Powders and Bulk Liquids

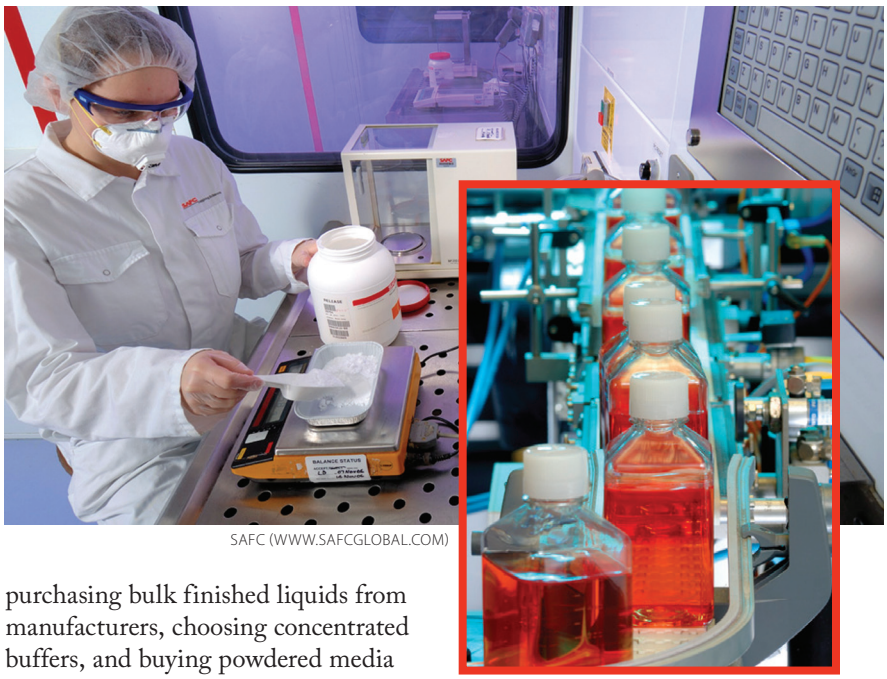
Economics of Large-Scale Culture Media and Buffer Preparation are Changing

by Eric S. Langer and Ronald A. Rader

The two major bioprocess fluids — culture media for upstream production and buffers for downstream processing — are classic single-use products. They are used once and then disposed of. The two basic options for both differ by physical state: powdered media and buffers ("powders" for in-house preparation of liquids by end users) and bulk liquid culture media and buffers, which are fully prepared by their suppliers ("liquids"). We conducted market research studies comparing the benefits and risks (value proposition) to bioprocessing facilities of using bulk liquids and powders — along with related trends.

Prepared liquids are universally used at the smallest scales. They are packaged in 1-L bottles for laboratory-scale applications. Today, nearly all facilities switch to using powders without consideration of alternatives as bioprocessing is scaled up. But modern trends are changing that equation: expanded single-use applications, shifts toward continuous bioprocessing, smaller-scale bioreactors in use at more advanced product phases, regulatory demands for increased sterility, a move toward process analytics, and demands for greater efficiency and productivity.

Given those trends, end users and suppliers both are reevaluating whether it is truly cost effective or prudent to default to in-house preparation of GMP culture media and buffers from powders. Alternatives include purchasing bulk finished liquids from manufacturers, choosing concentrated buffers, and buying powdered media preweighed in bags. So some companies are beginning to change their approach, particularly for scales that aren't so large.



SAFC (WWW.SAFCGLOBAL.COM)

Strategic Situation

In-house culture media preparation from powders has been the dominant choice for hundreds of years. In fact, about 90% of culture media sales involve powders and only about 10% involve liquids. Much the same division applies to buffers. Suppliers have yet to proactively market liquids as a viable option. That may be because such marketing would be a zero-sum activity: End users would purchase the same (comparable) volumes of media and buffers whether they are sold as liquids or powders.

Fully finished bulk liquids are also newer options than powders.

Essentially, all culture media and buffers purchased in bulk are now custom prepared. Few bioprocessors use noncustomized, nonsupplemented, generic culture media such as those commonly sold retail (e.g., in 1-L bottles). Most culture media now involve process-customized optimization and/or supplementation generally treated as highly proprietary by manufacturers. Although such an approach is generally cost effective and increases yields, purchasers receive only limited information about those products. Essentially, all media used for new bioprocesses are as free as possible of animal products — and

increasingly go so far as being chemically defined.

