BioProcess International eBooks

BUFFERS

NAVIGATING NEW DEMANDS ON DOWNSTREAM RAW MATERIALS

Robert Shaw, Angela Linderholm, Jennifer Bratt, and Steven Chamow

March 2021

Buffers

Navigating New Demands on Downstream Raw Materials

by Robert Shaw, Angela Linderholm, Jennifer Bratt, and Steven Chamow

Bioreactor titers for monoclonal antibody (MAb) processes have increased significantly since the dawn of the biopharmaceutical industry, yet such gains have instigated bottlenecks for critical, high-volume raw materials used in downstream processing, including buffer solutions. This BPI eBook explores what factors prompted current buffer bottlenecks and what options drug sponsors might consider to mitigate them.

Photo courtesy of Bristol Meyer Squibb.

THIS IS PROCESS OPTIMIZATION

PROPOR membrane filters

Validated bacterial retention
Excellent chemical compatibility
High flux rates

Parker's PROPOR filter range features a microbially retentive polyethersulphone membrane for fast, reliable and cost-effective filtration. The range has shown to speed up filtration time by up to 40% when filtering a wide range of buffers, including those which are more difficult to filter. Find out more at:
discover.parker.com/BufferFiltration

Parker

ENGINEERING YOUR SUCCESS.

Choices and Considerations for Battling Buffer Bottlenecks

Robert Shaw

Back to Contents

The biopharmaceutical industry has not needed to worry about the lowly buffer until recently. Compared with solutions such as cell-culture media and other complex bioprocess liquids, why would such a (seemingly) simple product command such attention? But improvements in cell-line development technologies, media-formulation technologies, and bioreactor feeding regimens and growth conditions all have contributed to increases in bioreactor titers that can be produced in bioreactors. Such advances have contributed to a "buffer bottleneck" downstream. Companies now find their hallways and workspaces crowded with buffer tanks and containers waiting to be used in downstream process steps, with tangential-flow filtration (TFF) and chromatography being the two most volume intensive. Because downstream purification is required for most, if not all, biopharmaceutical products, buffers and their preparation are topics that concern nearly every such company during scale-up, but those topics rarely receive direct attention. What are issues regarding buffers that the biopharmaceutical industry currently faces? How did those concerns arise, and what factors must be considered to address them? Below are answers to those and other critical buffer queries.

Bottleneck Background

Back to Contents

How did the buffer bottleneck form? Modern biologics companies sometimes report expression titers of 8–15 g/L for monoclonal antibodies (MAbs) from Chinese hamster ovary (CHO) cells (**1, 2**). Such quantities differ dramatically from CHO titers achieved in 1990–2010, when <1.5 g/L was considered typical (**3**). Titers average 3–8 g/L in today's industry (**4**), but a general increase in raw titer since the 1990s has contributed significantly to the buffer bottleneck. Other factors might have compounded that bottleneck, but the sheer amount of protein being produced at large scales has been a major contributor.

Does the bottleneck pertain to certain manufacturers or facility designs? Another key trend in the biopharmaceutical industry is a transition to multiuse facilities. The need to maximize capacity has spurred on production of multiple products

TEKNOVA
science matters

WE MAKE SOLUTIONS.

Consider us your potion masters. We've made ourselves the most agile, supportive, and responsive provider of high-quality bioprocessing media, buffers, and solutions so we can equip you with exactly the right solution at exactly the right time.

- Have a unique need? We're experts in custom formulation, dispense, and QC, with flexibility to fulfill complex manufacturing requirements.
- Have an impossible deadline? We offer unrivaled speed, with exceptionally fast delivery times for custom RUO and GMP products.
- Have stringent requirements? We're devoted to quality, from raw materials to fill-finish—with all manufacturing done in GMP-certified facilities.

When you're making magic, it's helpful to have an ace up your sleeve. Let us be the secret ingredient in your success.

E-mail: info@teknova.com or visit www.teknova.com to learn more

in the same facility, especially in the contract manufacturing sector. Regulatory acceptance of product changeover has enabled that trend. However, multiproduct operations still require relatively long downstream processing times. Including what is needed for cleaning/storage and rejuvenation/reequilibration, the volume of buffers needed to purify a product can increase considerably depending on bioreactor volume and titer. A recent report identified that the space needed for media and buffer chemical storage and preparation can account for ≥20% of space costs for large facilities (**5**). Therefore, both drug sponsors and contract manufacturers are facing a similar challenge: how to maximize production capacity and the number of products produced while ensuring that there is enough capacity to purify material downstream.

