Bioproduction

# Advances in outsourcing of process liquids for CDMOs

## Introduction

The buffers and liquid processing materials employed in pharmaceutical manufacturing are a significant factor in product quality, as well as in production efficiency and consistency. There has been continual advancement in many aspects of these process liquids and buffers (PLBs) in recent years.

The appearance of new therapeutic entities, manufacturing modes, process intensifications, and design goals such as improved sustainability, make biomanufacturing a very dynamic field. This progress has led to the development of novel processes requiring new materials, containment, and logistics.

Liquid processing materials include a number of products of diverse composition and volume. Cell culture media are complex formulations of nutrients and factors used to expand and maintain cell cultures *in vitro*. Unlike traditional media, which may contain undefined components such as serum or other biological extracts, defined media are composed entirely of known quantities of pure chemical substances. Process buffers include pH-buffered solutions used in such operations as equilibration, binding, washing, elution, and storage of product throughout its manufacture. Feeds and antifoams are concentrates used in lower volumes to condition culture media mid-process. Acid and base solutions are employed to adjust the pH of other liquids. Finally, there are a number of wash and rinse formulations that, while not an active part of the manufacturing process, are highly controlled as they operate upon product contact surfaces.

Two main PLB supply options exist for pharma sponsors or contract development and manufacturing organizations (CDMOs) to help facilitate the availability of a sufficient quantity of qualified, compliant product at the right time: in-house preparation or outsourcing. While this choice has existed for decades, significant developments in both pharmaceutical commercialization and vendor capabilities influence the final decision [1].

From cell culture media and feeds to finished product materials, there is a growing number of PLB formulations employed across the entire biomanufacturing workflow (Figure 1). To limit our scope here, we will focus on fluids used post–cell culture, leaving discussion of broth and media for other publications. It is surprising to some that such downstream PLBs make up the major portion of the total volume of liquid materials used in bioproduction.

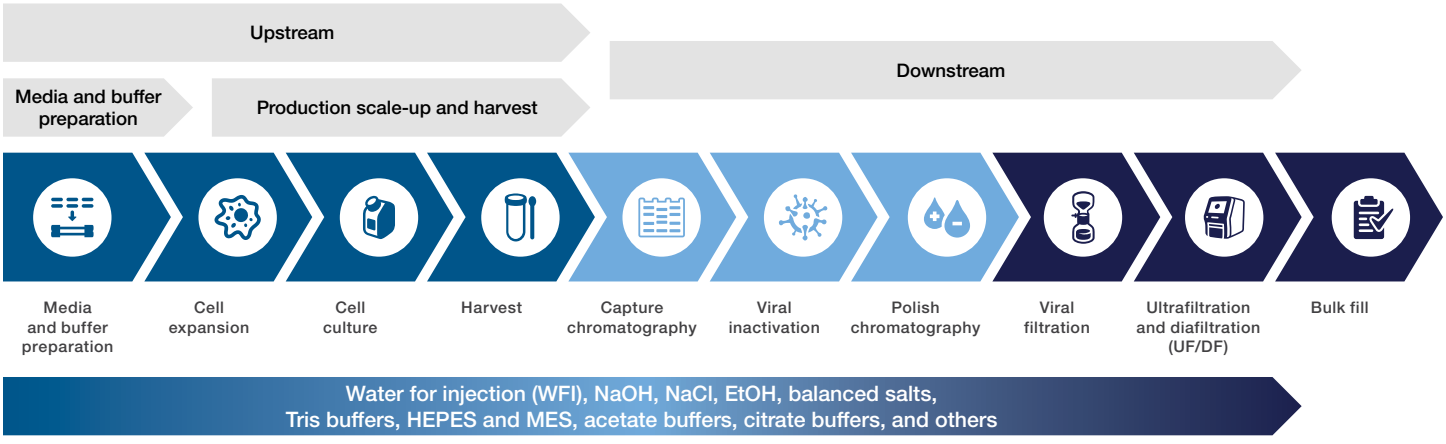


**Figure 1. Usage of process liquids and buffers throughout a general biomanufacturing workflow.**

In considering sources of contracted supply, an empowering development is the growing increase in outsourcing partner (OP) capabilities, infrastructure, and product offerings. There are now options for both pharma sponsors and CDMOs to choose from—ranging from smaller and focused local suppliers to larger, premier vendors of comprehensive, worldwide services.

