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Alternative buffer management strategies to achieve downstream process improvements

There has been significant change across the biomanufacturing industry over the last couple of decades, as increased complexity of biologics and a growing focus on smaller patient populations have led to a greater need for cost control and process efficiency.

As productivity has improved as a result, so too have titers and other areas of process development. These advancements in science and technology offer exciting promise in drug development; however, they also create challenges for those still utilizing legacy processes and systems.

For example, while buffer preparation and management can be carried out in multiple ways, an established approach is to manufacture buffers in house with the use of water-for-Injection (WFI) to hydrate powders in stainless-steel or single-use tanks. Although this method is established and ideal for large volumes, it requires significant infrastructure, including the footprint needed for large tanks and for warehouse space for holding as well as weighing and dispensing areas for raw materials.

There are other approaches to this critical bioprocessing step, although each call on capabilities and expertise that may not exist at some companies and/or are difficult to obtain. Understanding not only the alternative buffer management strategies available but also what resources are needed to execute them can help ensure you have the tools necessary to remain competitive in today's growing bioprocessing industry.

Buffer Preparation And Management Strategies

Buffers play a significant role in biopharmaceutical manufacturing, typically representing the major component by volume used in biopharma downstream processing steps to help control pH levels and stabilize reactions during purification. If there are deviations in purity levels, it will result in the loss of product or a product not meeting specifications. With higher titers leading to a greater demand for buffers, industry experts and organizations have focused on eliminating bottlenecks in buffer preparation that constitute a significant proportion of a facility's footprint, labor requirements, and equipment cost.

As part of this effort, BioPhorum (previously known as the BioPhorum Operations Group, or BPOG), an organization dedicated to driving future technology needs through industry collaboration, released its biomanufacturing technology roadmap in 2017[1] which included a chapter about buffer preparation. Specifically, BioPhorum outlined an economic analysis of three strategies for buffer preparation: traditional buffer preparation, buffer concentrates, and buffer stock blending.[2]

Traditional buffer preparation requires large bioreactor tanks, which not only require a large footprint but are also a significant capital investment. As companies pursue the smaller footprint of a modern multiproduct manufacturing facility, a buffer preparation and management strategy that requires a large portion of a facility is not ideal. This approach also presents bottlenecks from an operations perspective, as conventional approaches are labor intensive and time consuming.

For example, one batch of buffer could take up to 20 hours to produce (varies based on the size of the buffer), and some purification operations can require 10-15 different buffers. That adds up to a significant amount of time for preparation before the actual purification even begins.

Every buffer produced must also be tested rigorously, requiring time and effort from a manufacturer's valuable quality control and assurance resources. Each bag of buffer must then be stored in a dedicated space or container, where the quality of the buffer has to be maintained until it is used.

One of the alternatives to traditional buffer preparation is through the use of multi-component **buffer concentrates.** These are multicomponent solutions, such as salts like phosphates and sodium chloride, in concentrated form that must then be diluted with water-for-injection (WFI) in an inline dilution system, allowing buffers to be created as they are needed. This process can be executed relatively quickly and without operator input.

These concentrated buffer forms do not require large tanks for storage like the traditional approach and have created opportunities for buffer outsourcing through the handling of smaller volumes, which reduces or eliminates the need for a

	Traditional Buffers	Buffer Stocks	Buffer Concentrates
Customer application	– Ready to use – Hooks directly into column	– Used in conjunction with buffer stock blending skid	– Used in conjunction with inline dilution skid
Drivers	– Immediate space constraints – New product development – Limited volume needed	– Buffer formulation flexibility and control – RM cost savings – higher concentrations take up less space and minimize shipping costs	– Simplimifed buffer preparation – Improved process control – Decreased facility footprint
Product Examples	– 20mM potassium phosphate, 150mM NaCl – 50mM acetate, 2% Benzyl alcohol	– 50% NOH – 5M NaCl	– 30% Triton-CG110 ph adjusted – 10X PBS

Opportunity

FIGURE 1: Buffer handling strategies using liquid raw materials & associated workflow improvements.

dedicated buffer preparation area within a facility. It also gives time back to internal staff, such as Quality Assurance, so they can focus on more value-added tasks which is similar to buffer concentrates but uses single-component solutions as opposed to multicomponent solutions used with buffer concentrates.

There is also the option to use **buffer stock blending,** which is similar to buffer concentrates, but uses single-component solutions (as opposed to multicomponent solutions used with buffer concentrates). This increases the complexity of the delivery skid but significantly increases the flexibility of the system. The economic analysis by BioPhorum found buffer stock blending as "the most economically viable due to significant operational benefits, particularly regarding labor demand."[2]

In a recent collaboration with The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), BioPhorum designed and developed a buffer stock blending system "to support the preparation of buffers in-line and on demand from concentrated single-component stock solutions."[3] Among many benefits, the technology has the potential to realize a full transition to a single-use facility of the future with savings up to $100 million for each new facility. A detailed evaluation of this system is also presented in a recent PDA publication.[4]

Key Aspects for consideration

For implementation of flexible buffers and buffer stocks in solution, a manufacturing facility would have to consider the following aspects of buffers in their process.

