Updating the Economics of Biologics Manufacturing with 5,000-L Single-Use Bioreactors

A Paradigm Shift

By Mark Thomas Smith, Levi Morin Larsen, Kevin M. Mullen, and Jeffrey Johnson

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Biopharmaceutical pipelines with high production demands and low titers historically drove manufacturers toward large (e.g., 15,000 L) stainless-steel (SS) bioreactor facilities for efficiency's sake. Within the past two decades, single-use bioreactors (SUBs) with sizes up to 2,000 L have disrupted preclinical and clinical SS manufacturing networks, providing flexibility, modularity, and other advantages. Herein, we consider the implications and economics of large SUBs in upstream bioprocess. We compare 2,000-L and 5,000-L SUBs with 15,000-L SS bioreactors at manufacturing facilities and contract manufacturing organization (CMO) sites. SUBs of 5,000 L — such as the 5,000-L HyPerforma DynaDrive SUB — are promising technologies that provide volume efficiency, single-use (SU) flexibility, and cost effectiveness across a broad range of production volumes and titers.

Comparison of SS and SU Upstream Bioprocessing

A biologic's long journey from drug discovery through clinical trials is fraught with risks. After preclinical efforts to identify targets, leads, and finally drug candidates, the gauntlet of clinical trials begins. But ~90% of drug candidates that enter this stage fail (**1**). After a biopharmaceutical has passed this step and entered the commercialization pipeline, scaling up manufacturing is the next critical hurdle that must be cleared to produce a drug at the levels, speeds, and economies capable of meeting patient needs.

Traditionally, large biopharmaceutical companies have turned to facilities with multiple large SS bioreactors (e.g., 6 × 15,000 L), leveraging economies of scale to drive down production costs of anticipated new products from the clinical pipeline. In particular, biologics addressing large patient populations necessitate production volume to ramp-up substantially immediately after successful phase 3 trials. Large SS facilities have enabled rapid production increases if a facility is complete. That mitigates the risk of leaving myriad patients untreated and potentially billions of dollars on the table if production is insufficient to quickly meet the needs of new drugs.

On the other hand, the need to have most or all of a new production facility online at the end of phase 3 requires that a facility be planned and purchased without assurance of approved pipeline products. Large SS facilities can take three to five years (or longer) to plan, build, validate, and license. So the decision to commit to a facility must be made early, without guarantee that multiple pipeline products will be approved and that those products will require large production capacities. Of all drug candidates that reach phase 3 trials, 30–40% will fail. So the risk of premature commitment to uncertain future production needs looms large (**1**). And the capital-intensive nature of SS facilities places a large, undiscounted monetary outlay before product approval and eventual revenue streams.

SU technologies, particularly SUBs in upstream processes, are alternatives to traditional SS systems. SU-based facilities typically are smaller than their SS counterparts, so several SU facilities would be needed to match the full production capacity of a single SS facility (e.g., eight 6 × 2,000-L SU or three 6 × 5,000-L SU are about equal to one 6 × 15,000-L

SS). But small, modular SU facilities can be built more quickly and require substantially less capital than SS facilities. With shortened build times for SU facilities, biomanufacturers can commit to a facility build in mid to late clinical development stages, thus improving confidence of eventual product approval and reducing risk of economic loss.

Because SU bioprocess equipment subunits are flexible and mobile, they are easier to install than SS systems. Qualification of additional equipment also is simplified, including installation and operational qualification (IQ/OQ) concurrent with the operation of existing equipment. Such flexibility enables rapid equipment adjustments if a process or product requires modifications or improvements.

SU facilities also enable rapid product changeover in one to three days. In SS facilities, with long clean-in-place (CIP) and steam-in-place (SIP) validation cycles, product changeover can extend to seven days or more, or even weeks, mainly because of the need for disassembly of equipment for cleaning validation (e.g., disk-stack centrifuges). In the long term, extended product-changeover times can reduce the number of batches manufactured per year, decrease facility output, and increase cost of goods (CoG).

