Bioproduction

Buffers and process liquids for biopharmaceutical production: considerations for scale-up and outsourcing

Overview

- The global biopharmaceutical market is rapidly growing, with small and midsize organizations outpacing large organizations in market share growth
- When scaling up manufacturing, biopharmaceutical organizations are increasingly opting to outsource buffer and process liquid preparation
- Many factors should be considered before an organization decides to outsource, including manufacturing space, personnel needs, and analytical capabilities

Current trends in biopharmaceutical manufacturing

Small and midsize biopharmaceutical organizations are increasingly important drivers of innovation in the development of novel therapeutics, and biopharmaceuticals account for a rapidly growing percentage of new candidates in the clinical pipeline. The size of the total global biopharmaceuticals market in late 2022 was estimated to be $333.1 billion with a projected increase to $856.1 billion by 2030 [1]. The market share of small and midsize biopharmaceutical organizations is expected to increase at a projected compound annual growth rate (CAGR) of about 11% to reach $22 billion by 2025 [2]. In contrast, the CAGR of the 20 largest biopharmaceutical companies is projected to be just 5% to reach $24 billion over the same timeframe.

The explosive growth in the number of biopharmaceutical candidates in the clinical pipeline is due in part to fast-track processes recently implemented by regulatory agencies in the US and European Union for therapeutics intended to treat serious conditions and fulfill unmet medical needs [3]. Fast-track designation by the US Food and Drug Administration (FDA) significantly accelerates timelines for conducting clinical trials, filing for approval, and gaining authorization for market launch [4]. Fast tracking has greatly facilitated the introduction of new product classes, like vaccines and cell culture–based products for cell and gene therapy, into the clinical pipeline.

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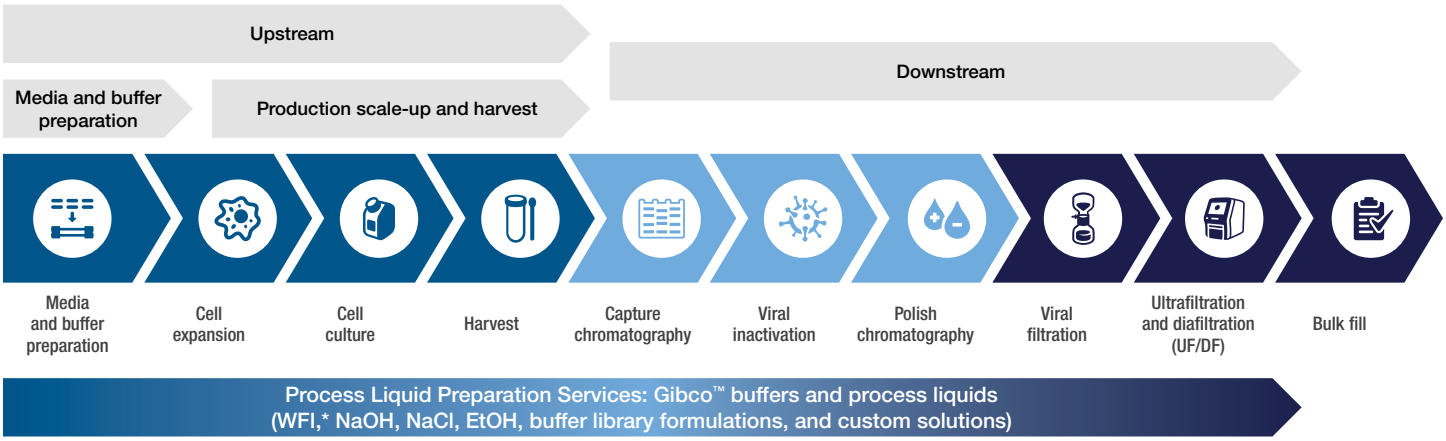
In addition to a rapidly growing market share and the introduction of new product classes, small and midsize biopharmaceutical organizations can expect to see continued increases in the costs of development and operations as well as ongoing pressure to reduce these costs [4]. The biopharmaceutical industry will also have to contend with inherent uncertainties around patient selection for clinical trials, dosing, and safety. Other uncertainties include clinical success, regulatory approval, and market success.

