Finesse

Solutions for the future of biomanufacturing

Dear Reader,

Biomanufacturers today face new challenges to produce more efficiently, with increased quality. Many facilities have a mix of old and new equipment, often running independently on custom software. Intensified processes require a higher level of automation and often call for the rapid addition of sensors, pumps, separation mechanisms such as filters, and other peripherals. Regulatory requirements are driving an increase in data collection, including comprehensive electronic batch records. Finally, efficient facility management demands integration of the overall process with plant Manufacturing Execution Systems (MES). These challenges demand smarter solutions.

Over the past decade, Finesse has introduced a customer-centric, Silicon Valley approach to biomanufacturing to address these challenges. We provide highly configurable – even customized – solutions that are built to optimize your unit operations. We can automate your processes and data collection, control and harmonize third party equipment, and provide smart sensors, controllers, bioreactors, and skids. We believe that intelligent, integrated systems are essential to your success.

We are pleased to provide this compilation of materials as a thought-starter and hope you find some informative pieces to help you consider how your business meets today's challenges. We at Finesse would be thrilled to work with you to help drive innovation and profitability with solutions that fit your needs.

Cheers,

Barbara Paldus, Ph.D.
Vice President and General Manager,
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Article

The future of biomanufacturing

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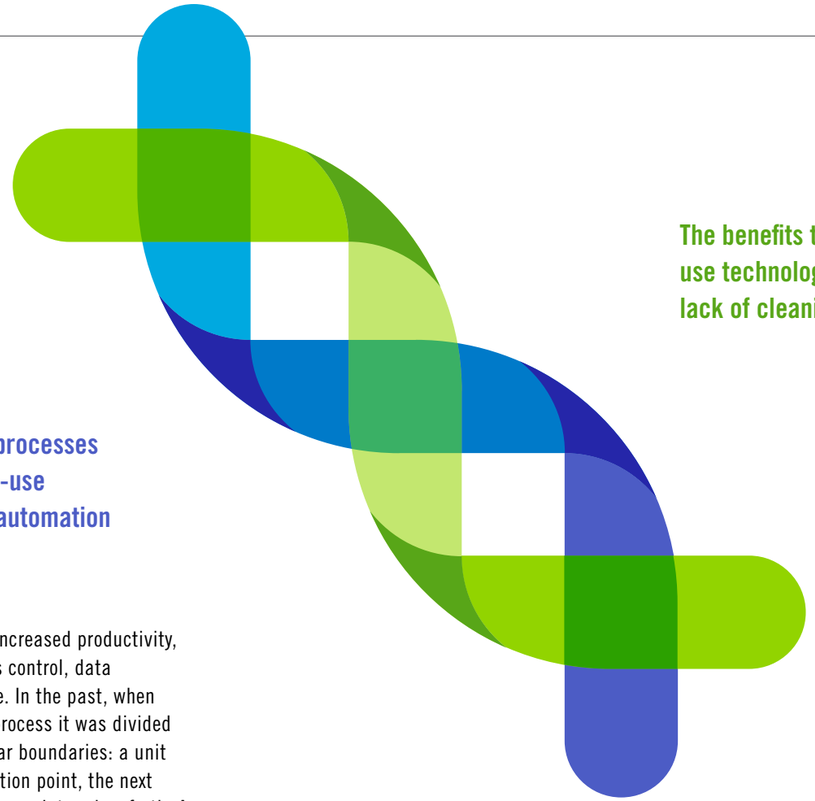

The biomanufacturing industry is undergoing a major shift, from single-product processes and stainless steel infrastructure to flexible, multi-product facilities using single-use technology. Though single-use is being widely adopted, there still exists a lag in automation and measurement to make the most use of the technology and data integration.

Next challenges in biomanufacturing

The next set of biomanufacturing challenges go hand-in-hand: (1) the scale-down of the bioprocess, and (2) perfusion/continuous processing (CP). The first is driven by the fact that production titers continue to increase; a 6 g/L titer is not uncommon anymore, and this figure is already past the limit of a lot downstream processing capabilities. The progress in production titers has created a gap in single-use processing, where the upstream productivity is mismatched with the throughput and capacity of the downstream equipment. For a typical 200 liter bioreactor — far below the 2000 liter scale — companies will need to run multiple cycles downstream (specifically chromatography) or run parallel single-use units to meet throughput demands, raising important questions about how to automate and configure the plant for that level of throughput. Chromatography equipment will have to be configured differently to handle the large volume, as will filtration equipment, as high amounts of protein will clog filters. In these cases, companies must ask themselves:

- Will we have automation to wash the filter?
- Will we have intermediate cleaning steps?
- How do we create the unit operation to handle that amount of protein?

CP offers many benefits, including increased productivity, but it brings complexities in process control, data recording and regulatory compliance. In the past, when engineers designed an end-to-end process it was divided up into unit operations that had clear boundaries: a unit operation batch followed by a transition point, the next unit operation followed by a transition point and so forth. A batch was comprised of this series of unit operations. This was regulated with unit operations in an organized manner.

With CP, there is continuous flow of material from the bioreactor through the last polishing step. How is a batch defined, now that product runs through all the unit operations continuously end to end? How is a process deviation documented when a batch fails? What are the affected materials in a failure? If a failure is detected at the end of the process, how does one know when the batch went bad, and can one keep the materials previously produced? With batch operations, it is much easier to determine the affected lots in a deviation.

The benefits to CP coupled with single-use technology are higher throughput, increased flexibility, lack of cleaning issues, and reduced operating costs. As downtime is minimized and titers are increased, products can be processed much more quickly than in standard batch operations. But as facilities scale processes down and link everything together, automation must be improved.

The benefits to continuous processing coupled with single-use technology are higher throughput, increased flexibility, lack of cleaning issues, and reduced operating costs.

Measurement in continuous processing

The addition of CP also drives the need for analytics. Continuous operations do not have the same intermediate cut-off points to perform analytics that batch operations do, so there is a need for in-line measurement to continuously measure the protein or antibody quantity at a certain point.

This presents a challenge for the analyzers themselves, as well as the issue of how process data is fed back and how the process reacts to it. In some cases, the analyzers simply do not exist yet, but where they do exist, they may take considerable time to provide results. If there is a reduction in quality or a failure during processing, this lag makes it difficult to determine the point in time at which the issue began and diagnose the quality or contamination issue. In the meantime, the CP process is producing materials and incurring operating expenses.

Automation: Addressing challenges and making use of existing infrastructure

Automation will play a major role in facilitating new processing strategies such as semi-continuous, perfusion, and continuous and will help bridge the gap for companies with existing infrastructure. It will enable more efficient dosing/feeding in the bioreactor, buffer dilution, pH changes in the process, and creation of gradients in the chromatography. In a continuous process with large amounts of buffers, automation will allow facilities to dilute concentrated buffers in-line to avoid sizeable liquid storage.

