WHITE PAPER

Maximizing scale up:
Critical considerations for buffer preparation

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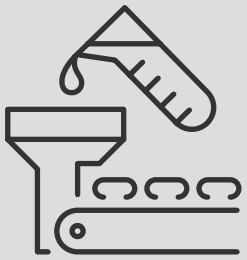
Buffers in Biomanufacturing

The complexity and criticality of buffer preparation have grown of late for several reasons. Advances in product offerings, bioprocessing materials, process technologies and facility design have increased the number of factors to be considered. For example, biopharmaceuticals have evolved from classical protein biologicals and vaccines to a diverse number of products and therapeutics such as mRNA vaccines and CGT therapies[1]. Downstream consequences of increased upstream volumetric productivity have also contributed to a demand for robust and economical buffer preparation.

The buffers and process liquids employed provide physicochemical functions in, e.g., pH maintenance and chromatography, and such biological functions as cofactors for enzymatic activity and nutrients for cell and tissue maintenance. They are used in pharmaceutical manufacturing from product development to fill-finish, can contain such special components as organic solvents, and can have such special formulation demands as sterility.

Buffers are applied throughout the processing train, including biological sample reception, upstream and downstream processing, resins storage, and as excipients in drug product. This determines such considerations as quality level, risks regarding safety and performance, and regulatory compliance. For example, buffers used in the manufacturing of a biotech product, upstream pharmaceutical operations, or as an excipient in a drug product, will require distinct assessments and controls.

Essential Requirements to Consider
Volumes required
Fluids and solids identity
Volumes, pH, and sterility
Production temperature shifts
Storage conditions and shelf life
In-process monitoring and control
QA and final QC testing and release
Difficulty and expense in preparation
Greenness of both process and product



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The precise final formulation of standard buffers used in even common processes vary because of optimization that accommodates rapidly evolving process understanding, intensification, and materials– as well as distinctions in production modes, and impurity profiles. It's not uncommon for process engineers to modify and performance-test even such standard formulations as 50mM phosphate, pH 7.4 for Protein A chromatography and 50mM sodium acetate, 250mM NaCl, pH 5.0 for cation exchange chromatography in order to optimize them for a particular product or process.

Basic Steps in a Buffer Development
Buffer product and process design
Materials and testing specifications
Technical transfer to operations
Support of scaled-up workflow
Process and testing validation
At-scale production activities
Final QC testing and release
Controlled storage/dispense

A consideration in buffer preparation involves the quality and regulatory requirements of GMP manufacturing. In GMP facilities every component of a buffer formulation, including the water, will have a stipulated specification to meet. The facility, process, and intermediate products, including buffers, must be maintained in accordance with general ISO and ICH guidelines and assessment by approved QA/QC procedures. This includes materials procurement, testing, and storage; WFI production and storage; materials weighing, dispensing, and hydration workflows; and final formulation acceptance, handling, and storage.

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Supply Strategies

Buffer preparation decisions to be made include outsourced (contracted) vs in-house production. If in-house, then the mode of buffer preparation must be determined[2].

Scale-up of single- or multi-component buffer solution preparation can determine a significant part of a manufacturer's facility footprint, labor, equipment, and operating costs. Careful consideration of many factors is important to insure sufficient buffer of acceptable quality, at the right time, and with defensible capital and operational expenditure. An example of this need is 20mM histidine, 20mM acetic acid, and 50g/L sucrose, pH 6 for final mAb diafiltration. A few essential means of buffer preparation exist and have been modelled to assess the economic impact on a facility's costs, design, and operation[2].

An important decision in buffer preparation by the manufacturer is whether to optimize and produce the needed buffers in house, or to contract-out for their design and/or preparation. Unfortunately, there is no universal answer to this question, as it follows such manufacturing criteria as the current process understanding, existing production and storage capabilities, and QA/QC support. Other considerations include projected demand, financial model, risk tolerance, and the need for buffers in remote manufacturing locations. For example, premiere contractors highlight their worldwide locations, eliminating a manufacturer's need to replicate buffer preparation facilities or ship long distances.