Powdered culture media and buffers will remain the leading physical form sold, being highly cost effective and preferred for large-scale bioprocessing. But certain trends could pressure this segment to change: e.g., emerging technologies to produce and dispense sterile powders and analytical technologies for contamination detection and media sterilization. Those might force changes in how media are packaged and delivered.

Comparable amounts of powder generally cost less than half as much as bulk liquid media. So bulk liquids are simply not cost effective at the largest scales or for dedicated, commercial, manufacturing facilities — if only due to shipping costs (for what is mostly water and thus quite heavy). But liquid manufacturers put more work into such products that adds value: preparing the liquid, quarantining it, performing related quality control (QC) testing, providing full documentation, and warranting product quality (including sterility). They provide fully finished product. By contrast, powder buyers must train their staff to handle and mix those media. That can increase contamination risks, and mixing often involves generic, inadequately designed and evaluated mixing protocols, equipment, and QC testing. Alternatively, bulk liquids from manufacturers are generally better prepared and more consistent in quality and formulation, thus providing better cell culture performance.

The ability to use liquids rather than powders may be determined by whether a facility can suitably handle powders or bulk liquids. To date, nearly all bioprocess facilities have been designed for powder use, with an estimated ≥20% of space and costs in larger facilities going to media and buffer powder storage and preparation. They need in-house utilities to produce water for injection (WFI), rooms for media/buffer preparation, holding/transfer tanks, heavy-duty mixers, and so on — as well as associated preparation staff. Companies with all that infrastructure are obliged to use powders.

By contrast, facilities built with bulk liquids in mind generally need only to include large, refrigerated receiving and storage areas, broader corridors, and heavy-duty flooring to move large volumes of liquids. Their needs are minimized for in-house WFI production, media/buffer-prep rooms, storage/holding tanks, mixers, and staff. Much as with single-use systems, that provides considerable savings in both initial capital investment and operating costs.

Comparing Liquids and Powders

Bulk liquid culture media and buffers are not new. However, the former is a subject about which additional data are needed:

- What are the differences between liquid and powder versions of the "same" product?
- Comparative cell culture performance: Which is better, manufacturer-prepared liquid media or those prepared in-house by users from powder?
- How are liquid media prepared: by diluting and mixing individual raw ingredients or by hydrating finished ground powders?
- Are studies needed to compare the full costs of using liquids with those of using powders?

Much needed information is missing currently, and comparative data regarding liquid and powder culture media need to be updated. However, it was only a decade ago that the industry complained of a severe lack of knowledge regarding single-use systems. That did not prevent their steady adoption. So it is likely that, assuming liquids offer benefits that are just as compelling, the switch from powders will also increase in coming years.

Trade-Off Analysis: Bulk liquid culture media are generally presumed to perform better than the "same" media prepared in-house from powders by end users. Liquids are generally usable for at best several weeks; powders remain usable for months or even years. It is generally assumed that culture media prepared in-house from powders will not perform as well as the "same" manufacturer-prepared liquid media. Powder ingredients degrade from the heat and mechanical shear of grinding, and powders contain hygroscopic components that adsorb water vapor, leading to inconsistencies in preparation.

Furthermore, liquids manufacturers have full knowledge and understanding of their products. They have better, larger-scale, and automated mixing equipment and know how to mix components in the proper order and under conditions that are validated to provide consistent, stable products. By contrast, powder users typically operate the same nonspecialized mixing equipment for multiple liquids and implement mixing protocols that are not as well engineered, automated, or validated as those of the suppliers. End users generally know less about the manufacture, contaminants, break-down products, cross-reactions, effects of process conditions, and so on regarding their media and/or buffers, whether liquids or powders. That can lead to much more preparation work and regulatory risk for in-house powder use.

Whether liquids or powders are perceived to provide advantages depends on user perspectives and biases. Concerning speed and flexibility, for example, some people consider liquids to be the best option: They can be ordered, delivered, and used without any necessary processing. That is, culture media may be poured directly into bioreactors. Other users consider the ability to keep powders on hand and prepare media/buffers as needed to be an absolutely necessity. They say it allows for immediate "tweaking" and changing of bioprocesses, with required media/buffers available on the same or the next day. Liquids do require weeks for delivery.

In addition to higher costs, liquids have some drawbacks. For example, bag or container leakage makes much more of a mess with liquids than with powders. Liquids also make their users more dependent on suppliers. But powders have their own downsides, including serious worker hazards from powder inhalation.