Updating existing infrastructure

One of the attractive qualities about single-use is that the components are easy to modify, unlike stainless steel equipment, which can require pipe cutting, welding, and the addition of ports. In a single-use context, the alteration is simply adding another tube, a sensor, or a junction by melting plastic. Though modification in the single-use sphere is relatively uncomplicated, automation must be added to maximize the potential of the technology. Flexible plug and play control systems will become critical in enabling older generations of single-use equipment to carry out more complex operations. Additionally, components such as pumps and valve controls must be scaled down and made more accurate for continuous and smaller-scale processing. These physical improvements will be necessary as dose amounts become smaller — at a certain point, companies may hit a limit where a dose is a single droplet coming from a tube, which puts the burden of accuracy (or availability/existence) on the system components themselves.

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There is an interdependency between measurement and real-time "action" that requires global process optimization

Global process optimization: from islands of data to integrated facilities

In the past, users would normally start with unit operations of a batch process, but as processes move from single process steps to continuous, these "islands of data" must be tied together through a layer of automation for communication. There is an interdependency between measurement and real-time "action" that requires global process optimization.

OPC from Microsoft, a protocol that allows for real-time vertical integration, provides connection between different kinds of controllers (e.g., Siemens or Emerson DeltaV), data storage in one large repository, and also allows all the unit steps to interact through the upper layer. A facility can also add a manufacturing execution system (MES), such as Werum or Syncade (Emerson), so that the plant network architecture [OU1] consists of multiple layers, which perform the following functions:

- **MES layer:** allows the vendor to create and optimize a recipe based on all of the unit steps, and subsequently operates the automation islands in synchronicity with one another and accounts for transition steps to complete the batch. This upper layer contains the master recipe and electronic records of each batch.
- **Harmonization layer:** OPC provides open connectivity between controllers and the MES layer, effectively tying the islands of data together.
- **Control layer:** oversees and controls each unit operation and gathers process data in one repository (called a historian database)
- **Measurement layer:** provides the process parameter information to the control and MES systems

Without the "upper layer," data is not integrated and there is nothing to tie the transition between operations together. The integrated approach is a more streamlined process because a facility's information systems and actions can function as a whole. If a problem is detected in one part of the process, the batch can be stopped before consuming a significant amount of materials (if a protein were of suboptimal quality, a facility would not want to waste the chromatography resins to purify a protein that would not go into an end product).

Integrated facilities

The benefit of integrated facilities is to provide user flexibility, and, in the case of multi-product facilities, the ability to reconfigure the process train depending on the campaign of the molecule being produced. The ability to mix and match equipment is extremely important, as certain vendors may have better solutions than others for a particular process step. This flexibility also has benefits for supply chain integrity and price: if a vendor has a quality or supply issue, or if they have a price elevation over time, the option to add a new supplier can provide stability or reduce costs.

Reconfiguring the process train

For multi-product facilities, it is critical that reconfiguring the process train is as fast and easy as possible. Because two products may have very different titers, variables like equipment selection, the order in which equipment is used, and the number of steps or cycles per piece of equipment should be easily re-configurable.

The traditional MES system is designed for one product and one process, with the goal of maximizing yield at the lowest possible cost. But multi-product facilities must be able to rapidly respond to product (and thus, process) changes using existing equipment in cases like the following:

- Depending on the vectors the CDC issues each year, a facility producing flu vaccines may need to reconfigure the product mix or amount they will produce that year.
- A company may have various orphan drugs in its pipeline, and depending on a change in demand, the population, or a new approval, they may need to ramp up production quickly.

The top MES layer is what can allow a facility to transition from Product A to B to C in a validated manner quickly, as it enables a facility to take unit operations in and out of utilization without losing integration.

Closing thoughts

The current challenges in biomanufacturing will be overcome with innovation in both automation and in measurement. The complexity of CP means that the challenge goes beyond simply automating each step, but being aware of the interdependence and transfers in between those steps, which will make the monitoring more complicated. Advanced sensors, yet-to-be developed, will further enable the flexibility of multi-product and CP facilities. But with the ability to measure new parameters comes a need for more sophisticated automation to react to the new information, which may, in turn, require new measurements.

With many companies building new plants based on single-use, the technology has clearly moved into production in the last 5 years. The limits of bioprocessing have changed, where companies (such as Juno Therapeutics or Novartis) hope to extract stem cells or CAR T cells from an individual, process them in a "micro-factory" and then re-inject them into a patient. Each "micro-factory" is envisaged to integrate all required process steps to produce an injectable — conceptually comparable to a medical device. With hundreds of micro-factories creating personalized products under one roof, facilities will have to ensure robust data management, process control, and sample tracking are in place to be certain that the benefits are maximized safely and that end products are delivered to the right patients. Biomanufacturing companies will have to address hurdles, but the future is filled with opportunities for novel process control, analytic technologies, and ultimately, more effective therapeutics.*

A universal control platform

G3 systems are modular by design, so the hardware configuration can easily evolve with any process, and integrate additional functionality and third-party peripherals as needed.

Universal control systems

Universal controllers combine with our flexible software to enable all scales of upstream and downstream processes. Based on the DeltaV® control platform from Emerson Process Management, Finesse TruBio® software is an open, fully configurable software solution that can control any bioreactor from lab through production scale.

Finesse has designed its bioreactor hardware to be highly configurable and easily adapted to both cell culture and fermentation applications. By leveraging SmartParts™ components, all G3 controllers have the capability and flexibility required to optimize any process, whether in the laboratory or in a cGMP-compliant manufacturing plant. The G3 control platform incorporates innovative features that enhance the productivity, quality, and reproducibility of batch, fed batch, or perfusion processes.

Upstream process scale-up strategies need not be limited to one bioreactor vendor. G3 controllers have been designed to easily connect to most brands of glass, single-use, or rocking bioreactors.

G3Lab Universal

The G3Lab™ Universal controls bench-top bioreactors (single-use or reusable up to 20L) and rockers (up to 50L). The system consists of a utility tower and a TruFlow™ gas manifold. G3Lab Universal controllers minimize footprint while maximizing process flexibility. G3Lab Universal systems enable fully traceable cGMP process scale-up or scale-down in the laboratory environment.