Choosing the Supply Approach

In recent years, determination of best in-house production approaches has been revealed by software to produce computer modelling, as well as vendors providing such modelling as a service[3]. These greatly increase the ease, economy, and accuracy of such calculations. User- or vendor-configurable process modelling software, with cost of goods being one of the key outputs, is now widely used in biomanufacturing. They can model the cost, value, and impact of the many options in the production mode and final process design.

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In-house or Contracted

The decision to design, tech transfer, and produce buffers in house or outsource for those activities follows consideration of:

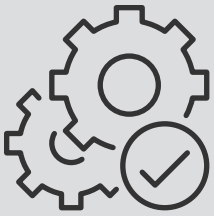
- Formulation, process design, and material specification
- Volumes, timing, production, and testing requirements
- Manufacturer's existing suites, equipment, and personnel
- Manufacturer's existing analytical, QA, and QC capability
- Anticipated evolution in the buffer types and volumes
- Number of geographical locations where buffers are used
- Manufacture's financial distributions, timing, and totals

Production consistency is supported by preparing buffers in batch sizes sufficient to supply the entire bioproduction workflow. However, this can increase the suite, equipment, and even materials handling needs.

Beyond nominal materials and facility scheduling, manufacturers must consider the potential for deviations and failures, including mis-formulation and contamination which can have both financial and manufacturing scheduling implications.

The timing and scheduling of production, both currently and as anticipated in the future, are important, as they can impose a conflict for use of common suites, equipment, or personnel. One advantage here in contracting out is a premiere vendor's capability to produce an unforeseen lot that would otherwise conflict with an in-house production schedule or lot size capability. So, traditional in-house buffer supply methods can not only impose financial and operational stress, but processing bottlenecks as well.

The results from process modelling will provide values for such alternatives as the manufacturer's total budget and timing of capital costs, available production suites, equipment, required service, materials procurement and (environmentally controlled) storage, trained personnel, appropriate quality systems capacity, and the footprint and cost of appropriate buffer storage. When assessing the availability of appropriate personnel and facilities – any environmental, health, and safety (EH&S) concerns in the use of any required caustics and/or flammable organics must be considered. Finally, there is the consideration of disposal of production waste as environmentally sustainable waste handling has become a major factor in large-scale manufacturing. The optimal buffer management approach is dependent upon the factors outlined above– and will vary by buffer product, process, and manufacturer.



The **timing and scheduling of production,** both currently and as anticipated in the future, **are important,** as they can impose a conflict for use of common suites, equipment, or personnel.

Should in-house preparation of large-scale lots be selected, the next decision includes choosing between 1) traditional batch, 2) dilution of multi-component concentrates, and 3) blending of single-component ultra-concentrates.

In-house Preparation

There are three basic ways to approach the preparation of single- or multi-component buffer solutions, in either fixed vessels or SU equipment, ready for use at the required concentration[2].

1. Traditional batch approach

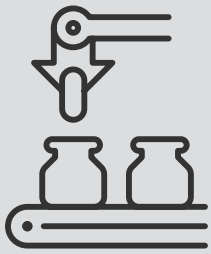
The traditional approach to single/multi-component buffer preparation is to produce an individual batch by dispensing a prescribed volume of fluids by weight, mass flow, or volume measurement– followed by sequential dissolution of the powders while mixing[4]. In-line or at-line testing is used to ensure that aspects of the operation proceed within defined values, as well as that the final formulation meets the buffer product specifications. This results in a 1x concentration of a buffer ready for use or validated storage.