Another notable trend among biopharmaceutical manufacturers is outsourcing [5]. Scaling up activities like in-house buffer and process liquid preparation requires time, personnel, and facility space that a small or midsize organization may not have or may not wish to reallocate [6]. Most biopharmaceutical organizations outsource to some extent, and the wide range of outsourcing services offered spans the entire process from development to manufacturing [7]. The decision to outsource should be considered carefully, as excessive outsourcing can erode in-house capability over time. However, for example, outsourcing activities that do not require a high level of expertise can enable an organization to focus on its core competencies and eliminate the need to expand capacity for low-value tasks. This can make it easier to scale up operations and help expedite navigation of lead drugs from clinical trials to market. Outsourcing can also enable access to more advanced technologies and a diverse pool of skilled professionals for activities that require specialized expertise such as production of buffer concentrates.

The importance of buffers and process liquids in biopharmaceutical manufacturing

Biomanufacturing buffers and process liquids are used to maintain pH or to stabilize components such as proteins. They are used as solvents, as diluents, or for cleaning purposes and provide necessary cofactors for enzymatic activity and supply nutrients to cells [8]. They are employed throughout the biomanufacturing workflow from biological sample receipt to upstream processing, downstream processing, storage of chromatography resins, and production of final drug products (Figure 2). Since 10–20 times more buffer may be needed for downstream purification processing when an upstream process is scaled up, robust and economical buffer preparation is critical for avoiding downstream bottlenecks [5].



* Water for injection.

Figure 2. Usage of buffers and process liquids throughout a general biomanufacturing workflow.

Factors to consider before outsourcing buffer and process liquid preparation

While it is not always practical to outsource buffer and process liquid preparation entirely, outsourcing some portion of it can have important benefits for an organization depending on its priorities. An organization that is thinking about outsourcing should consider the following factors [8]:

- **Space in the manufacturing facility—**Scaling up in-house preparation activities may take up a significant amount of space or impinge upon the use of shared suites, equipment, or personnel.
- **Time and labor required—**Additional personnel and equipment may increase operating costs.
- **Potential formulation errors—**Deviations and failures due to formulation errors can be costly and upend production timelines.

- **Special requirements—**Preparation of biomanufacturing buffers can be highly complex. For example, the use of concentrated buffer components requires an experienced operator as well as tanks and other equipment designed to withstand corrosive materials. Biomanufacturing buffers may also have special quality requirements like sterility that will depend on their formulations and the processes for which they are used (e. g., manufacture of final drug products).
- **Quality control (QC) and quality assurance (QA)—**An organization must assess its analytical, QC, and QA capabilities to determine whether its existing quality system and capacity are sufficiently robust for in-house current good manufacturing practice (CGMP) buffer preparation.
- **Storage capacity—**Buffers that are used for CGMP processes must be stored in a temperature-controlled environment with periodic quality testing by trained personnel.

There are clearly many variables to consider before deciding whether to outsource buffer and process liquid preparation. Cost may be the most important factor for some organizations, but the entire biomanufacturing workflow and different buffer preparation philosophies in the industry should be evaluated to determine whether outsourcing is the most suitable option [9]. The evaluation should take into account the number of buffers and process liquids needed for the entire workflow, their volumes, and the capabilities of the existing facility, equipment, and personnel. The cost-effectiveness of outsourcing can also be assessed with the help of process modeling tools and software.

Benefits of outsourcing

While there is no one-size-fits-all approach to outsourcing, it has the potential to:

- Streamline buffer and process liquid preparation
- Reduce costs
- Mitigate risk
- Enhance quality control
- Simplify data management and documentation
- Address environmental health and safety concerns
- Minimize storage requirements
- Meet needs for customized packaging or other raw materials

A skilled outsourcing partner should be able to supply buffers and process liquids of consistent quality at a cost per liter that is more than offset by savings in capital, labor costs, and the cost of single-use consumables [8]. Organizations that outsource can also benefit from quality control enhancements and efficiencies of scale that would otherwise be unachievable [10].