G3LAB UNIVERSAL COMPATIBLE BIOREACTORS

Glass	**Total Volume (L)**
Finesse SmartGlass	1, 3, 7, 15
Applikon	1, 2, 3, 5, 7, 15, 20
Sartorius STR®	1.6, 3, 6.6, 13
Eppendorf (NBS)	1.3, 3, 7.5, 14
Single-Use	**Total Volume (L)**
Millipore Mobius CellReady™	3
Eppendorf (NBS)	1, 5, 14, 50
Xcellerex XDR™	10
CerCell CellVessel	all sizes ≤ 75
Rocker	**Total / Working Volume**
Finesse SmartRocker	50L / 25L
GE WAVE Bioreactor®	50L / 25L
Sartorius Biostat® RM	50L / 25L

G3Lite+

G3Lite+™ systems control single-use Thermo Scientific HyPerforma™ SUB (50L to 2000L) and Millipore Mobius CellReady™ (50L to 200L) bioreactors. G3Lite+ controllers are fully self-contained, movable units that can be operated singly or networked. They are engineered to optimize capital cost without sacrificing the option of use in cGMP-certified production facilities.

G3LITE+ COMPATIBLE BIOREACTORS

Single-Use	**Total Volume (L)**
Thermo Scientific HyPerforma™ SUB	All Sizes ≤ 2000
Thermo Scientific HyPerforma™ SUF	All Sizes ≤ 300
Millipore Mobius CellReady™	All Sizes ≤ 200
Xcellerex XDR™	All Sizes ≤ 2000

G3Pro Universal

The G3Pro™ Universal controls single-use bioreactors (25L to 2000L) and mixers (50L to 2000L). The system consists of a utility tower, a TruFlow gas manifold, and a vessel adapter box specific to the vessel being controlled. G3Pro controllers can be mounted on fixed skids or movable carts, can be quickly reconfigured or expanded for multi-product applications, and have complete cGMP documentation.

G3PRO + G3FLEX COMPATIBLE BIOREACTORS

Single-Use	**Total Volume (L)**
Thermo Scientific HyPerforma™ SUB	All Sizes ≤ 2000
Thermo Scientific HyPerforma™ SUF	All Sizes ≤ 300
Millipore Mobius CellReady™	50, 200
Xcellerex XDR™	50, 200, 500, 1000, 2000
Pall PadReactor®	25, 50, 300, 600, 1350
Sartorius STR®	50, 200, 500, 1000

G3Flex

G3Flex systems are custom designed to run unique or highly complex processes in challenging environments (e.g., BSL-3). G3Flex systems can be fully integrated or modular. A typical system will include a utility tower, pump tower, and gas manifold, with optional accessories for perfusion, harvest, or gravimetric feeding.

Product Focus

Smart software

The Finesse Smart software suite harmonizes and upgrades existing, proprietary upstream and downstream control systems that may no longer meet current bioprocess needs. Our software is a cost-effective means to extend the useful life of existing capital, unify the user interface for a variety of controllers, and aggregate process data in a common, robust DeltaV historian.

Photo courtesy Lincoln Journal Star

TruBio

TruBio provides automation hardware independence, allows for seamless acquisition of third party data and unifies all upstream process trains to enable easy scaling from development to full production. TruBio also supports SCADA and OPC connectivity to third party devices. It has been developed with the latest GAMP revision methods and is validated for cGMP applications.

TruChrom™ and TruPur™

TruChrom and TruPur have recently been developed to control common third party chromatography and purification skids. Both are based on the same robust, validated software platform as TruBio and allow for integration and control of downstream processes.

SmartLab™ data management software

SmartLab software features make it easier to view and manage your lab data. Automated data collection saves time and resources, and generates fewer errors than manual methods. Operators can remotely monitor equipment in real time on easy-to-navigate screens. SmartLab also provides statistical data analytics and reports that can be viewed, retrieved, and emailed in various formats.

Features and benefits include:

- Intuitive user experience
- Automatic data collection
- Seamless data aggregation
- Reporting flexibility
- Statistical data analytics
- Real-time equipment monitoring
- Quick return on investment

Before SmartLab

Finesse bioreactors

Finesse offers bioreactors in rocker, autoclavable glass and stirred-tank single-use models, which can be controlled with Finesse and third-party controllers. All are designed to optimize yield for R&D, cGMP and personalized medicine applications.

SmartRocker™ rocking bioreactor

The Finesse SmartRocker allows the user to configure the rocking motion from a smooth waveform that minimizes shear force for sensitive cell lines to an aggressive motion that maximizes oxygen transfer for robust cells having high oxygen consumption.

Each Finesse SmartBag bioprocess container is embedded with a novel SmartPuck sensor comprising three sensors (pH, dissolved oxygen, and temperature).

SmartVessel™ 3-liter single-use bioreactor

The Finesse SmartVessel provides all the features and functionality of the 3-liter SmartGlass bioreactor in a single-use implementation.

The SmartVessel is shipped gamma-radiated and requires no autoclaving, which reduces man-hours and accelerates process development. Constructed from durable materials, the SmartVessel is latex-free, phthalate-free, BPA-free, animal component-free and ISO10993/USP CLASS VI-compliant.

SmartGlass™ bioreactor series

Finesse SmartGlass bioreactors are available in 1, 3, 7 and 15-liter sizes and are designed to be fully hygienic to ensure complete process sterility and minimize lost batches.

SmartGlass vessels have been optimized to minimize downtime for cleaning and setup. The motor adapter uses coupling adapter windows and an alignment marker for effortless assembly. The head plate design allows easy assembly and disassembly of components for rapid reconfiguration.

Finesse single-use sensors

Finesse has designed an innovative range of single-use sensors with a patented optical design using only USP Class VI materials. Finesse single-use sensors are sterilized in place, so that process sterility is guaranteed. They are pre-calibrated, and provide full traceability information using a gamma radiation resistant SmartChip™.

TruFluor pH and TruFluor DO

TruFluor pH and TruFluor DO single-use sensors consist of an optical probe with an embedded temperature sensor.

SmartPuck pH+dO2

Embedded in each Finesse SmartBag bioprocess container, the SmartPuck sensor comprises dissolved oxygen, pH, and temperature sensors in a compact assembly. SmartPuck sensors leverage the technology behind the Finesse TruFluor pH and DO sensors.

TruTorr® headspace pressure sensor

The TruTorr pressure sensor is a single-use solution for measuring headspace pressure.

Single-use solutions for cell culture scale-up and technology transfer

A question and answer session with
Barbara Paldus, Ph.D.
Vice President and General Manager
Finesse, part of Thermo Fisher Scientific

What types of single-use equipment are most accepted by industry and what is still lacking in these technologies?

Single-use media and storage bags are the most routinely used in bioprocessing. Single-use bioreactors up to 1,000L volumes have also gained significant ground. However, robust single-use sensors are now available but not integrated into these bioreactor platforms; the mainstream adoption of pH and dissolved oxygen optical sensors is hopefully imminent.