2. Concentrates and in-line dilution

This approach begins with preparation of stock concentrates of multi-component solutions stored at an appropriate temperature as components of the final buffer. The buffer product is produced through automated dilution and monitoring in dilution skids, at the time of need. This generally requires a dedicated concentrate preparation for each buffer, although distinct buffers having the same ratio of components may be produced with the same concentrate. The main advantages here are the reduction in storage space for buffer concentrates and their commercially availability. Dispensing and material handling efforts are not multiplied, as only WFI is added at the time of final buffer preparation. The maximum concentrations possible are determined by such factors as the solubility of the individual components and the number of common counter-ions involved.

3. Ultra-concentrated stock blending

Here, ultra-concentrated, single-component liquid stock solutions are components of the final buffer. These are produced through automated mixing, dilution, and conditioning with WFI in automated mixing skids. The final buffer may be prepared just-in-time and supplied on-demand to the process without prior storage or stored as any pre-prepared buffer. Buffer parameters, including pH and the concentration and ratio of components, are entirely tuneable resulting in many final buffer-type potentials. There is a very broad, but ultimately limited scope of



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buffers to be prepared this way, depending only upon the availability of concentrated component stock solutions. Here too, the main advantages are the commercial availability of single-component concentrates, and the reduction in their required storage space.

Generally, capital costs between these approaches are higher for 2 and 3, because of the mixing skids required. However, net economy can be better in these approaches, based upon consideration of the other parameters listed in *In-house* or *Contracted* above.

Contracted Preparation

Buffer production processes at biomanufacturing scale are labor intensive, take time, require validated materials, a highly trained staff and fully equipped facility space[5]. Working with skilled contracted producers can improve efficiency and consistency while providing quality and economy in a timely manner[6]. Contracting can also alleviate the in-house shifting of resources away from other biomanufacturing needs. In most cases, the significant billed cost per liter from contracted production is more than offset by savings in capital, labor, single-use consumables, and other production costs.

Burdens Alleviated by Contracted Buffer Preparation
Material procurement / supply chain
Process design and technical transfer
Buffers preparation and storage suites
Tanks and automated dilution mixing skids
Quality systems for both raw and final products
Materials dispensing and WFI preparation needs
Shifting of in-house resources from other demands
Operating expenses for preparing intermediate solutions
Overhead costs for personnel not required for other processes

While there are several advantages to outsourcing buffer and liquids preparation, choosing the right supplier is key to your outsourcing success. Many suppliers of process development and product formulation exist, but its best to secure one with the experience to ensure, e.g., that the buffers are properly formulated for scale-up before transfer is initiated. A vendor providing a clear and comprehensive product brief will ensure precision in such details as materials sourcing, product specifications, processing operations, and particular filtration materials (e.g., animal origin free).

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Commercialized Buffer Products
Dry raw materials
• Individual dry components in specified packing sizes
• Precise, trusted-weight services with digitized labeling
• Availability in choice of standard packaging buckets/bags
• Custom packaging connecting directly to a hydration process
Final hydrated buffers
• Hydrated single- or multi-component, filtered and tested formulations
• Ready-to-use concentrated stock solutions supporting in-line dilution
• Availability in a variety of containers, sizes, and dispensing formats
• Production, testing, and shipment from multiple sites worldwide

Experienced suppliers also aid in the development of such logistics as staging of materials, manufacturing, and product hold– and delivery in cadence for usage in production. They can have the knowledge to assist in testing for quality, stability, and release; as well as data management and generating certificates of analysis. By leveraging premier custom production services, a manufacturer can receive approved buffer produced in lot sizes larger than can be handled within their facility.

Beyond the benefits mentioned above, contracting for design and production services can often be less expensive than adding facility capabilities, personnel, and footprint. The right outsourced producer can help mitigate unnecessary risk and provide ready-to-hydrate dry powders or liquids in standard or customized packaging. Another feature is the availability of durable bottom- or top-emptying secondary packaging. A knowledgeable and compliant vendor can help reduce formulation and specification errors, performance audit challenges, and unforeseen additional costs.

