic and just in time. This shift dramatically reduces staging requirements, simplifies scheduling and enables a more agile manufacturing operation.

ADVANTAGES OF A HYBRID APPROACH

As biologics manufacturing becomes more complex, buffer preparation strategies must continue to align with operational efficiency, financial considerations and stringent regulatory requirements. Most production facilities benefit from a hybrid strategy that reflects the diversity of buffer types, volumes, risk profiles and manufacturing modalities that will be required to support diverse pipelines.

Large-scale biologics operations, particularly monoclonal antibody (mAb) manufacturing, often generate medium (10,000–50,000 L/year) to high (>50,000 L/year) buffer volume demands. Addressing these requirements through traditional, fully manual preparation approaches can overwhelm daily operations and strain labor, space and scheduling. High-volume, buffer-intensive unit operations such as chromatography and tangential flow filtration therefore tend to deliver the greatest return on investment when supported by ILD or ILC, which enable real-time or just-in-time buffer generation.

Masterflex® Inline Dilution Single-Use System for diluting concentrated buffer solutions with water to achieve the desired buffer concentration.

In continuous manufacturing programs, the importance of these intensified approaches is even more pronounced. Because downstream steps are sequentially dependent, real-time buffer availability is essential to maintain process continuity and avoiding disruptions.

Conversely, programs that require relatively small buffer volumes per batch (typically <10,000 L/year) or buffers with higher risk profiles, such as formulation buffers, may not justify additional capital investment beyond existing in-house infrastructure. In these cases, internally prepared buffers or externally sourced RTU solutions can remain the most practical option.

Therapeutic modality further influences strategy selection. Cell and gene therapy manufacturers often prioritize speed and flexibility and may lack extensive water-for-injection infrastructure, making RTU or concentrated solutions particularly attractive. Larger, multitherapeutic biologics facilities, by contrast, often favor inline systems that provide flexibility across multiple processes and products.

Relying exclusively on MIH preparation, or on any single buffer preparation strategy, can limit flexibility and amplify operational and quality risks. The most effective buffer preparation models are intentional and targeted, integrating MIH, RTU, ILD and ILC approaches to dynamically address true bottlenecks and adapt to fluctuating production demands rather than enforcing a one-size-fits-all solution.

STRATEGIC BENEFITS BEYOND EFFICIENCY

While efficiency improvements are a consistent outcome of intensified buffer preparation, the strategic advantages extend further. Risk reduction is one of the most significant benefits. Buffer preparation failures, such as incomplete dissolution, incorrect composition or out-of-spec parameters, are not uncommon and can lead to delays, rework and uncertainty.

Reducing manual handling also delivers meaningful workforce and ergonomic benefits. Handling large volumes of hygroscopic powders is physically demanding and poses safety risks. Minimizing these activities improves operator safety and allows skilled personnel to focus on higher value tasks.

From a broader strategic perspective, buffer preparation is not a differentiating capability for drug manufacturers. Shifting buffer preparation toward intensified approaches or specialized partners allows organizations to reduce non core infrastructure while improving reliability, scalability and operational focus.

PARTNERING FOR A STRATEGIC ADVANTAGE IN BUFFER PREPARATION

Across all approaches, partnership is central. Intensifying buffer preparation is not a transactional change; it is a strategic shift that affects quality, operations and facility design.

Avantor® partners with manufacturers to evaluate buffer preparation within the context of their overall manufacturing

strategy. This begins with identifying where constraints exist, whether related to space, labor, quality risk or scheduling, and aligning the appropriate mix of solutions.

For some organizations, improvements in dry raw material handling, such as direct-dispense solutions, deliver immediate and measurable benefits. For others, the adoption of concentrates, ILC or RTU buffers has the greatest impact. Avantor has invested in building a portfolio of standardized buffer concentrates with established stability, enabling customers to move quickly while maintaining flexibility for customized needs.

To further support identification of the best buffer preparation strategy, customers can leverage the Hybrid Buffer Strategy Assessment Tool,[1] a structured evaluation framework for determining the most suitable solution for operational goals.

THE FUTURE OF BUFFER PREPARATION

Over the next decade, intensified buffer preparation is expected to become standard practice. In existing facilities, ILC and ILD will be retrofitted to accommodate on-site expansions in place. As new facilities are designed, intensified methods will offer an opportunity to reduce required cleanroom space or reallocate that space toward increased therapeutic manufacturing capacity.

Greater reliance on supplier quality systems, increased digitization and shorter timelines from material receipt to readiness for use are also anticipated. As the industry continues to modernize, buffer preparation will receive greater attention as a foundational driver of operational and cost efficiency.

If biomanufacturing is to fully realize its potential, one of its most resource intensive operations can no longer be performed the same way it was decades ago. Rethinking buffer preparation represents a powerful opportunity to unlock efficiency, resilience and scalability across downstream manufacturing.

Masterflex® Inline Conditioning Single-Use System designed for formulating targeted buffer solutions from individual buffer stock components and water.

1. A strategic assessment tool for modernizing buffer preparation in biologics facilities.