What trends do you see in single-use technologies?

We see the increasing adoption of single-use sensors for upstream bioprocessing for pH, dissolved oxygen, and pressure. We see increasing interest in 2,000L bioreactors for large-scale production. Finally, we see increasing efforts being placed in developing small-scale single-use bioreactors with integrated optical sensors for research and process development.

What are the main requests by single-use technology end-users?

On the upstream side of single-use, integrated single-use sensors and intelligent automation are the two most significant requests. Price has also become a touch point with customers. On the downstream side, there is increasing demand for single-use solutions and sensors as well.

What processes are easiest to transition to disposable technologies and why?

Media mixing and buffer preparation unit operations are the easiest to transition to disposable technologies because the processes are very robust and do not involve significant real-time measurement or control. The single-use vessels employed most mimic their stainless steel counterparts in geometry and functionality so that process transfer to single-use can occur rapidly. Because change-over of the solution composition is frequent in mixing applications, the single-use liners and bags present an immediate advantage as they are sterile and prevent any form of cross-contamination from batch to batch.

The next easiest process to transition is cell culture as again the bioreactor vessels and sensors have been modeled on their stainless steel predecessors. While process automation is more complex in cell growth than in mixing applications, control solutions exist today that put single-use skids on equal footing with their sterilizable counterparts. In fact, overall titers in single-use bioreactors are increasing to levels that allow for higher yields in smaller vessel volumes today. Moreover, the flexible configuration of single-use bioreactor bags provides an advantage in the development of continuous processes in single-use over stainless steel.

Do you see any existing or emerging companies currently gaining competitive advantages through single-use processes?

Emerging and existing CMOs are focusing on single-use technologies. In most cases, single-use enables emerging companies to create capabilities at greatly reduced capital expenditures and gain a foothold in the market. For established companies, single-use allows them to increase capacity quickly, diversify their offering and more fully utilize their capacity.

How accepted are single-use processes with regulators?

Single-use technologies appear to be gaining not only widespread acceptance but support with regulators. While existing cGMP processes are likely to continue using stainless steel infrastructure, many new products are going directly into single-use production equipment.

If a pharma company were looking to adopt single-use technologies for the first time, what advice would you give them?

There are three key considerations:

1. Consumable or single-use operating costs will far exceed the initial capital investment, so do not lock yourself into a single-source situation, especially on the bag films and tubing sets. Qualify at least two vendors for each unit operation of your processes to ensure security of supply chain and price. Consider using universal controllers for each unit operation to facilitate the interchange of bioreactors, filters, and chromatography columns.

2. Transition as many process steps to single-use as early as possible in the development phase, to not duplicate process optimization and validation efforts. Growth or separation yields can be quite different in single-use equipment, so the earlier you know what works and what doesn't for your cell line and your product, the more informed decision you will make when planning a single-use pilot or production facility.

3. Don't shy away from hybrid solutions, because certain downstream unit operations do not yet exist in single-use, especially for large-scale production processes. Select the production volumes that make sense at each process step, and create a best-of-breed solution. Many stainless skids work well with CIP sterilization and do not require significant plant infrastructure such as high pressure steam.

What are the hurdles to broader adoption of single-use technologies?

The major hurdles today are bag prices and bag standardization. The industry will need to recognize that consumables will become commodities like in other industries, and create the standards bodies to allow for interoperability of equipment and consumables.

What are the most common mistakes you see end-users making when considering or implementing single-use products?

End-users forgo training in the technologies and assume that they require no attention to detail. This can often lead to misuse of the equipment compared to its intended use. Also, a lack of due diligence on vendors can lead to wrong decisions and failed expectations.

What do you see as the future for disposable technologies specifically regarding their adoption, materials of construction, and processing capabilities?

At Finesse, we see the future for disposable technologies as quite bright. The shorter lead times, easier operation, and consistent yields that result from a transition to single-use will continue to drive the conversion to single-use. Having witnessed the early adoption cycle (2006 to 2011), we believe that single-use applications in mixing and cell culture are now firmly entrenched, and will continue to expand for orphan drugs to biosimilars. As downstream technologies evolve, filtration and chromatography steps will follow in adopting of single-use platforms.

In the last three years, most of the large consumable vendors have updated their films to minimize not only leachables and extractable profiles, but also by-products from the multi-layer film tie layers. Many suppliers have introduced at least one new film indicating progress in producing higher purity materials for both bags and tubing sets. We see ongoing development and evolution of these materials as the community understands the requirements on these plastics better and optimizes them for bioprocessing.

Finally, with a strong incipient movement to continuous processing underway, we see processing capabilities increasing with perfusion in smaller volumes. This should ultimately lead to solutions for personalized medicine.*

Article

Continuous processing optimization with smarter tools

Barbara Paldus, Ph.D.
Vice President & General Manager
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Due to a paradigm shift in the pharmaceutical industry, there is rising pressure to come up with faster, more cost-effective ways to produce drugs for the patients who need them.

As orphan drugs and personalized medicine begin to replace traditional blockbuster products, pharmaceutical companies are looking at new and innovative ways to quickly and efficiently deliver drugs to target populations in the thousands rather than the millions. In addition, the need for lower drug prices has been pushed into the spotlight not just by regulators on Capitol Hill, but also by the advent of biosimilars. As a result of these changes, industry experts must find a way to produce drugs that addresses the issues around both drug pricing and time to market while also maintaining quality and profits.

Based on production volume, most of today's blockbuster drugs are still manufactured in stainless steel facilities. Yet, these facilities take at least five years to launch and offer little to no flexibility in the face of changing demands. In addition, traditional and fed batch production models used in these facilities require huge development costs and are fairly substantial in terms of ongoing manufacturing. If a drug is more successful than expected, many companies are not prepared to scale up to meet the new demand. At the same time, a drug that doesn't meet its original demand expectations while a large stainless steel facility is being built for it results in a significant loss of non-recoverable capital expenditures. Conversely, for orphan or precision medicine drugs, rapid product turnover in manufacturing is far more important than capacity (volume).

Single-use technology (SUT) has long been viewed as a viable solution to this growing problem. It offers the flexibility to change a production configuration to meet demand while also offering a number of other cost benefits, such as savings related to the elimination of clean-in-place (CIP) and sterilization-in-place (SIP) processes. However, traditional and fed batch models fail when trying to adapt to single-use flexibility due to the required rewriting of code and revalidation.

The best way to utilize the flexibility of single-use is to pair it with a modular automation system in a continuous processing configuration. This setup eliminates the limitations and burdens of manual control while optimizing the throughput from upstream to downstream. Despite the many benefits this paradigm provides, the industry still has many concerns about continuous processing. Through the application of technology available today, manufacturers can reap the significant cost savings provided by a continuous processing strategy while also applying the controls necessary to successfully monitor and control it.