Advantages of Outsourcing Production
Reduction of facility, quality, and personnel burden
Decrease in raw material, safety stock, and storage demands
Expert advice in production efficiency and environmental sustainability
Delegation of buffer material sourcing and secondary supplier maintenance
Promotes high OTIF by delegating buffer materials and product to specialists
Reduction of personnel and facility demands for dangerous chemical handling
Alleviate environmental, health, and safety (EH&S) and mis-formulation concerns
Can reduce the aggregate cost of ownership while improving efficiencies and quality
Overhead costs for personnel not required for other processes

A knowledgeable and compliant vendor can help reduce formulation and specification errors, performance audit challenges, and unforeseen additional costs.

ECONOMIC CASE STUDY

Analysis using baseline mAb models defined and published by Biopharm Services

Considerations
• In-house consumables include bags, tubing, materials, and chemicals
• This study assumes outsourcing 10/12 purification buffers, excluding phosphoric acid and acetic acid
• This is based on a 2,000 L mAb process at 56 kg/yr

Conclusions
• In-house prep including consumables is more expensive
• Outsourced buffer prep reduces labor
• Increase in materials is offset by savings in capital, labor, single-use consumables, and other production costs

Scenario 1: In-house buffer prep

Cost type	USD/year
Capital	2,501,860
Materials	459,857
Consumables	1,400,058
Labor	1,219,198
Other	837,510
Total	6,418,483

Scenario 2: Outsourcing buffer prep

Cost type	USD/year
Capital	1,787,321
Materials	767,651
Consumables	1,099,185
Labor	873,930
Other	602,169
Total	5,130,256

$700K
CapEx avoidance

$300K
annual labor savings

$300K
annual single-use consumables savings

Conclusion

There are many considerations in the choice of approaches to buffer and process liquids supply. Factors to consider involve the buffer type, volumes, and timing required– as well as a manufacturer's finances, facility, and personnel available. The most important decisions involve in-house vs contracted production and, if in-house, the overall production approach. For many, contracting for commercially available assistance in both the development and production of large-scale process buffers is the optimal approach.

Ready to discuss scalable buffer preparation with a technical specialist? Visit https://www.thermofisher.com/simplifybufferprep

About the Author

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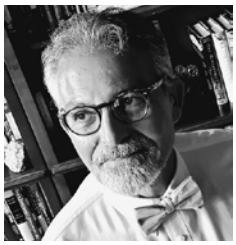

Bill has over 20 years' experience in biotechnology product and process development. He now presents oral papers on bioproduction at international conferences and composes articles and book chapters on such topics such as biopharmaceutical technologies, Pharma 4.0, and sustainable biomanufacturing practices. He enjoys serving on a number of biotechnology committees and panels, such as the BioProcess International Editorial Advisory Board, and as a member of the AFDO/RAPS Healthcare Products Collaborative Artificial Intelligence in Operations Team.

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Thermo Fisher Scientific's Process Liquid Preparation Services is part of a global team with over 60 years of experience delivering cGMP chemicals, process liquids and buffers and solutions to biopharmaceutical companies.

Our process liquid and buffer solutions can help you mitigate risks, streamline processes and maintain regulatory compliance from pre-clinical trials through commercialization so you can focus on what you do best—innovating and producing life-changing medicines.

References

1. BioPhorum Technology Roadmap for the Biopharmaceutical Manufacturing Industry https://www.biophorum.com/wp-content/uploads/bp_downloads/Overview-1.pdf
2. https://www.biophorum.com/wp-content/uploads/bp_downloads/An-economic-evaluation-of-buffer-preparation-philosophies-for-the-biopharmaceutical-industry-December-2019.pdf
3. BioSolve Process software or service, Biopharm Services Ltd, Chesham, Buckinghamshire, UK https://www.biopharmservices.com/
4. https://journal.pda.org/content/early/2022/08/19/pdajpst.2021.012660
5. https://www.pharmamanufacturing.com/home/article/11303287/the-case-for-outsourcing-buffer-preparation-in-pharma
6. https://bioprocessintl.com/2016/outsourcing-buffer-preparation-activity-increasing/