## PLB diversity and evolution

The earliest predecessors of protocols defining solid and liquid manufacturing components can be traced back thousands of years, such as a recipe for beer recorded in Sumerian literature around 1800 BCE [2]. Today, we have a number of rules to help control quality and efficiency in PLB production [3]. These requirements continue to increase as the number and diversity of high-volume PLB formulations increase. Such formulations are used in a wide range of bioproduction processes, including:

- Reaction media preparation and neutralization
- Buffer conditioning
- Viral decontamination
- Diafiltration
- Chromatography

Individual PLB needs range from the water used in equipment rinses, flushes, and storage, to the harvest and active pharmaceutical ingredient (API) diafiltration buffers and diluents used in purification. With this diversity have arisen unique quality, safety, and disposal requirements for solutions of problematic organics such as toluene and acetonitrile that are employed in oligonucleotide production.

Overall, demand for PLBs is growing for two reasons:

- **Increased use of new purification materials—**Versatile chromatography materials such as mixed-mode resins and process modes such as intensified continuous chromatography, a type of multi-column chromatography (MCC), can require unique PLB components, concentrations, and volumes.
- **Development of new product types—**Next-generation products such as cell and gene therapies, viral vectors, mRNA vaccines, and others may require sterile, isotonic, cryogenic, and even nutrient-fortified buffers.

Manufacturing parameters include the components in PLB formulations as well as their volumes, formulation stringency, and production timing. Adding to the complexity is growing employment of different PLB components such as polyols, polysorbates, stearates, surfactants, antioxidants, preservatives, and moiety-specific eluents.

New biopharmaceutical product types such as cell and gene therapies, mRNA vaccines, and oligonucleotide-based therapies require process-specific PLBs. For example, the amino lipids used in the production of mRNA–lipid nanoparticle formulations in some SARS-CoV-2 vaccines are a potential source of reactive impurities that can inactivate the mRNA. The API must therefore be specifically protected from fragment generation, depurination, and deamination resulting from pH extremes, peroxides, aldehydes, and RNases, as well as from base oxidation induced by redox-active metal contaminants or light. Developments are also occurring from the demands of such new dosage forms supporting inhaled and buccal delivery, microneedle patches, synthetic vesicles, hydrogels, and nanoparticles.

For many of these newer products or manufacturing modes, the final processes or at-scale configurations are yet to be finalized, and this imposes a need for higher flexibility and agility in PLB final formulations, volumes, and production timing. Recent advances in process automation, monitoring, modeling, and control can be factors in these processes as well.

The number of criteria employed in bioprocess design is also growing. Drug developers now address such goals as increased environmental sustainability, geographical security of supply, and meeting the needs of emerging markets. Designing facilities and establishing materials supply to support these developing goals are now imperative.

Beyond these developments in the PLBs themselves, there has been an evolution in their primary packaging systems, polymer films, scale, and porting configurations. Finally, requirements such as considerations of Scope 1, 2, and 3 carbon emissions are altering the criteria employed in process design or OP qualification [4,5].

## Outsourcing of PLBs

There are many considerations in the decision to produce process liquids in-house or to outsource them to validated supply partners. Classic factors in this decision include product quality and consistency, production speed and economy, and risk management [6].

A primary consideration in PLB preparation involves the quality and regulatory requirements of RUO or GMP manufacturing. In GMP facilities, every component of a buffer formulation, including the water, will have a stipulated specification to meet. The facility, equipment, processes, and intermediate products must be maintained in accordance with applicable ISO and ICH guidelines, and follow approved QA/QC procedures. Activities to accomplish such goals include:

- Materials procurement, testing, and storage
- Water for injection (WFI) production and storage
- Component weighing, dispensing, and hydration workflows
- Final formulation testing, acceptance, handling, and storage
- Documentation development, control, and distribution
- Container compatibility, cleaning, leachables, and closure validation

OPs both understand these regulatory particulars and have established facilities, materials, and procedures for accomplishing them.

The appearance of new products and production modes is driving an evolution in the nature of intermediate products and final dosage forms to be supported. This has heightened the need for process flexibility and PLB formulation latitude. And the recent move from a traditional batch approach to concentrates and in-line formulations has added to the stringency of programs such as just-in-time delivery and new QC processes for incoming materials.