Efficiency and flexibility through end-to-end processing

When it comes to facility utilization, the cost per gram of an antibody is directly correlated to the usage of the facility. A large facility operating only three months of the year leaves nine months during which the capital invested in the facility simply lays fallow. Smart factories that use continuous processing and automation enable a high degree of utilization due to process flexibility and multi-product production. The adoption of these modern facilities, while an intimidating change for some, is the next logical step in a history of process evolution.

Dating back to the 1980s, production was achieved through very simple batch processes with little involvement by personnel, limited monitoring, and minimal to zero process control. As the demand for higher titer increased, drug processes became more sophisticated and the industry moved toward a fed batch model. A process in this type of model took between 7 and 20 days to complete, depending on the complexity of the fed batch and what was being done to the cells.

As the realization that parameters played a critical role in reproducibility grew, experts began adding pH, dissolved oxygen, and temperature monitoring to the bioreactor to increase success. To coax out either the protein or the monoclonal antibodies desired, a substrate was introduced or the temperature was shifted. In addition, more refined process control was implemented, including various strategies for how to feed and ship the cells.

Over time, this manipulation of production platforms resulted in much higher titers but also questions around how to appropriately adjust downstream operations. In the past, when titers were low, batch time for upstream was about two to three weeks with downstream processing taking about two to five days. As titers improved, upstream could run for around two weeks, and the downstream became a bit more intense. This reduced the capacity mismatch but did not eliminate it. With continuous processing, the upstream and downstream are unified. Upstream no longer runs constantly with downstream skids being activated and utilized for only small increments in time. Matching the upstream and downstream capacities drives down the production costs to the raw materials and leaves a process that can be used over and over.

Higher titers and batch concerns fuel continuous processing fears

The pharmaceutical industry does not have a reputation for being open to change, and for good reason. Not only are human lives at risk, but

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The automation solutions available offer unique and innovative ways to overcome the platform's biggest challenges.

also millions of dollars can be lost should a problem occur with just one batch. However, while fears about change are valid, concerns regarding continuous processing may just be the result of a lack of knowledge about a platform that is still so new to, and sparsely used by, the industry.

One concern is related to the handling of higher titers. Some feel that despite the added efficiency a continuous processing strategy offers, it is going to be more costly to implement. Thankfully, companies like Thermo Fisher Scientific, GE, and Sigma-Aldrich offer sophisticated media support for cell cultures with higher titers. In addition, cell lines are now more robust. As continuous processing becomes the well-trodden path as opposed to the novelty, the timeline for development will be reduced, ultimately resulting in cost savings.

Higher efficiency and production can also be achieved through the smaller footprint of continuous processing if capacity is utilized properly. For example, when running perfusion, which retains the cells while fresh media flows into the bioreactor, the cell population may take five days to reach its peak. Once the cell population is at and maintained at its peak, the downstream can run for up to 60 days at this maximum cell population. This is especially beneficial with slow-growing cells because once they have finally grown and built up their population, a large quantity of product can be produced and purified. Thus, both the media and chromatography column will be fully utilized with little or no waste; in a fed batch process, harvest after two weeks limits the use of the downstream columns and effectively restarts the long waiting period to reach peak population and product production after each batch. Therefore, in fed batch mode, upstream and downstream efficiency and material utilization are reduced as cell productivity is in a start-and-stop mode, thereby reducing overall productivity of the facility. In a multi-product facility running continuous processing, the output and productivity of the facility can grow as more lines are added.

Another concern about continuous processing is related to the continuous flow of product from a production skid and what effect this will have from a regulatory perspective. With traditional methods, a batch is easily defined as the final product or material from a sequence of processes. In a fed batch environment, there is an exact point when a process begins and ends and a well-defined plan of how to manage it. When something goes wrong, it is much easier to determine how much product has been affected. If materials are constantly flowing through a continuous processing platform, where does a batch begin and end? This is where automation can play a key and enabling role. Constant monitoring of materials notifies operators when a problem occurs, and any material collected before that error is usable. There is also the concept of micro-batching, where a batch is defined in time periods. By defining a batch with specific time frames, a batch can be deemed "good" or "bad" based on when it was produced.

How can automation be used to overcome objections to continuous processing?

With continuous processing, there are many moving parts operating at the same time as well as data and batch records that need to be managed. To do this successfully, this type of platform must be:

Scalable — enable rapid process transfer into higher production volumes in order avoid repeating optimization at each scale-up step

Flexible — allow for multiple products to be run through the platform while also easily validating them

Universally controlled — ensure multiple bioreactors from any vendor can be controlled at a commercial scale; allow for rapid changeover using preset configurations.

Because of the implementation of SUT in a continuous processing platform, the design can be adjusted based on client needs. However, the principle of feeding in fresh media and nutrients while constantly producing products remains the same. With a perfusion setup, this step can require up to 12 pumps (compared to only a few in a fed batch operation). An offline analyzer with an integrated auto sampler allows for monitoring and control of viable cell density during this process by pumping the sample into various analytical instruments and sending data back for analysis.

Cell separation can be done in a variety of ways. However, because the method of perfusion is more suitable for unstable active pharmaceutical ingredients (APIs), it has become the most widely used in a continuous processing platform. Perfusion can be done using one of the five different cell retention methods listed here. These methods require pressure monitoring to ensure optimal filter performance, which is critical with single-use bioreactors and required for feedback control and alarming.

Tangential flow filtration (TFF) — Flows media through a filter while holding cells back. The filter is then flushed to put the cells back into the bioreactor.

Alternating TFF — Retains the cells and puts new media back in, and then the cells can be flushed back through the filter. Pressure monitoring is required for both forms of TFF.

Floating filter filtration — Retains cells inside the bioreactor while removing spent media from the vessel and backfilling it with fresh media. This method is popular for rocking (wave) bioreactors.

Acoustic separation — Separation is performed in a resonator chamber with an acoustic field generated by a transducer. Ultrasonic forces produced in the standing wave field aggregate and hold the suspended cells against flow. These cells are then flushed back into the bioreactor. This method is popular with glass vessels up to 20 liters.

Centrifugation — For cell culture where the product is excreted by the cell, a fixed volume is removed from the bioreactor and backfilled with fresh media; the supernatant is separated from the cells in the centrifuge and harvested while the cells are flushed and returned to the bioreactor. This method has been scaled up to 1000L in volume.

Like every other part of a continuous processing platform, perfusion requires automation and monitoring of key process parameters. A considerable amount of data will be generated for regulatory compliance and to prove the process is running the same every single time.