- How are the buffers connected to the unit operation? Aseptically, under laminar flow conditions etc.
- What are the critical quality specifications of the buffers? pH, conductivity, concentration etc.
- What are the typical sizes need for the buffers for optimum flexibility?
- Space and logistical needs to move the buffers between suites in the facility.
- EHS&S considerations including hazardous material, single-use waste disposal and handling requirements.
- Quality sampling and tailgate sampling to test buffers without direct bulk material contact.

How To Determine The Best Solution For Your Facility

Looking at the cost and complexity of in-house buffer preparation, the adoption of hydrated, premade liquid, buffers and buffer concentrates is a cost-, time-, and resource-saving alternative that should be considered for your downstream processing operations.

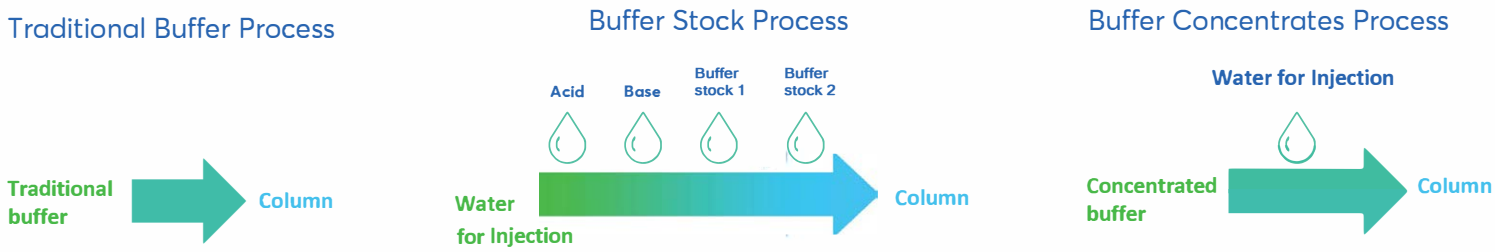


FIGURE 2: Buffer handling strategies using liquid raw materials process visual

Depending on the size of your operations and facility, different buffer management can be applied, as a stand-alone solution or in combination, in order to achieve workflow improvements:

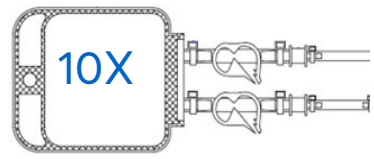
- Powder hydration in fixed stainless-steel tanks or single-use buffer prep reactors
- Multicomponent buffer concentrates with in-line dilution
- Single component stocks with buffer stock blending
- Ready to use cGMP 1X buffers

BioPhorum's chapter in the technology roadmap on the economic analysis of buffers is one of many valuable tools you can use to determine which approach is the best fit for your facility. You should also complete an evaluation of other factors, such as scale, batches of drug produced per year, raw materials used and other site attributes.

Avantor recognizes the challenges of identifying the right buffer solution for your facility and operations and is equipped with a wide range of capabilities to help you achieve the industry-wide goal of improving the efficiency of your bioprocessing operations. Our team of experts can help optimize your buffer preparation process and solution and provide various options based on the specific needs of your product and process, including customized solutions using components from a multitude of vendors. Our expertise in single-use technology, chemical properties, and equipment allows us to take a holistic approach to customer support.

For example, if a customer wants to move away from solid hydration into pre-made buffers, Avantor can provide ready-made buffers at 1x concentrations, which is important when time is critical. For a customer running their facility at full speed but wants to reduce costs and improve throughput, Avantor has the capability to provide buffer concentrates and buffer stocks as well as offer advanced equipment options, such as in-line dilution (ILD) systems.

And because Avantor is a manufacturer of many of the solid components used in buffers, our team can leverage these resources to make and deliver pre-made liquid solutions as



1. Avantor buffer concentrate in single-use bag

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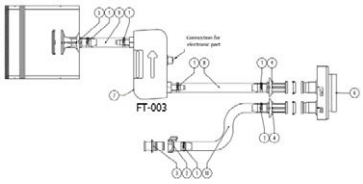

2. Avantor single-use fluid pathways (inline pH, conductivity, static mixer, mixing holding vessel)

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3. System: on-demand ready-for-use solution

FIGURE 3: Buffer prep strategy using in-line dilution (ILD), single use systems & buffer concentrates delivered as raw materials.

needed, in single-use or multi-use systems. Quality concerns common with outsourcing are alleviated by not only our dedication to providing customers with the best product possible but also with remote access to raw material and finished good data about our products before they even ship out of our facility.

With so many critical bioprocessing steps overshadowing the importance of buffer preparation and management, considerations about how to produce buffers economically at a large scale are often not made early enough. As scale goes up, the demand for buffers increases as well, putting a considerable strain on site operations and quality teams. Outsourcing to an expert like Avantor can reduce this burden as well as give you access to in-house expertise that will help guide you toward the most effective and efficient buffer management strategy.

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