Premade PLBs offer many valuable features (Table 1). Of course, there are potential cost efficiencies for developers to consider. In addition, outsourcing can provide manufacturing benefits such as access to high-quality materials and state-of-the-art facilities. With premier OPs, production scale can often be flexible while the product is being developed and transitioned to market. Experienced OPs can also help companies manage various risks and improve operating efficiency. Some of these features are especially valuable in projects where final production demand is yet to be established.

**Table 1. Potential features of partnering for PLBs.**

| Features | Factors to consider |
|---|---|
| **Financial** | |
| Cost savings | Potential areas for cost savings include capital investments in facilities and equipment, specialized personnel hires, and budgeted full-time employees (FTEs) |
| Improved cost control | Outsourcing can help ease prediction, timing, and control of development and manufacturing costs |
| **Manufacturing** | |
| High-quality materials | OPs can provide qualified and validated materials, key analysis technologies, and proven packaging |
| Access to specialized expertise | OPs typically employ personnel with experience in development, quality control, and regulatory compliance |
| Access to state-of-the-art facilities | OPs often provide new, state-of-the-art and process-specific procedures, equipment, and facilities |
| **Flexibility and speed** | |
| Scalability | Outsourcing can allow companies to scale up or down based on specific needs, without dedicated facilities |
| Geographic reach | OPs can work with pharma sponsors or CDMOs in different geographic regions, assisting in matters related to regulatory compliance, operating expenses, and local markets |
| Time-to-market | OPs can help accelerate time-to-market by leveraging their experience with existing infrastructure |
| **Risk management** | |
| Regulatory compliance | Experience of OPs in regulated manufacturing and qualified material sourcing helps support compliance |
| Supply risk | OPs have focused and established material sourcing and capabilities, mitigating supply risk |
| Focus on core competencies | Outsourcing allows pharma sponsors or CDMOs to focus on core competencies such as R&D, marketing, and regulatory affairs |
| **Organizational efficiency** | |
| Creative solutions | Premier partners can advise on best practices and applicable guidelines for standard formulations, as well as support the development of creative solutions to unique challenges |
| Reduced administrative burden | Outsourcing can simplify administrative tasks such as personnel training, environmental health and safety (EHS), quality control, and procurement |
| Strategic partnerships | Strategic collaborations with OPs can lead to more reliable and stable manufacturing relationships |
| Objective assessments | An experienced OP can provide a knowledgeable and unbiased assessment of particular project goals and status |

Premier OPs have facilities to easily expand to greater scale when needed, allowing developers to, for example, reduce the extent of their production suite or refrigerated warehousing. Consider also that despite an OP's need for profit, they have built-in efficiencies that can be passed to their customers—such as their savings in volume material sourcing, existing experienced and qualified personnel, previously optimized processes, and existing QA documentation.

Increasing speed-to-market and transferring PLB risk are of particular value to some pharma sponsors or CDMOs. Contractually based operations offer improved control of cost consistency, financial timing, and simplified supply chain management, while allowing pharma sponsors or CDMOs to focus on core competencies. Beyond the contracted material supply, an experienced partner can provide advice on, for example, process and product optimization and de-risking the supply. The geographic source flexibility provided by some PLB suppliers can offer environmental sustainability, supply continuity, and local regulatory requirement value.

Contracting with a premier OP can provide access to specialized experience in product development and specification, employing state-of-the-art facilities, procedures, and equipment. Such OPs support both standard and customized formulations in validated standard or customized packaging and transport. Furthermore, the number of standard product offerings available at scale for manufacturing purposes is growing.

Products with full validation packages available from premier OPs now include culture feeds and antifoams, WFI, NaOH, NaCl, and ethanolic solutions. So, beyond standard formulations such as PBS, complete and previously filed documentation is now available for the newer and more complex buffers presenting incremental quality and safety requirements.

Consistency, flexibility, rapid turnaround time, and risk management are pivotal factors in considering buffer management solutions—especially when supplies are needed on short notice. Finally, outsourcing can help reduce many demands on pharma sponsors or CDMOs (Table 2). Key among them are savings afforded by the potential for reduced equipment requirements, simplified operations, and access to specialized analytics and expertise.