Smart systems, which are a valuable way to capture this data, also mitigate the need to train and retain highly skilled operators. In terms of process control, these systems offer unique advantages. These include weight management of several feeds with only one scale, pre-calibrated sensors with long-term drift resistances, cascade control, preconfigured settings, and custom software. They are also specifically designed to address the challenges of process intensification.*

Summary

While continuous processing is perceived as adding complexity to biopharma operations, this complexity is not only manageable with automation, but it is also a way to improve the industry's aging business models. While skepticism exists, the automation solutions available offer unique and innovative ways to overcome the platform's biggest challenges, much as cruise control and auto parking have enabled for drivers of cars. Doing so requires not just knowledge but also the willingness to push the boundaries of modern technology to improve patient care. Innovative biopharmaceutical companies are already leading the way in this arena, as significant advances in bioproduction efficiency are expected over the next three to five years.

Automation, modularity allow mAb biotech to cut scale-up time

Created in cooperation with Life Science Connect

Original developers of biosolutions and products, especially those facing the debut of biosimilars in core markets, have an urgent imperative to reduce manufacturing costs via increased productivity and yields. In turn, this drives a wide range of business decisions, including capital investment, process choices and design, and equipment selection.

To this end, for example, bio-developers are adopting more sophisticated processes, such as perfusion, to address low titer cell lines and reduce raw material costs. They're also seeking more sophisticated and flexible R&D and PD capabilities in several ways by deploying equipment to enable simultaneous development of multiple products; automate rapid experimental design and implementation; optimize processes; and gain better analytical insights, especially for PAT and regulatory compliance.

"With the Finesse SmartSystem, we can cut out the errors along with a lot of time and cost to ensure faster time to market and, ultimately, greater profitability and competitiveness."

Introducing AlphaMab, a fully equipped bio-developer and producer

AlphaMab Co. Ltd, a fast-growing bio-developer and producer, is one such company looking for those kinds of capabilities. Founded in 2009 and located in Suzhou, a city about 60 miles northwest of Shanghai, AlphaMab's R&D center consists of more than 60,000 square feet of offices and labs, fully equipped for investigating, commercializing, and producing the latest in biologic products.

Its BDS and FFP suites are built to meet the rigorous cGMP requirements of the CFDA, FDA, and EMA. After those facilities opened in 2013, the Jiangsu CFDA certified them for biologics manufacturing. Facilities also include a pilot plant, GMP production, and a fill-and-finish plant.

At AlphaMab, more than 100 scientists are engaged in a wide range of activities that include target validation, hit screening, H2L, PK/PD, pharmacology, cell line construction, process development, scale-up GMP manufacturing, and IND filing. Currently, the staff is involved in almost 60 projects including treatments for autoimmune diseases, blood clotting issues, diabetes, infections, tumor immunology, cancer, ophthalmology, and osteoporosis. Of these, nearly 20 are technology transfer projects.

AlphaMab uses lab-scale bioreactors in 1L, 3L, and 15L sizes, with antibody production projects in the 5 g/L to 10 g/L sizes, and sometimes more. While it still uses glass vessels in its R&D and PD labs, the company has adopted single-use bioreactors across all its cGMP manufacturing facilities, instead of the glass and stainless steel vessels it used before.

Many challenges of scale-up, especially across different projects

According to Dr. Ting Xu, CEO at AlphaMab, the company facilities have quickly matured: "We now have a number of development platforms, including ones for prescreening as well as yeast and phage displays, so we can screen humanized antibody sequences plus nano antibodies, too. Our protein engineering capabilities include a patented mixture platform and an EI-specific platform. And our process R&D and pilot production platforms include DHDP production, in addition to our fill-and-finish platform."

Xu points out that scaling up production from lab to pilot to full commercial production raises many challenges — especially across many different projects. "Mainly, the key difficulties are understanding the depth of process and the impact of parameters on process scale-up," he says. "These must be known in order to guide how we set our parameters for consistency during scale-up, so we can ensure cell growth, viability and yield and, ultimately, product quality."

AlphaMab has been an early adopter of single-use technology to help boost productivity in its cGMP manufacturing, while also reducing scale-up cycle times and costs. The company used to favor stainless steel equipment, but migrated to a single-use model for many reasons.

"For starters, stainless steel is expensive and time-consuming to deploy," Xu explains. "Once deployed, it has a high risk of cross-contamination, thus requiring time and resources to clean, sterilize, and validate. Then there's constant maintenance that commands even more time and money. The business case for single-use technology is compelling on many levels."

What AlphaMab found unique about the Finesse G3 SmartControllers for bioreactors is their versatile ability to scale-up and scale-down.

Automation, a bio-development and production accelerator

One complement to single-use technology is having a consistent automation platform across AlphaMab's different upstream and downstream phases, which the company defines using a Quality by Design (QbD) approach.

"Because each process is special," Xu says, "it's difficult to have one common platform for all projects. But starting from a small lab project to a complete process scale-up using one platform, especially the controller, can help to increase our success rate. Of course, this depends on the accuracy of sensors and stability of the controller, which is what we were looking for."

Specifically, for AlphaMab's glass-vessel, bench-top bioreactors in its R&D and PD labs, the company deployed a Finesse G3Lab Universal modular control configuration. This consists of a utility tower and a TruFlow gas manifold, which are sized to minimize the footprint while providing company researchers with maximum process flexibility.

In its cGMP facility, AlphaMab installed single-use Thermo Fisher Scientific HyPerforma bioreactors, each using a Finesse SmartSystem with G3Lite SmartControllers. The system consists of a control tower featuring Finesse SmartPart transmitters and actuators, the latter controlling four mass flow controllers.

Finesse SmartParts are intelligent, modular, plug-and-play hardware building blocks for measuring and controlling bioprocesses. They have built-in diagnostics and factory calibrations, can be auto-detected by AlphaMab's network, and provide optimized local control of its various bioprocess functions.

"Previously we were using glass, bench-top bioreactors from Applikon and Sartorius, but chose the Thermo Fisher Scientific platform with Finesse G3 controllers because they offer proven performance, stability, and reliability, plus Finesse provides good service and support," Xu says.

Finesse SmartSystem scalability and flexibility

What AlphaMab found unique about the Finesse G3 SmartControllers for bioreactors is their versatile ability to scale-up and scale-down. "The scalability of the Finesse G3 control platform helps us facilitate process transfers from 0.5L to 2,000L," says Xu. "This enhances the quality, productivity, consistency, and reproducibility across our processes, whether we're using batch, fed-batch, or perfusion."