Including cleaning and rejuvenation/ reequilibration, the volume of buffers needed to purify a product can **INCREASE** considerably depending on bioreactor volume and titer. A recent report identified that the space needed for media and buffer chemical storage and preparation can account for ≥20% of space costs for large facilities.

Build-or-Buy Conundrum

Can't companies just outsource preparation of buffers? Traditionally, buffers have been prepared in house, then used immediately or stored in tanks for short periods. With production volumes increasing, companies now face the question of whether to build or buy buffer capacity. Should they invest capital and resources to produce buffers or spend money on high-value manufacture of their therapies? If outsourcing is an option, should all buffers be produced elsewhere? What logistical considerations arise when outsourcing buffers?

Not all buffers are equal. Buffers that can be outsourced (also known as *process solutions*) fall into at least three categories: cleaning/storage buffers, rejuvenation/reequilibration solutions, and running/elution buffers. More types certainly could be evaluated; however, considering even those three kinds reveals major differences in their chemical complexity, risk, quality, and cost (Table 1).

Table 1: Comparison of buffers by type, chemical complexity, hazardousness, precision (range of specification), and cost

Buffer Type	Complexity	Hazardousness	Precision	Cost
Cleaning/storage	Low	Potential for hazard	Low	Low
Rejuvenation/reequilibration	Low to medium	Low risk	Medium	Low
Running/elution	High	No risk	High	High

Cleaning/storage solutions such as sodium hydroxide and alcohol solutions may be simple in chemical composition, with quality requirements having relatively broad ranges. Other high-concentration solutions such as chaotropic agents also are simple in concept. They sometimes are referred to as "nuisance buffers" because they can require specialized equipment (NaOH, guanidine HCl), facility licenses (alcohols), handling, and containers. The requirement for scale-up of manufacture, therefore, can be very costly, and the need to outsource may seem attractive.

Supply Chain Management: Because of the proximity of many buffers to a final therapeutic product, supply-chain management is key. Impacts can be felt in logistics, timelines, and quality. Individual raw-material suppliers should be on a routine audit schedule and carefully managed. Rigorous qualification of raw

thermoscientific

Simplify. Streamline. Accelerate.

Confidently manage process liquid and buffer preparation, as well as cGMP chemical supply chain workflows when you collaborate with us.

Learn more at **thermofisher.com/innovateproductivity**

ThermoFisher SCIENTIFIC

materials as well as incoming inspections for each material are required. In addition, good relationships and supply agreements with key suppliers can be developed to cover the security of supply concerns. It should be noted that during process development and at clinical scale, the grade of chemicals used might not be as important an issue as it would be for commercial distribution (see section below on chemical grades).

What are key considerations for buffer specifications? Buffers are produced according to standardized chemical measurements, including specific ranges for pH, osmolarity, and conductivity. The "nuisance buffers" noted above typically have broad ranges of acceptance for use; however, operating specifications are much tighter for the other two buffer categories.

One problem that a sponsor might encounter when first outsourcing buffer production is that a contractor's specification ranges are wider than required. That can be especially troublesome for small-volume production. Wide ranges of specification also beget storage concerns. Vendor-produced buffers are manufactured, tested, released, shipped, received, and sometimes dispensed into other containers before application. That process can take months longer than a sponsor planned. Moreover, outsourced buffers almost always are shipped in bioprocess containers rather than the kinds of hard-plastic, glass, or stainless-steel tanks that are used for in-house manufacturing. Therefore, process sponsors must determine how precise their specification ranges need to be and whether an outsourced solution can meet those criteria consistently.

A specification range needs to be met throughout a buffer's entire shelf life. Many companies do not have or think that they need a shelf-life determination for their buffers, so they might not have validated all conditions required for evaluating buffer stability. In an outsourced situation, all such criteria must be validated according to current good manufacturing practice (CGMP) standards.

A specification range needs to be met throughout a buffer's **ENTIRE** shelf life.

Navigating Outsourcing Challenges

Back to Contents

What questions should drug companies ask when outsourcing buffer production? Buffers are generally some of the easier solutions to make. A buffer is defined as a weak acid/alkali and its salt in solution. The effective pH of the buffer species is combined with other components, typically sodium chloride, to facilitate purification and stability of protein products. But for such a simple solution, a number of questions should be asked regarding its preparation. As mentioned previously, pH, conductivity, and osmolarity are key specifications for many buffers.

Batch size: If a single batch of buffer is preferred, what is the largest batch size (single tank) that a vendor can produce? Can multiple batches be combined into a single lot?