Table 1: Average industry pricing for simple and complex culture media

	Simple Culture Media (e.g., DMEM, minimal/no supplements)		Complex Culture Media (e.g., chemically defined CHO)	
Volume Purchases	Industry Average, Bulk Liquids Pricing	Industry Average, Powder Equivalent Pricing	Industry Average, Bulk Liquids Pricing	Industry Average, Powder Equivalent Pricing
1,000 L	$25.80/L	$12.40/L	$51.70/L (as liquid)	$22.30/L (as liquid)
30,000 L	$20.10/L	$9.90/L	$35.80/L (as liquid)	$17.30/L (as liquid)

Table 2: Average industry pricing for simple and complex buffers

	Simple Buffers (e.g., salts, NaCl, NaOH)		Complex Buffers (e.g., concentrated urea, complex phosphates)	
Volume Purchases	Industry Average, Bulk Liquids Pricing	Industry Average, Powder Equivalent Pricing	Average Powder (Equivalent Pricing)	Industry Average, Powder Equivalent Pricing
1,000 L	$13.10/L	$5.10/L	$43.20/L (as liquid	$22.00/L (as liquid)
30,000 L	$9.60/L	$3.70/L	$32.80/L (as liquid)	$17.00/L (as liquid)

Water is often heated to 80 °C (176 °F) to promote powder dissolution during mixing, and that can present a hazard as well.

Trends Favor Increased Use of Liquids

A number of trends are making liquids more attractive for adoption than powders. Diverse technological advances continue to provide the ability to do more (or the same) upstream with lower volumes of culture media — and buffers downstream — which better enables adoption of bulk liquids. Liquid-favoring trends include ever-improving cell lines, expression systems, and culture media; adoption of single-use systems; biosimilars and other new entrants fracturing markets; and increasing potency of products. All those enable companies to use smaller bioreactors and less culture media. With bioprocess advances, high-performance culture media and buffers become more critical and complex, which also generally favors manufacturer-prepared liquids.

Use of liquids makes particular sense for flexible facilities based on single-use systems and modular construction. Many of the same benefits of disposables apply to liquids as well: flexibility, smaller capital investment, lowered operational costs, and elimination of some labor.

Other factors favoring liquid culture media include certain business trends: Biopharmaceutical companies increasingly seek to operate leanly, which includes outsourcing noncore activities such as preparation of media and/or buffers.

Culture media and buffers increasingly involve research and development (R&D) or proprietary technology from their suppliers. Whenever that is the case, products typically are priced at least twice as much as those manufactured from formulations provided by end users. Culture media suppliers generally would prefer instead that end users optimize their proprietary culture media formulations, which generally boosts yields significantly. As with any industry segment in which proprietary formulations are involved, the culture media/buffers industry has an ingrained culture of secrecy that contributes to holding back liquids and other new market developments. It also affects end users who express an acute lack of knowledge concerning their media and buffers.

Contamination Issues — Liquid Benefits: Culture media and buffer fluids remain the only major parts of bioprocessing that are not fully sterilized. Culture media are not heat, radiation, or otherwise sterilized, which could degrade them; and they are not virus filtered, which would be costly, cause bottlenecks, and add risk because filters can entrap bacteria that can release endotoxins. Rigorous supply and manufacturing controls have enabled routine use of nonsterilized culture media and buffers. Furthermore, fresh liquid media (whether prepared by manufacturers or end users) are promptly "sterile" filtered, and drug products are virus filtered at the fill–finish stage. So product contamination is not a significant problem. But sterile filtration of culture media removes only bacteria, not viruses.

We are likely to see a ratcheting-up of expectations regarding culture media microbial contamination — directed at facility-wide (not product-specific) virus contamination. Note that the Framingham, MA, manufacturing facility of Genzyme was contaminated with an animal virus from an animal-derived culture media component. That led to facility closure for remediation, with Genzyme losing sales and big pharma Sanofi ultimately acquiring the financially weakened company not long after. Detection methods are improving, with assays in development that can detect all viruses, not just those known or specifically tested for.

Most bioprocess professionals see no current problem with a lack of sterility in culture media. But with the Genzyme precedent, company executives are obligated (if only to investors) to be more cautious and proactively defend their facilities against virus contamination — fixed, stainless steel facilities in particular. A number of leading companies (e.g., Genentech (Roche)) are working to adopt culture media sterilization technologies including high-temperature–short-time (HTST) heating and UV light treatment. Once those methods become adopted for commercial manufacturing, their wider use is likely to become inevitable for new bioprocesses.