Another distinction that sets the Finesse G3 SmartControllers apart is their adaptability to third-party systems and peripherals. For example, in addition to the

"Previously we were using glass, bench-top bioreactors from Applikon and Sartorius, but chose the Thermo Fisher Scientific platform with Finesse G3 controllers because they offer proven performance, stability, and reliability, plus Finesse provides good service and support."

Thermo Fisher Scientific bioreactors AlphaMab deployed, the Finesse G3 SmartControllers are compatible with single-use, glass, and rocker systems from Applikon, Sartorius, Eppendorf, Millipore, Xcellerex, CerCell, and GE. This enables customers to automate a wide range of both legacy and new-build infrastructure using what they determine to be best-of-breed solutions.

In combination with the Finesse G3 SmartControllers, AlphaMab has found the Finesse TruBio® DV (DeltaV®) software extremely useful in controlling the bioprocesses of its cell culture operations. Finesse developed the hardware-independent software system based on the Emerson Process Management DeltaV control platform.

"Having the DeltaV automation control engine in the TruBio DV software was an important factor in our selecting the Finesse automation platform," says Xu. "It really gave us confidence we were making the right choice."

What's more, he notes, the Finesse automation controller platform is proven globally, with more than 1,500 lab-scale and nearly 500 large-scale bioreactors installed and operating across more than 60 customers. "This helped reduce any sense of risk in choosing Finesse G3 controllers for use in our R&D and PD labs as well as for use in the single-use bioreactors we use in our cGMP manufacturing," he says.

Finesse TruBio DV software, pre-configured and ready to use

The cGMP-compliant TruBio DV software comes pre-configured with algorithms for controlling bioprocess parameters such as pH, dissolved oxygen, temperature, and pressure. With tridundant sensor loops as well as unlimited gas and liquid addition capability, the software can be used with glass vessels, wave rockers, and, like the Finesse G3 SmartControllers, most brands of single-use bioreactors.

Xu reports that his staff especially likes the flexibility, easy operation, and precision control of AlphaMab's Finesse automation control system. "In particular, they like the ease of configuring parameters for DO and pH control. This has helped them more easily and quickly define and then use the same scale-up standards for the same projects," he says.

Executing scale-up standards for one project — or many projects simultaneously

"In the scale-up process, you have to find the key control parameters that affect your critical quality attributes, but each project has its own characteristics," Xu explains. "For example, some may be more sensitive to speed, some to pH, some to the concentration of CO2. By finding your own control range of key parameters, you can conduct a successful scale-up process. The Finesse SmartSystem platform is a huge help in accelerating the technology transfer phases of our operations by enabling us to execute a scale-up standard across an entire project."

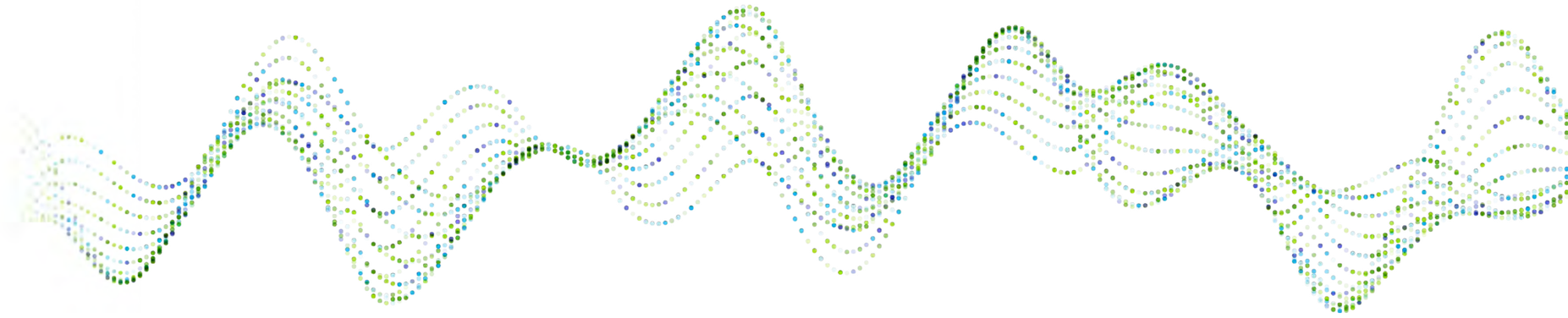
By migrating from glass to single-use bioreactors while also automating with the same scale-up standards using the Finesse SmartSystem with G3 SmartControllers and TruBio DV software, AlphaMab achieved two key goals: it reduced its scale-up cycle times to as little as 12 months, and it upheld its QbD standards, which ensure the quality of its process. The Finesse SmartSystem is also helping AlphaMab to manage the scale-up and technology transfer of as many as 20 projects at a time.

"Doing multiple scale-ups, each with their own technology-transfer standards, without an automation platform would be nearly impossible, not to mention error-prone," says Xu. "But with the Finesse SmartSystem, we can cut out the errors along with a lot of time and cost to ensure faster time to market and, ultimately, greater profitability and competitiveness."★

Article

Is automation the disruption pharma R&D needs?

Barbara Paldus, Ph.D.
Vice President & General Manager
Finesse, part of Thermo Fisher Scientific



Optimizing pharma for efficiency and accuracy

According to a recent report from PhRMA, U.S. biopharmaceutical companies spend more than 13 times the amount of R&D per employee than all other manufacturing industries.[1] This is because potential drug candidates require lengthy and complex testing to ensure they are safe and effective for patients. Yet, despite all of the money invested, only about 12% of the drug candidates that make it into Phase 1 testing are approved by the FDA. While knowledge about a disease and its potential treatment is not lost with "failed" candidates, innovative research tools must be used to avoid spending time, money, and effort on products that have limited endpoint efficacy. Through the implementation of automation, data management, and analytical technologies, pharma has the opportunity to breathe new life into a number of areas of the biologics drug development process.

Technology and automation have completely transformed our world, from how we communicate to how we conduct business — and even how we spend our leisure time. They have had a profound impact on almost every industry, but most notably on industries such as finance, automotive, chemical, and home management. In manufacturing, it has become clear over many decades that technology and automation can be used to drive quality and efficiency. These benefits are especially critical in the pharmaceutical industry, where there is an added focus from companies and regulators on the use of technology and automation to improve drug development processes. For example, the FDA process analytical technology (PAT) initiative focuses on improving the understanding of manufacturing processes using data analysis, process monitoring, and continuous feedback. Through the continued development and application of automation, non-value-added activities are eliminated, allowing for increased speed, efficiency, and accuracy.