Specification Tolerance: What are realistic ranges for buffer pH, conductivity, and or osmolarity? For example, a pH range of 7.0 ± 0.05 might not be consistently achievable at large scales.

Specification Adjustment: What methods does a vendor use to adjust pH? For example, addition of an acid or base to meet a specified pH can change other parameters (e.g., conductivity) depending on how much adjustment is needed.

Verification of Specification: Temperature, calibration standards, type of equipment, and so on all can lead to small discrepancies between measurements. As an example, the water that is used for buffer preparation typically comes from a central water-for-injection (WFI) line, and that generally is heated. If a buffer is made using hot WFI, which promotes dissolution, are pH and conductivity monitoring performed with in situ probes that are temperature compensated? Is the water temperature always the same? Are samples taken, cooled to room temperature, and then verified to be in specification before filtration and filling? These factors are all part of process validation. Verification of process validation should address such considerations.

Mixing Validation: What mixing validation has been performed in the production vessel? That question is especially important if the vessel is only partly filled. How are the chemicals added to the mixing vessel? Validation work should include both chemical dissolution requirements, particularly of raw materials that may come in "chunks," and pH equilibration requirements.

Grade of Chemicals: Different grades of chemicals can be used for buffer manufacture. American Chemical Society (ACS) and United States Pharmacopeia (USP) standards are only two of several grades. Of greater consideration is whether buffer chemicals need to meet multicompendial/pharmacopoeial grades for products destined to be licensed by different regulatory authorities. It is important for end users to review what chemicals are used as well as their suppliers and grades to understand similarities and differences between internal and outsourced formulations.

Filling: How many samples are taken during filling and at what points in the process? Is a fill volume specified for each vessel or bioprocess container, and what is the tolerance for fill/head space for each fill unit?

Filtration: What filtration does a buffer require? Are redundant 0.2-µm sterilizing filters needed (e.g., to meet regulatory requirements), is prefiltration necessary, and is integrity testing performed/required before and after filtration? Does membrane chemistry (e.g., nylon, polyvinylidene fluoride (PVDF), or polyethersulfone) influence your choice of filter? Some filter-membrane materials adsorb buffer components to their surfaces. Some membranes exhibit high stability at high pH. A filter compatibility test might be required to answer such questions.

Tail-Gate Samples: What are *tail-gate samples*? Typically, samples of a specified volume (e.g., 500 mL to 1 L) are filled separately so that buffers do not need to be sampled from filled containers. A tail-gate sample is used by a quality control (QC) team to verify that a buffer is meeting specifications and serves as a sample for an incoming raw-material identity test.

A well-conceived strategy for both scale-up and outsourcing of buffers will help to address some bottleneck issues **PROACTIVELY**.

Expiration: Has a buffer's shelf life been validated for container (product contact surface) and storage temperatures? When using an outsourced product, a sponsor company must consider how much time will be needed for

- manufacturing
- testing and release
- shipment
- receipt and storage at a receiving facility.

Shipping Studies: Have shipping studies been performed? (Please note that some buffers tend to precipitate upon agitation/vibration.) What are the temperature limits for exposure, especially during shipping? Remember that buffers might not be shipped in temperature-controlled conditions and that freezing or very high temperatures can occur (e.g., while sitting on a loading dock waiting to be processed). Temperature-controlled shipping is an option, and for buffers used at the end of a downstream process, it might be a critical requirement.

Could concentrates help solve buffer bottlenecks? Certain buffers (e.g., cleaning solutions) can be made easily at 5× or 10× concentrations, then diluted for use in batch or in-line mode. Other buffers cannot be concentrated because of their salt compositions and solubilities. Concentrates certainly could decrease how many containers a company needs to ship as well as the volumes of those shipments. Yet concentrates are not an ideal choice for all buffers, and batch or in-line dilution adds another step in the manufacturing process that a sponsor organization will need to validate.

Proactive Buffer Strategies

Back to Contents

Buffers typically are simple solutions, and they are used in nearly every biopharmaceutical downstream process. Increasing titers in bioreactors and the growing prevalence of multiuse, multiproduct facilities have enabled production of large quantities of MAbs and other therapeutic proteins, all of which require purification. But downstream processes can be limited by how much buffer they require — and by how much is ready for use. Outsourcing is an option, although it begets several different questions that do not need to be addressed when developing an in-house supply. Concentrates are an option for some buffers and solutions, but they cannot address totally the buffer bottleneck. A well-conceived strategy for both scale-up and outsourcing of buffers will help to address some bottleneck issues proactively.