Additional SU-based facilities can be constructed when production demand exceeds existing facility capacity. But one large SS facility can meet production needs for multiple drug products because one 6 × 15,000 L facility at 3 g/L average titer can produce ~3,000 kg/yr. Assuming a median single-product market demand of 200 kg/yr, such a facility could support 15 different products (**2**). That capacity could be beneficial because only a single facility needs to be built, even for a large future pipeline or a large blockbuster, high-demand drug product. On the other hand, that suggests that such a facility might operate for prolonged periods at low use and low efficiency if a biomanufacturer does not have 15+ successful products move to commercialization, if products do not meet full market expectations, or if pipeline timelines falter. Biomanufacturers facing small pipelines and low production demands will rarely, if ever, reap the economies of scale offered by large SS facilities.

By comparison, smaller SU facilities might need more frequent buildouts over time to meet production demand of large markets and pipelines. Although multisite construction may seem to be inefficient, delaying construction of future capacity can be beneficial. SU facilities can be built to provide capacity for growing markets or new products in demand, thus leading to higher levels of use and lower capital expenditures (CapEx). That reduces overbuild and the ensuing underuse that typically is associated with large SS facilities. SU facilities can be built to copy all or most design factors of an existing SU facility, thus streamlining facility planning, shortening construction timelines, and enabling future facilities to focus on design and technology improvements (**3**). SU facilities also can be built to suit specific geographical markets and regional regulations. Meeting regional needs has become increasingly important to meeting governmental and supply security concerns in the COVID-19 era.

Another consideration during facility design is overall manufacturing performance. Innovations in cell biology and bioprocessing have resulted in high-intensity, high-titer cell cultures. The historical assumption that SS facilities always will be the economically sound choice for large-scale biomanufacturers is becoming less tenable because mid- to small-capacity facilities can satisfy future high-titer product demands and pipelines. Small, flexible, multiproduct facilities can satisfy diverse production needs (**4**).

New technology transfers are being paired with high-intensity cultures, so large-volume SUBs now can fill a void present over the past 15+ years in SU processing. A good example is the 5,000-L Thermo Scientific HyPerforma DynaDrive SUB. SU facilities promise to enable true economic efficiencies, even for high-demand biologics, while they continue to provide the flexibility and speed of SU technologies.

Considerations of Facility Economics

Myriad variables should be considered in facility economics. Below we highlight a few key considerations that heavily influence the economic efficiencies of a biomanufacturing facility.

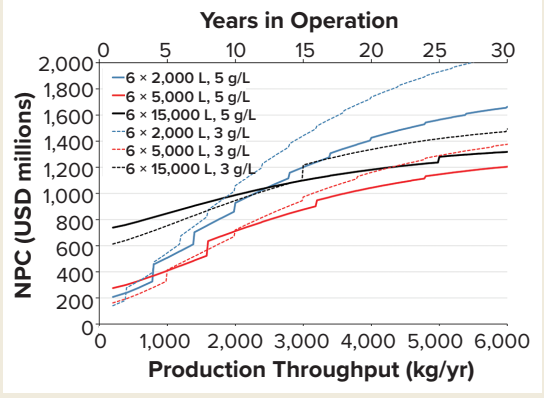
Total Anticipated Production Demand (kg/yr): How large is the pipeline being supported? How large is the mature market demand of each product in that pipeline?

Production Demand Ramp Rate (kg/yr/yr): What fraction of the pipeline will reach commercial approval? When are products expected to reach commercial approval?

Titer (g/L): How much does each bioprocess produce? What are the production performance ranges run in bioprocesses of multiproduct facilities?

Each of the above variables can affect a facility's economics significantly and thereby shift its

Figure 1: Perspective of total facility ownership costs in terms of net present cost (NPC); discounted operating costs are captured in the primary slopes of the lines. Steps in the lines represent discounted costs of a new facility required to support production demand. Data are at a 200-kg/yr/yr production ramp.



preferred configuration, depending on a biomanufacturer's pipeline and outlook. Below, we examine the influence those variables have on the economic considerations of facility selection and compare 6 × 2,000-L and 6 × 5,000-L SU bioreactor facilities with a 6 × 15,000-L SS bioreactor facility. We further consider the alternative production route that CMOs provide with 2,000-L and 5,000-L SUBs and a 15,000-L working-volume SS bioreactor.