**Table 2. Demands on pharma sponsors or CDMOs that can be reduced by partnering for PLBs.**

| Category | Demands |
|---|---|
| **Equipment and materials** | • Equipment selection, qualification, and calibration efforts<br>• Materials specification, screening, qualification, and validation<br>• Finding or qualifying primary to tertiary material suppliers |
| **Infrastructure** | • Equipment maintenance, validation, and acquisition<br>• Classified manufacturing footprint and processing equipment<br>• Manufacturing space, equipment, and raw materials storage |
| **Technology** | • Maintaining current data and modeling technologies<br>• Incorporating advances in data and modeling systems<br>• Process development and reconfiguration design and build |
| **Scale-up** | • Anticipated evolution in buffer types and volumes<br>• Supporting new capacity and facility expansion needs |
| **Quality control** | • Timing, production, and various testing requirements<br>• Analytical systems, QA/QC documentation, and personnel |
| **Compliance** | • Operations complexity and compliance, and environmental health and safety (EHS) risk<br>• Upgrades to meet new EHS and sustainability demands<br>• Process, formulation, and waste specification documentation |
| **Risk management** | • Manufacturing misformulation and contamination risks<br>• Process bottleneck and materials procurement risks<br>• Financial, scheduling, and resource conflict potential |

Compared to smaller or newer firms, the more premier OPs can provide increased intellectual property (IP) protection and data security. Because of larger data and technical services departments, they may have:

- Advanced systems to supply newer encryption techniques in data transmission
- Multi-factor authentication in access to data and programs
- Blockchain technology in transmitting files
- Advanced data loss prevention techniques
- Segmentation and isolation of their networks
- Event management and incident response procedures
- More systematic software and patch management for their internal systems

In summary, the valuable features and reduced demands afforded by partnering for PLBs can provide significant benefits to the developer. They can help lower PLB and other costs, mitigate key bottlenecks, and improve production efficiencies and flexibility.

## Choosing a supply partner

Sponsors, including CDMOs, are increasingly teaming up with contracted vendors for their culture media, buffers, and process fluids. However, the long-term success of teaming up with a supply partner depends greatly upon many factors, and a number of salient distinctions are crucial in developing a successful, long-term partnership [7].

Of course, supplier experience, trust, and reputation are important, but for many, a diverse geographical footprint and extensive formulation capability can be a particular benefit. Technical support from specialists regularly involved in these products, and the ability to advise upon product usage and optimization, or to supply ancillary products, are often invaluable. OPs can also provide objective assessments of development status and suggestions for manufacturing streamlining.

While there is much pressure to reduce cost and lead times as much as possible, it is obviously important to consider any potential implications on product quality and consistency, and supply chain reliability. In developing a systematic approach to selecting and qualifying the right OP, drug developers can establish a dependable supply of compliant PLBs, allowing them to proceed with confidence.

There are many areas to consider in the selection and qualification of a suitable vendor. The importance and priority of each may vary, depending upon such factors as the nature of the product and in-house capabilities of pharma sponsors or CDMOs. However, there are several key criteria involving the drug developer's experience, specific capabilities, operating infrastructure, and processing standards.

Primary business and contractual factors include maintaining regulatory compliance and safeguarding IP. The OP's general ability to maintain regulatory compliance serves to both protect patient safety and avoid fines for noncompliance. An acceptable OP must demonstrate compliant manufacturing facilities, accredited in the region they operate, and be able to provide current documentation to validate compliance. IP protection has always been a concern, but today an OP must demonstrate a current data security infrastructure and policies as well as a dedicated cybersecurity program to help reduce data risks and respond to future threats.

An acceptable OP must demonstrate that they possess the necessary facilities, operating infrastructure, and well-documented procedures to both establish product quality and consistency at all scales, and address challenges in an efficient and economical way.

They should possess an in-depth procurement program that qualifies raw materials of appropriate specifications from reputable suppliers. Tools for this program include dedicated QC labs assessing incoming raw materials with current analytics in their screening protocols and modern digital inventory management systems.

Facilities should support meeting requirements such as reducing contamination risk. These requirements include procedures to establish that animal origin–free and other designations can be maintained. Newer features are becoming standard such as unidirectional processing with separate material and waste flows supported by integrated operating systems for real-time monitoring. Equipment used in production must have appropriate qualification packages supporting the specific activities employed.