Acknowledgment

Back to Contents

The author gratefully acknowledges the input, expertise, and critical review provided by Andra Kunzler, director of cell culture media research, and development at Cytiva.

References

1 Huang YM, et al. Maximizing Productivity of CHO Cell-Based Fed-Batch Culture Using Chemically Defined Media Conditions and Typical Manufacturing

Equipment. *Biotechnol. Prog.* 26(5) 2010: 1400–1410; https://doi.org/10.1002/btpr.436.

2 Takagi Y, et al. The Enhancement of Antibody Concentration and Achievement of High Cell Density CHO Cell Cultivation By Adding Nucleoside. *Cytotechnol.* 69(3) 2017: 511–521; https://doi.org/10.1007/s10616-017-0066-7.

3 Rader RA, Langer ES. Thirty Years of Upstream Productivity Improvements. *BioProcess Int.* 12(1–2) 2015: 10–14; https://bioprocessintl.com/upstream-processing/expression-platforms/30-years-upstream-productivity-improvements.

4 Shukla AA, et al. Evolving Trends in MAb Production Processes. *Bioeng. Transl. Med.* 2(1) 2017: 58–69; https://doi.org/10.1002/btm2.10061.

5 Langer E, Rader R. Powders and Bulk Liquids: Economics of Culture Media and Buffer Preparation Are Changing. *BioProcess Int.* 12(3) 2014: 10–16; https://bioprocessintl.com/upstream-processing/biochemicals-raw-materials/powders-and-bulk-liquids-350510.

About the Author

Robert Shaw, *a member of BPI's Editorial Advisory Board, is executive director of the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB), 100 Bureau Drive, MS 8543, Building 224/A105, Gaithersburg, MD 20899; 1-301-975-6822.*

Back to Contents

Q&A on Issues in Buffer Supply

Angela Linderholm, Jennifer Bratt, and Steven Chamow, with S. Anne Montgomery

With the bioindustry's current focus on COVID-19 vaccines, antivirals, and treatments comes concerns about meeting demands for bioprocessing materials and consumables. A number of recent articles point to potential supply-chain shortages of essential buffer components (**1–8**). Biopharmaceutical supply-chain management is a complex task in the best of times, but suppliers of buffer components now are keenly aware of threats to delivery of such critical, high-volume materials.

For insights into how some companies are trying to supply sustainable levels of raw materials, we asked two industry experts to answer a few questions based on their recent experiences. Laura Kaepplinger is a global business segment lead for Angus Chemical Company (a manufacturer of buffer chemicals), and Adi Kleiman is senior director of supply-chain sourcing and procurement for Emergent Biosolutions (a large-scale user of buffer chemicals).

Given the differences in environmental regulations between countries that can affect the availability of raw materials, what is the best practice to ensure a sustainable relationship between consumers and suppliers?

Kaepplinger: As we have experienced in the pharmaceutical industry, environmental regulations and blue-sky initiatives can cause temporary or permanent plant shutdowns that can lead to short supply or delayed availability of critical raw materials. The best way to mitigate this risk is to work with raw-material manufacturers that produce their products using processes that are fully backward-integrated and have multiple sources of qualified raw materials, reinforcing supply-chain security. Having more than one plant producing the same end product, coupled with a strong inventory position of finished goods as part of a strong business continuity plan, provides consumers an added layer of security.

Alternative energy sources are being explored to lessen disruption to the environment. How are chemical suppliers expanding their capabilities to use more "green" or recycled materials in large-scale manufacturing?

Kaepplinger: Beyond using energy management systems and renewable power, chemical companies are using sustainable raw materials to develop greener products. Certified sustainable raw materials are renewable and can be traced to the point of origin. International standards have been developed to guide sourcing and manufacturing. Recycled and biobased raw materials are

The best way to mitigate this risk is to work with raw-material manufacturers that produce their products using processes that are fully backward-integrated and have **MULTIPLE SOURCES** of qualified raw materials, reinforcing supply-chain security.
— L. Kaepplinger (Angus Chemical Company)

Back to Contents

displacing petroleum-sourced raw materials in many applications. Product innovation for consumer and industrial markets has led to greener approaches in manufacturing for life-science applications.

What are some of the causes of these material shortages?