Evaluating the cost-effectiveness of outsourcing

When constructing a process model using modeling software, consider the following factors [8,10]:

- Formulation, process design, and material specifications
- Volume, production schedule, and testing requirements
- Existing suite capacity, equipment, and personnel
- Existing analytical, QA, and QC capabilities
- Anticipated changes in buffer types and volumes
- Number of separate facilities in which buffers and process liquids are used
- Operating cost

Eliminate bottlenecks and improve efficiency

Outsourcing buffer and process liquid preparation can reduce the number of bottlenecks in the manufacturing workflow. A reliable outsourcing partner can provide buffers and process liquids on demand in the quantities needed without disrupting the production schedule or straining in-house capabilities. Even when smaller batches are needed for research or cell and gene therapy applications, outsourcing buffer supply can still have significant benefits. An organization that outsources buffer and process liquid preparation can utilize its resources more efficiently, enjoy assurance of supply, and establish the groundwork for easy scale-up [10]. The organization can also request a process walk and lean assessment of its weigh, dispense, and hydration workflow to identify more opportunities to improve efficiency, mitigate risk, and reduce costs.

Simplify quality control, data management, and documentation

A biopharmaceutical organization can greatly simplify its preproduction workflow by outsourcing raw material sampling, QA inspections, and QC testing. Quality-related activities often create production bottlenecks, and smaller organizations may lack the manpower or expertise needed to scale up QA inspections and QC testing. Outsourcing quality-related activities can thus help manufacturers avoid production delays, reduce the workload for personnel, and mitigate regulatory risk. An outsourcing partner who can manage quality testing, quality data, and the documentation needed to satisfy regulatory requirements can also make the CGMP transition easier by facilitating the traceability of CGMP raw materials and buffers and generating certificates of analysis [8]. A skilled outsourcing partner may even be able to help set specifications for custom buffers and buffer components.

Address environmental health and safety concerns

Some biopharmaceutical facilities are not equipped for handling certain hazardous materials, such as caustic chemicals and flammable organic solvents. Outsourcing buffer and process liquid preparation can reduce environmental health and safety (EH&S) risk, since the outsourcing partner does all of the weighing, dispensing, and hydrating.

Minimize storage requirements and customize packaging

A biopharmaceutical organization with an automated bioprocessing facility can benefit in several ways by outsourcing to a vendor that can supply buffer concentrates and concentrates of individual buffer components for in-line dilution. When final buffers are needed, the concentrates are diluted with WFI in automated dilution skids and monitored in-line. One advantage of using concentrates instead of traditional 1X batch solutions is that it reduces the need for material handling and dispensing. Other advantages include the widespread commercial availability of individual buffer components as concentrated stocks and the fact that concentrates require less storage space than traditional 1X solutions. Concentrates provide high flexibility in dilution as users can adjust the final concentration depending on specific process conditions. In the end, they support environmental sustainability goals due to a reduced impact through transportation and storage, and reduced waste. Some premier vendors offer custom packaging for direct connection to hydration processes, and they may be able to package single or multiple buffer components as dry powders in specified quantities.

Conclusion

Preparing bioprocessing buffers and process liquids at manufacturing scale is time-consuming and labor-intensive. It also requires devoted facility space and storage capacity, an assurance of supply, and traceability with quality documentation. When a small or midsize biopharmaceutical organization wants to scale up its processes, it may find that it lacks the space and production capacity to prepare buffers and process liquids at manufacturing scale. It may also be difficult for an organization that lacks a robust quality system to achieve or maintain CGMP-level regulatory compliance.

An outsourcing partner who facilitates a reliable supply of buffers and process liquids, readily accessible quality documentation, and traceability can help an organization successfully navigate scale-up. Outsourcing buffer and process liquid preparation, quality testing, and storage can significantly streamline operations and reduce regulatory risk. An organization that outsources buffer and process liquid preparation will not have to sacrifice floorspace or expand its capacity for these activities, and outsourcing quality testing to an experienced partner can greatly simplify documentation and CGMP-level regulatory compliance.

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