Supply-chain management has become an increasingly important factor. Tools to establish this include redundant manufacturing suites and multi-site networks. An important aspect of these systems is the harmonization of production equipment, materials, and workflows to establish comparable performance across regions. Validating OP production to the same standards will help maintain equivalency of the product.

Developers should also demonstrate equivalency in raw material quality, including compatibility in sourcing procedures, material specifications, analytics, and QA/QC frameworks. Ideally, validation of a particular primary partner is accomplished during technology transfer, but this is not always a possibility.

The ability to investigate batch failures and product inconsistency or drift is important for long-term security of supply. The ability of an OP to establish initial competency is only a first step. Premier drug developers will have the knowledge and tools supporting detailed investigations to resolve production challenges as efficiently as possible.

Premier OPs have developed specialized standard single-use systems contributing to the efficient and economic supply chain of outsourced PLBs. Recent developments include new standard films, connectors, and bioprocess container (BPC) styles, as well as customized, customer-specified BPC configuration capabilities (Figure 2). Other customized solutions available include real-time stability testing in the desired packaging configuration and comprehensive surveys of extractables and leachables.

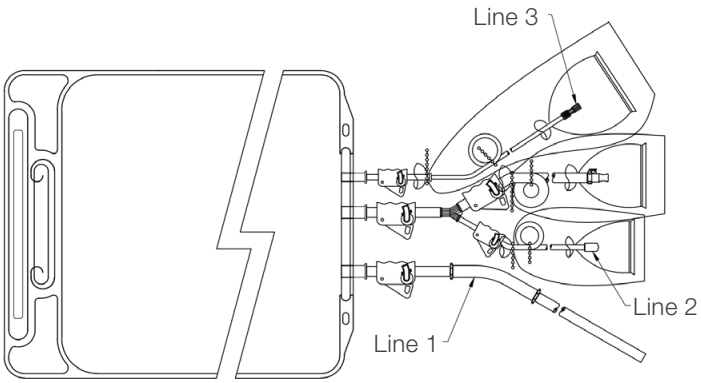


**Figure 2. Example of a single-use BPC with multiple line sets for fluid transfer.**

## Advances in single-use systems

Single-use (SU) biomanufacturing refers to the employment of polymer-based flexible-walled BPCs and accessories throughout the process train in the production of biopharmaceutical and biotech products. Its acceptance and incorporation has grown steadily since its introduction some 20 years ago. SU containers are established as a key component in the outsourcing of fluid products, given their advantages applying to both the OP and drug developer [8].

Primary SU benefits include reduced risk of both adventitious and cross-contamination, and quicker setup and turnaround times. In reducing service demands and classified area footprint, SU systems reduce capital investments both initially and during capacity or facility expansions. By reducing the need for extensive cleaning and sterilization between batches, they consume less energy and water. This reduces not only operational activities and environmental burdens but also the time and expense of related equipment maintenance and validation procedures. Finally, even process development and optimization activities are more efficient, owing to the ease of SU unit and train reconfiguration, and rapid batch turnaround.

## Environmental sustainability

Environmental sustainability is a growing concern in all aspects of pharmaceutical manufacturing. SU bags, tubings, and connectors are a particular concern, as unlike carbon, they become a highly visible waste. Science-based comparisons of the cradle-to-grave environmental burdens generated by both SU and classical, durable systems have provided interesting understanding [9].

For example, because the operation of SU systems consumes less cleaning/sterilizing materials and energy, they always help reduce environmental burdens such as carbon and waterway eutrophication. However, the total amount of reduction depends upon such factors as SU product shipping logistics and local service grid characteristics. For example, if a plant's power comes from a hydroelectric source, the burden of generating hot water and steam is much less than if it were to come from fossil fuel. Life cycle assessments have become a required process to reveal the actual net value in this subject. Those responsible for making improvements in this area range from governments to final product consumers. Intermediate participants such as drug developers, OPs, and such consortia, e.g., the Bioprocess Systems Alliance (BPSA), are making great progress in reducing the burdens from usage of SU plastics. Solutions are diverse and developing, and are efficiently referred to in the phrase "rethink, reengineer, reduce, reuse, and recycle" [10].

Example solutions that OPs have already provided include improvements in both the design as well as the material component fibers and plastics in totes, crates, and drums. Solutions are also occurring in operational logistics, such as in returnable packaging systems [11].