Total Facility Ownership Cost

One aspect of facility economics is to examine the total cost to own a facility over the course of its lifetime and in terms of net present cost (NPC) (**5, 6**). An NPC perspective provides a quick impression of when facilities must be built with respect to production demand, as indicated by stepwise increases in each line in a graph of NPC. Concurrently, annual operating costs are indicated by the general slope of each of those lines. With this approach, both capital and operating costs are discounted with respect to time as determined by the production ramp rate, which embodies market demand growth and new-product commercialization. For example, 200 kg/yr/yr means demand increases by 200 kg/yr every year in a product facility network as a result of product demand increases and product launches.

Production ramps embody anticipated production need increases, which typically are caused by new product approvals and growing markets for existing products. For an estimated 200-kg/yr median single-product production requirement, a production ramp rate of 200 kg/yr/yr could represent a single median-demand product being approved annually (**2**).

Consider total expected market demand: A 6 × 15,000-L facility at capacity produces ~5,000 kg/yr at an average titer of 5 g/L (assuming 80% use). That suggests that a commercial portfolio with an expected production <5,000 kg/yr (25× products at 200 kg/yr average) will underuse a large SS facility. Thus, justifying the upfront capital outlay of a SS facility can be difficult for all but perhaps the largest commercial pipelines. By comparison, with similar average titer of 5 g/L, a 6 × 5,000-L facility and 6 × 2,000-L facility have production capacities of ~1,800 kg/yr, and ~750 kg/yr, respectively. That equates to 9× and 3–4× products at 200 kg/yr demand for the 5,000-L and 2,000-L facilities, respectively. The comparatively low capital costs of those SU facilities and their pipeline-appropriate capacities position such SS alternatives favorably for future bioprocessing.

Although the CapEx of SU facilities (2,000–5,000 L) are lower (represented by the left-most point of each line in Figure 1), operating expenditures (OpEx) (represented by the slopes of lines in Figure 1) are higher for SU than they are for SS facilities. The larger OpEx of SU facilities primarily are caused by the consumables-heavy SU systems. Tying costs to actual production is beneficial for reducing risks associated with large upfront capital outlays. Specifically, if production demand falters for SU facilities, you simply do not spend the cost of consumables, thus removing that risk. For SS facilities, regardless of pipeline and market success, expenditures are made up front in the form of facility CapEx, which depreciate regardless of whether a facility is used. Thus, the low upfront CapEx of SU facilities provide economic flexibility that SS facilities cannot. That is not without risk, however, because SU facilities do create a certain dependence on external vendors for assurance of supply (**7**).

The effect of titer on facility selection is immediately apparent: As titers increase, the need for large facilities diminishes, even if total production demand remains high. Furthermore, SU facilities become economically favorable despite having higher consumable operating costs, primarily because of capital costs associated with facility buildout. As Figure 1 shows, a 5,000-L SU facility has a lower NPC at all production levels than a 15,000-L SS facility does, thus highlighting the clear economic advantage.

Equation 1:

$$CoG_{weightedaverage\_year\_n} = CoG_{wa.n} = \frac{\Sigma_{i=0}^{n} (\frac{kg}{yr})_i \times CoG_i}{\Sigma_{i=0}^{n} (\frac{kg}{yr})_i}$$

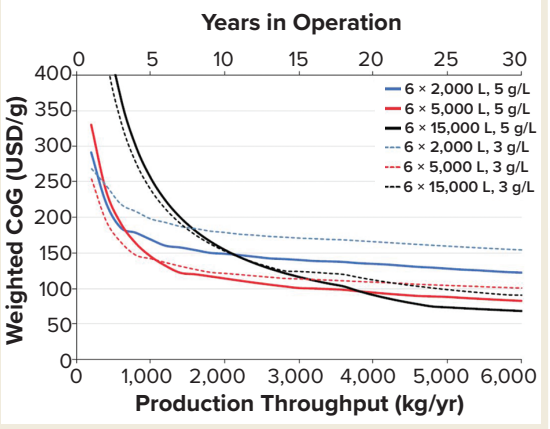
Although higher titers are the future, it is important to consider existing products in the facility because existing products may also have increased production demand. Considering this, 2,000-L SU facilities can quickly face a struggle to compete economically across titers, particularly lowered titers. In comparison, even at relatively low titers of ≤3 g/L, a 5,000-L SU facility promises to be more economically efficient than 6 × 15,000-L SS facilities, even out to larger production demands of >6,000 kg/yr, because they provide an economy of scale that is required by lower-titer processes along with the flexibility of SU technologies. That positioning makes future 5,000-L SU facilities attractive for production of future high-titer products, while remaining economically viable for current or legacy lower-titer processes.