Thus far, culture media sterilization technologies generally work best or are applicable only with liquids. Larger-scale new bioprocesses may shift to using bulk liquid culture media if manufacturers can better implement such sterilization with economies of scale. In fact, if media

sterilization becomes more prevalent, then in-house preparation of media from powders by end-users could someday become a legacy process restricted to applications that do not need to comply with up-to-date good manufacturing practice (GMP).

Culture Media and Buffer Prices

Tables 1 and 2 present results from our interviewing and surveying several dozen media and buffer company executives and end users at some of the largest bioprocessing facilities. The results represent average contracted delivered costs for comparable volumes (as end fluids) for "simple" (e.g., generic products commonly sold retail) and "complex" (often custom-manufactured) media and buffers.

Overall, comparable amounts of simple and complex media powders cost about twice as much as bulk liquid culture media. There was general consensus among culture media executives and end users that prices for both media and buffers are rather reasonable. That includes both powders and bulk liquids comparably marked up relative to manufacturers' costs. Prices reported generally varied within ±33%, which confirmed industry sources and end users noting that prices for many of the "same" products from different manufacturers often vary by 2× (100%). Reported pricing and manufacturers agreed that culture media prices include only "token" discounts as quantities increase because prices are largely determined by number of batches rather than batch size. So the cost for 5,000 L and 10,000 L, if prepared in the same large vessels, would be fairly similar.

Both industry sources and end users consider the prices of bulk liquid media and buffers to be fair. Prices for powders and liquids are comparably marked up, particularly considering all the added work performed and suppliers' quality guarantees for liquids. Although quantitative studies are not available — with bulk liquids providing specific benefits and powders having a number of downsides — the former appear to make economic sense for a growing number of applications and end users.

Value Proposition

With the price differentials fairly reflecting the added value of bulk liquids — the additional work done by their suppliers — they are seen as a good deal for facilities that can adopt their use. Liquids are well-suited for new facilities and process lines:

- companies seeking to operate leanly and minimize capital investment, operating costs, and staff
- small- and mid-size bioprocessors (using ≤2,000-L bioreactors)
- flexible facilities making multiple products and at different scales
- modular facilities and those based on single-use systems
- companies seeking to avoid occupational hazards for workers
- GMP-challenged facilities (e.g., in developing countries, where in-house liquids preparation simply cannot attain GMP standards).

For an increasing number of end users, any one of the downsides with powders and/or benefits provided by liquids can tip the equation (presuming their facility allows this) in favor of the latter. Yet for many companies particularly at large scale, powders are and will remain far more cost-effective — or are simply seen as required to, for instance, provide independence from vendors.

Simon Vincent is market manager at SAFC, a leading supplier of large-scale powder media and liquids. He says, "The greatest benefit to end-users regarding both powder and liquid media and buffers is that we can leverage our >40 years of experience in manufacturing these products to ensure consistency, quality, and performance at all scales, all the way to the bioreactor. Although certain large-scale applications will continue to lean toward powder media and buffers, the equation is changing. Especially as more single-use/disposable production facilities come on line, the potential benefits of 'outsourcing' preprepared bulk liquid media and buffers are going to become evident."

The Future

Liquids use and markets will grow in coming years. Adoption rates for both media and buffers will accelerate as manufacturers study and disseminate information concerning costs, benefits, and risks involved. In the near future, liquids adoption should continue to be restricted by facility design. However, as more new facilities adopt upstream single-use systems at larger scale, we expect to see bulk liquids becoming increasingly adopted by such larger facilities as well.

As use of bulk liquids increases, culture media and buffer manufacturers will provide more customized manufacturing services related to such products. That will require some partnering with and educating end users about making liquid–powder core decisions as bioprocessing scales-up (similar to deciding between single use and stainless steel). Meanwhile, we may find major media and buffer companies establishing regional or even on-site liquid procurement options. Those could include regional "hydration centers" in major biotech hubs preparing liquids for local delivery, liquids manufacturing outsourced to contract manufacturing organizations (CMOs), and perhaps modular facilities manufacturing liquids on-site.

Powders always cost less (for comparable amounts of hydrated liquid) than the "same" products purchased as bulk liquids. But with powders, end users get an unfinished product that requires quite a bit of work before it can be used. Increasingly, bioprocessing facilities and process lines operating under the largest scales — such as anchored by ≤2,000-L (single-use) bioreactors — are prime candidates for cost-effective adoption of liquids.

Corresponding author ***Eric S. Langer*** *is president and managing partner, and* ***Ronald A. Rader*** *is senior director of technical research at BioPlan Associates, Inc., Rockville, MD; 1-301-921-5979; elanger@bioplanassociates.com, www.bioplanassociates.com.*