## Future directions

Standardization of flexible containers and buffer systems would improve efficiencies, and a number of consortia are currently addressing this issue [12]. Recent developments in artificial intelligence (AI) and machine learning techniques are showing promising gains in process efficiencies, material and product logistics, and electronic traceability. AI-empowered systems are aiding in analyzing large datasets from manufacturing processes to identify patterns and optimize production parameters. They can process and analyze vast amounts of multiparametric data generated during the manufacturing process, identifying trends and insights challenging for traditional methods. They are helping to facilitate product quality, and reducing the likelihood of faulty products reaching consumers.

AI-empowered digital twins can predict equipment failures by analyzing data from sensors and production systems, enabling proactive maintenance (Figure 3). AI algorithms can analyze data from the supply chain to optimize inventory management, demand forecasting, and distribution logistics. They can assist in ensuring compliance with regulatory requirements by continuously monitoring processes and providing real-time alerts on deviations or anomalies. Finally, AI algorithms can optimize energy usage in pharmaceutical manufacturing facilities by analyzing consumption patterns and recommending strategies to minimize energy waste.

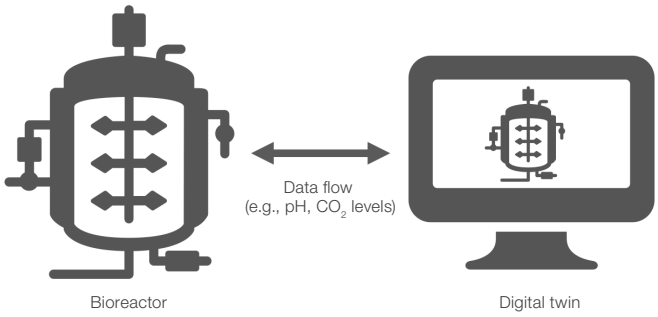


**Figure 3. Representation of a digital twin, or virtual model, of a physical object.**

OPs are continuing to improve the equipment and processes for end-to-end fluid and cold chain management, materials storage and inventory, and shipping of SU containers of any size.

Each player in the value chain is working through many channels to reduce environmental burdens in PLBs. Factors here include more efficient pharmaceutical processing, container production, sustainable materials sourcing, and development of more sustainable polymer films. Also being examined are greenhouse gas sources, shipping efficiencies, and greener packaging designs. One promising example is the development of X-ray–based container sterilization as a greener alternative to standard gamma-ray–based methods.

Finally, development of both the technology and regulatory guidance in the buffer manufacturing process is ongoing. For example, in-line buffer conditioning from concentrates is becoming a popular alternative for batch production [13]. In considering contamination control strategies (CCS), the pre-use post-sterilization integrity test (PUPSIT) is named as an element of quality risk management (QRM) in a recent revision of EU GMP Annex 1 [14].

## Conclusions

The outsourcing of buffer and production fluid generation has become increasingly popular for CDMOs for reasons of speed, efficiency, and even economy. Contracted suppliers have dedicated equipment, personnel, and experience to reliably supply tested and ready-to-use products in the newest packaging. OPs are adopting advanced technologies such as continuous manufacturing, SU systems, and process analytical technologies, to enhance efficiency, reduce costs, and improve quality. They are now focusing on providing flexible manufacturing techniques, including multi-use facilities, adaptable manufacturing processes, and scalable production tools.

Premier OPs are providing regulatory experience to navigate the complex regulatory landscape and help support compliance with global regulatory requirements. In response to recent supply chain concerns, they are increasingly involved in optimizing supply chain management for their clients—helping to facilitate raw materials supply and effective inventory management. By leveraging newer data management and analytical tools, they are accommodating the larger datasets generated by the increased analytics applied during manufacturing to enhance process understanding, optimize production processes, and improve overall efficiency and quality.

Premier OPs draw upon their experience in other departments to support PLBs employed in such areas as gene therapies, mRNA vaccines, and oligonucleotide drugs to address the unique challenges associated with these advanced therapies. Some can provide ancillary services such as specialized project management, which may not be immediately obvious in considering the outsourcing option. OPs are increasingly offering end-to-end services, encompassing product development from early stages. It has become the business of premier OPs to respond to CDMO concerns regarding every aspect of PLB production, packaging, validation, documentation, and distribution.

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