Overall, the NPC perspective of total facility cost of ownership suggest that as titers increase and robust 5,000-L SUBs become available, the economic advantages of SU facilities become very significant. So there are few cases of production demand in which large SS facilities remain economically more efficient.

True Cost of Goods

An alternative perspective when considering the cost of a facility is the overall cost per gram of product. A facile, potentially misleading comparison would be to examine the CoG of a facility at full use. For example, at 3 g/L titer, a 6 × 15,000-L SS facility at full capacity results in a cost per gram of $90/g annually. But three 6 × 5,000-L facilities can match throughput results in $103/g annually — which is a ~14% reduction for the SS facility. However, such an outlook fails to capture the reality that production in a new facility ramps up with pipeline and market growth, which can lead to many years of underuse. That can increase CoG during the years that facilities are not used fully. Although operational CoG generally will reduce proportionally to facility use, the annual capitalized contribution remains the same regardless of use. So a more holistic view would be to consider the time- and use-weighted average CoG as shown in Equation 1, in which (kg/yr)$_i$ is the throughput at year *i*, and CoG$_i$ is the CoG at year *i*.

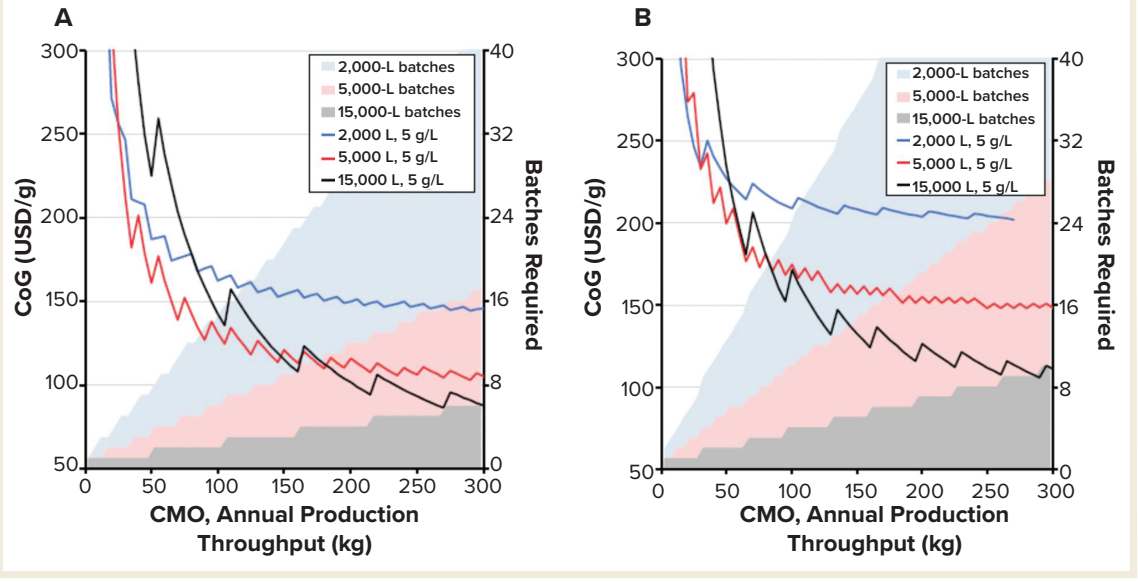
Figure 2: Weighted cost of goods (CoG) for greenfield facility builds; CoG in year 1 are weighted by CoG of previous years to highlight actual net present CoG at the given year and production throughput. Graph displays weighted CoG with a production ramp rate of 200 kg/yr/yr.



When that holistic view is taken, the large capitalized cost of SS facilities increases the weighted average CoG during facility ramp-up (Figure 2). The effects of inefficiency caused by an SS facility's underuse propagate throughout the facility's lifetime, preventing true economies of scale until high use is achieved (e.g., 5,000-L and 15,000-L CoG crossover for 5-g/L titer at ~3,800 kg/yr, ~60% use of an SS facility). Additional challenges that can hamper an SS facility's efficiency include product changeover and technology transfer of new products. As discussed above, long product-changeover times in SS facilities can decrease throughput, making it more difficult to effectively transition to new or other molecules in an SS facility. In our model, that potential changeover time is assumed to be zero, suggesting that weighted CoG in SS facilities is likely to be higher than depicted. Thus, facility selection must take carefully into account expected production demand ramp rate associated with market growth and newly approved products and each product's maximum-expected market demand.