Kleiman: Current shortages experienced due to the COVID-19 pandemic are being caused by

- increased global demand due to the need to produce SARS-CoV-2 vaccines and therapeutics
- pandemic-related shortages in poly(*p*-phenylene vinylene) (PPV)
- import challenges due to port closures
- reduced or unpredictable human resources due to COVID positivity, presumption, or exposure
- reduction in the number of employees on site due to COVID-regulation reduced capacity
- redirection of supply to local needs and with reduction of some importing (mainly from Asia).

What financial and timeline implications have you faced due to limited or lack of availability of materials?

Kleiman: Financial and timeline implications have included the need to

- maintain a much higher inventory than usual. We've increased our financial risk by buying future potential needs in advance (already securing 2022 and 2023 even) and making investments in more storage area to accommodate the increased inventory (safety stock).
- increase our prices significantly because of shortages
- purchase expensive PPV at risk before qualifying it as a backup source
- increase resources needed to monitor shipments, resolve challenges, find alternatives, and manage suppliers — all of which add significant increases in time.

Have you applied mitigation or contingency planning based on your experiences?

Kleiman: Yes, several mitigation plans are in place, including strategies for mapping products and continually evaluating their risk levels; increasing inventory; identifying and qualifying alternative products and redundant suppliers; placing orders to cover the next several years; sharing material between sites; and working closely with suppliers to understand, anticipate, and mitigate gaps.

Risk management is an important part of planning and scheduling for production when experiencing imminent or potential raw-material shortages. To date, the Emergent team has minimized production schedule impacts by designing and finding creative solutions, such as taking on risk and costs as a contract development and manufacturing organization (CDMO) to start production without all materials on hand, with the expectation that relevant components will be received just in time. Where we

> Where we have experienced raw-material shortages, it has required a significant effort from sourcing and procurement organizations to **MINIMIZE** the production impact.
>
> — A. Kleiman

BACK TO CONTENTS

BACK TO CONTENTS

have experienced raw-material shortages, it has required a significant effort from sourcing and procurement organizations to minimize the production impact. In some cases, alternative options were identified and required a quicker qualification process than normal, which increased the amount of effort from functional stakeholders (e.g., quality assurance, quality control, manufacturing systems and technology, and so on). By deploying these different strategies, the manufacturing demand continues to be met, and any delays have been limited to a few days.

References

Back to Contents

1 *An Economic Evaluation of Buffer Preparation Philosophies for the Biopharmaceutical Industry*. BioPhorum Operations Group: London, UK, December 2019.

2 *NIIMBL–BioPhorum Buffer Stock Blending System: A More Advanced Concept for Buffer Manufacturing*. BioPhorum Operations Group: London, UK, December 2019.

3 Anwar R. Buffers: Pharmaceuticals. *Slideshare* 5 January 2018; https://www.slideshare.net/Soft-Learners/bufferspharmaceutics.

4 *Coronavirus Outbreak Underscores the Weakness of Traditional Supply Chain Strategy*. Kearney: Chicago, IL, 2021; https://www.kearney.com/covid-19/coronavirus-outbreak-underscores-the-weakness-of-traditional-supply-chain-strategy.

5 Deorkar N. Enhancing Cleanroom QC and Efficiency Through Direct Dispense Technology. *CleanroomTechnology.com* 11 October 2017; https://www.cleanroomtechnology.com/news/article_page/Enhancing_cleanroom_QC_and_efficiency_through_direct_dispense_technology/134757.

6 Hesselink W, et al. Implementation of Single-Use Powder Delivery Systems in Continuous Bio-Manufacturing Processes: A Case Study. *PharmaiQ.com*; https://www.pharma-iq.com/events-disposablebiomanufacturing/downloads/implementation-of-single-use-powder-delivery-systems-in-continuous-biopharmaceutical-manufacturing-processes-a-case-study-from-avantor.

7 ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. *US Fed. Reg.* 66(186) 2001: 49028–49029; https://database.ich.org/sites/default/files/Q7%20Guideline.pdf.

8 Pillar M. The Real Threat to Biopharma Supply Chains: Bioprocessing Materials. *BioProcess Online* 12 May 2020; https://www.bioprocessonline.com/doc/the-real-threat-to-biologics-supply-chains-bioprocessing-materials-0001.

About the Authors

Back to Contents

Angela Linderholm, *PhD, is associate project scientist at the University of Californa–Davis School of Medicine, Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine.* ***Jennifer Bratt,*** *PhD, is project manager, and* ***Steven Chamow,*** *PhD, is senior vice president of CMC development at Alira Health, Framingham, MA.* ***S. Anne Montgomery*** *is cofounder and editor in chief of* BioProcess International, *anne.montgomery@informa.com.*