Like the NPC perspective, the CoG weighted average (CoG$_{wa}$) approach suggests that SS facilities become comparatively cost-effective only for large production demands. For example, a 15,000-L SS facility crosses over 5,000-L SU facility after 20 years of operational ramp-up, when ~4,000 kg/yr are required (for a 3-g/L titer process at a 200-kg/yr/yr

Figure 3: Annual cost of goods (CoG) from a contract manufacturing organization (CMO); (A) CoG and batch count required of a process at 5-g/L titer, and (B) CoG and batch count required of a process at 3-g/L titer. Note that CMOs with large SS bioreactors will require a minimum number of batches, typically eight to 10 or more, due in part to the associated technology transfer costs, which are not included in this model.



ramp). Inefficiencies of underuse during production demand ramp-up have lasting effects on the weighted CoG, thus preventing SS facilities from being cost-competitive for decades. In addition, increasing titer shifts all weighted CoG downward, further emphasizing the efficiencies of SU facilities.

CMOs As Manufacturing Alternatives

CMOs provide an alternative to a full facility build for biologics production. They can serve multiple strategic roles in biologics manufacturing. Working with CMOs enables some advantages, including

- early route to clinical manufacturing, particularly for smaller biopharmaceutical companies without an established product or manufacturing suite
- delayed decisions to commit to or build a full facility, thus defraying associated CapEx risks
- baseline or overflow manufacturing capacity as production demand fluctuates.

But some potential strategic drawbacks to working with a CMO include

- technology transfer friction
- lack of manufacturing timing and control
- reservation costs and contract lock-in.

Smaller biopharmaceutical companies, particularly virtual companies with limited capital, can leverage collaboration with CMOs to work from process development to commercial manufacture. This process can help establish clinical success and potential long-term manufacturing without substantial capital outlay. CMOs also can be leveraged by large biopharmaceutical companies for clinical stages, but many of them have one or more dedicated sites for clinical manufacturing. The likely reasoning for bringing clinical manufacturing in house is to ensure that priorities and timelines can be maintained flexibly. High demand for the CMO space has led to reported average wait times for manufacturing slots of 9–18+ months (**8**). Long lead times make it critical to engage CMOs early for successful and timely partnerships (**9**). In comparison, some SU facilities manufacturers have publicized modular SU facilities that provide similar or shorter timelines from planning to IQ/OQ, suggesting a new path to timing flexibility (**10, 11**).

After weighing the potential benefits of working with a CMO, it is appropriate to consider next how to choose the right-sized CMO from an economic standpoint. We consider using a CMO with a 2,000-L SUB, 5,000-L SUB, or 15,000-L SS bioreactor and the number of batches required to achieve a desired annual throughput.

Leveraging CMOs obviates the necessity of investing extensive capital into a facility. However, most monoclonal antibody (MAb) production processes still will require relatively large upfront

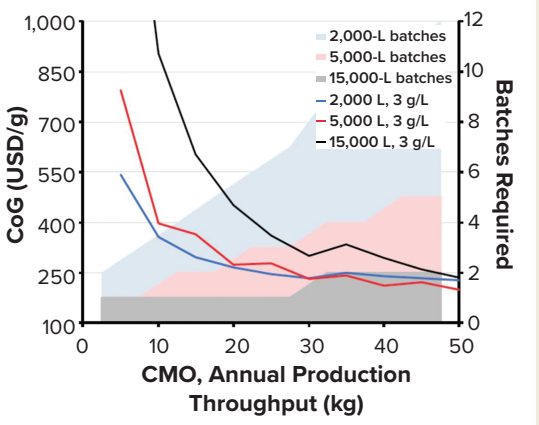
purchases of dedicated nonconsumables, including chromatography columns and specialty equipment. Such high-cost items warrant evaluation of equipment-use efficiencies or estimations of the number of batches per column that can be performed in a column's lifetime (number of cycles) or expiry window of those columns. That approach applies particularly when large reactors are paired with small annual production throughput (e.g., 15,000 L, 50 kg/yr), in which the size and cost of a protein A column alone can exceed the residual materials cost of a single batch. In such cases, low-volume production in all reactor volumes drives up CoG, particularly for 15,000-L reactors. The high costs of columns can be mitigated to an extent with high-cycle columns or other alternatives, which can reduce process costs and offer strategic implications in regulatory filings for clinical or commercial-phase productions.

In addition to considering the potential inefficiencies of nonconsumable use, use of the *n*th batch should be taken into account. It is important to evaluate how much of the final batch will be required to meet production demand and how much will be considered to be excess production. For example, if only 10 kg is required in a process with 3-g/L titer, a 15,000-L bioreactor provides nearly 10× material overage of the demand and an effective CoG more than twice of those of 2,000-L and 5,000-L bioreactors at the same production demand (Figure 4). Thus, for early and even certain late clinical phases, large SS reactors rarely make economic sense, and smaller batch SUBs offer a substantial cost advantage.

On the other hand, 2,000-L and 5,000-L SUBs are competitively priced with one another at low demands (<50 kg/yr), with 2,000-L SUBs at marginally lower cost at low-production demand (<30 kg/yr) (Figures 3 and 4). Above ~30 kg/yr production demand, 2,000-L SUBs lose their marginal cost advantage to 5,000-L SUBs, and 5,000-L SUBs remain lower cost compared with 15,000-L bioreactors up to 75–150 kg/yr production, depending on titer (3–5 g/L) (Figure 3).

Strategically, a 5,000-L SUB in a CMO is a propitious solution for products that are expected to be in the 30–150-kg/yr demand range from a CMO production capacity. In early clinical phases, CoG are competitive with 2,000-L bioreactors, even at low-production throughputs that typically are associated with preclinical and early clinical phase demands. Early phase production moving directly to a 5,000-L

Figure 4: Small-scale CoGs from a CMO; this is a zoomed-out price perspective of Figure 3B at 3 g/L. At very low throughputs, such as those required for early preclinical and clinical stages, one or a few reactions can readily achieve desired production demand for that stage.



production volume enables demands to be met smoothly and cost-effectively for 30–150 kg/yr, without the need for additional technology transfer and associated costs and risks. Indeed, even above 150 kg/yr, it might be desirable for production to remain at 5,000-L volumes because of costs and timeliness associated with technology transfer to a 15,000-L SS bioreactor.

If production demand grows to more than ~150 kg/yr, a 15,000-L SS bioreactor CMO becomes economically efficient and a clear economic choice. However, economic considerations would be balanced best with strategic considerations not owning a substantial fraction of the production process. Although CMOs operating 15,000-L SS bioreactors are likely to continue to play a key role in biopharmaceutical production, their economic and strategic value for median production demand is likely to shrink as a fraction of the CMO space as bioprocess technologies improve.

A New Option for Biologics Manufacturing

As production technologies improve and market requirements change, the biopharmaceutical industry's approach to manufacturing also must be updated. With titers increasing, SU technologies improving, and biologics targeting smaller markets, the economies of scale that were promised by large SS facilities are viable only for high-producing manufactures with an array of large-market drugs in the pipeline. Indeed, the blockbusters of yesteryear requiring metric tons of product annually are

becoming increasingly unusual as myriad smaller markets and orphan diseases are targeted. Furthermore, as biosimilars arrive in the market, the production demand of a single manufacturer can slacken. Overall, such shifts in the industry point to a need for smaller and flexible facilities that can be brought online on demand.

In that regard, the flexibility, modularity, and speed with which SU technology can be leveraged makes it advantageous for use in commercial manufacturing. Critically, the typical 2,000-L maximum volume for SUBs cannot compete efficiently with large SS facilities at medium to large production scales, particularly for legacy and moderate titer processes. The addition of 5,000-L SUBs provides a new level of implementation options that are generally more efficient than large SS facilities and 2,000-L SU facilities. Facilities with 5,000-L SUBs compete effectively with large SS-based facilities with respect to the following areas:

- NPC and CoGs
- low and high titer
- high and low market demands
- high and low production demands.

That outlook suggests that 5,000-L SUBs represent a new option for biologics manufacturing that provide economic and operational efficiencies that are difficult to find in SS facilities or 2,000-L SU facilities.

Thermo Fisher Scientific is pleased to introduce the 5,000-L HyPerforma DynaDrive SUB. For more information, go to thermofisher.com/dynadrive.

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