The same potential rings true for technology and automation in drug development R&D, where pharmaceutical scientists and researchers are bogged down with manual tasks such as bioreactor cleaning and tubing management, or manual data entry and retrieval. In addition, because the systems used to run experiments are fairly complex, the people who design the equipment are often the only ones who truly know how to run them. This is commonplace in smaller companies where there are fewer resources. Through the use of automation, R&D experts can alleviate the burden of many of the aforementioned time- and labor-intensive tasks. Their time can then be used to focus on activities that leverage their expertise and extensive training, such as figuring out the metabolic pathways to optimize cell lines and expression systems and selecting the optimal way to increase titer. Appropriately designed user interfaces for automation systems can also enable scientists to create sophisticated design of experiments (DoE) to collect and analyze valuable data.

Only about 12% of the drug candidates that make it into Phase 1 testing are approved by the FDA

Furthermore, R&D experts and their clinical counterparts can perhaps avoid facing the difficult and time-consuming task of determining how to scale up a process that was created with very simple lab equipment to one that is run in a sophisticated and automated manufacturing environment. In the event of regulatory approval, having the R&D and cGMP processes automated with the same platform facilitates rapid tech transfer and saves on both time and associated cost of scale-up/scale-down.

Using data to make better decisions

In today's research environments, data is often collected manually and stored in Excel spreadsheets. Not only is this time-consuming and prone to error, but the data is often not collected in real time. While spreadsheets are useful, they are not the optimal database for this field. Databases (such as SQL) for the upstream and the downstream process data can be used to form a library from which global process optimization can be achieved. Additionally, having this data and real-time analysis provides researchers (or the manufacturing group) with the capability to detect issues as they arise. This allows some ability to proactively implement change as needed and eliminates the time spent collecting batch statistics to determine where errors may have occurred. By leveraging technology and smart automation systems, knowledge about multiple areas of the drug development process is gathered into one interface, where scientists can analyze it and make connections between observations.

Finally, as regulatory oversight moves closer to R&D, the integration of analytical information from R&D process runs, data management, and data harmonization become critical. For development and scale-up of a process, accurate data management and accurate process measurement are needed from the beginning of when the cell line was developed. This batch data can then accelerate the regulatory review by providing additional support to demonstrate batch optimization and reproducibility, which is often a high-risk, high-dollar part of the regulatory approval process. In the future, as process analytics become an integral part of the batch record and regulatory approval review, the data about the process will become as important as the process itself; only then will the FDA PAT initiative, defined in the Guidance for Industry PAT as a "Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" truly fulfill its original promise.

...Smart facilities demonstrate "the ability to quickly move from upstream to downstream automation without compromising the project budget or timeline."

Doing more with less: the R&D budget struggle

A 2016 global life sciences report from Deloitte identifies squeezing profit margins, patent expiries, and rising R&D costs as factors driving more focus on operational efficiencies.[2] Taking into account the increased scrutiny of healthcare costs, the explosion of the biosimilar market, and global competition, it becomes clear that pharmaceutical companies are faced with a daunting task of delivering innovative therapies while maintaining profit levels and maximizing shareholder value. The report notes, "Achieving these often-conflicting objectives is likely to require that companies transform their business and operating models and embrace disruptive technology advancements that can concurrently reduce costs and speed time to market for new products and services." While the majority of new drug development costs are still embedded in the clinical trials, having a robust and scalable production process for the drug is equally critical so that revenue can be quickly generated post approval. Therefore, efficient process development remains crucial to commercial success.

An example of this type of process transformation is embodied in the Finesse SmartLab™ platform announced earlier this summer. SmartLab includes the Finesse TruBio®, TruPur™, and TruChrom™ bioreactor control software suites as well as Finesse SmartSystems. It leverages the G3Lab™ Universal hardware platform that is being rapidly adopted by the R&D community. In addition, the SmartLab system allows for the harmonization of analyzers and bioreactor controllers from a wide variety of suppliers while also offering statistical analysis tools and electronic batch reporting. This flexibility enables researchers to move away from using Excel spreadsheets and gain efficiency in the development of new biologics. This in turn reduces the R&D costs of investigating new drug candidates that are still at high risk of failure.

SmartLab is the first end-to-end data management system to integrate leading third-party DoE software, multivariable data analysis (MVDA), recipe management, data visualization, and seamless analyzer connectivity. This offers life sciences research and process development groups a novel and cost-effective data archiving solution, centralized data/recipe mining for DoE or statistical analysis, and remote access to process reports, plots, and live trend visualization against a "golden batch." SmartLab can also notify researchers by email or text when batch reports are ready for viewing, when online values are out of range, and when network connections are down.

The Final Step: Scaling From R&D To cGMP

To satisfy the needs of late-stage regulatory testing (Phase 2 and 3), the R&D process must be scaled to batch sizes that are at least several hundred liters. This intermediate step between research and full production also serves as an opportunity to optimize cell productivity and viability. However, in today's facilities, the research automation tools are often provided by different vendors than the larger-scale development and production tools. This leads to a difficult transition due to a lack of cohesive data management and confusion around process parameter transfer.

An effective approach that avoids many of the aforementioned pitfalls was announced earlier this summer. Iceland biopharmaceutical company Alvotech opened a hybrid facility in the University of Iceland Science Park that leverages automation in an effort to drive operational efficiency.[3] According to the release, the facility enables the company to "produce higher yields, significantly reduce labor and capital expenses, and maintain flexibility in operations management systems." It uses the same automation in both R&D and production to enable rapid scale-up and technology transfer using the Finesse TruBio, TruPur, and TruChrom platforms. Through the use of these systems, a process developed in a 10-liter glass vessel can now be rapidly scaled up to a 50- or even 1,000-liter scale in process development and then transferred as an electronic recipe file to a 2,000-liter production scale. Other advantages of this approach to global factory automation were outlined in the announcement:

- The open architecture allows Alvotech to choose the equipment best suited and priced for its operations, regardless of equipment manufacturer in both R&D and cGMP production.
- Process flow can be designed in a modular and scalable manner while maintaining quality and regulatory compliance in electronic batch records at the same time.
- The flexibility of the system lets a user select the level of automation required for each unit operation in both R&D and cGMP production.
- Users can focus simultaneously on the compatibility of single-use materials between upstream and downstream for global process yield optimization. The same materials are used from R&D through cGMP, just at different volumetric scales.

Overall, these types of smart facilities demonstrate "the ability to quickly move from upstream to downstream automation without compromising the project budget or timeline." It is this type of change that will allow the industry to survive in a new era that requires a fine balance among innovation, efficiency, and cost.*

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2. Deloitte, 2016 — https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2016-life-sciences-outlook.pdf

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Article

Iceland provides many opportunities for Alvotech, producer of biosimilars

Bruce Blau

Photos courtesy Alvotech

In June 2016, the world's attention was captivated by a modern-day David and Goliath sports story, as the national football team from the small island of Iceland reached the quarter finals of the UEFA Euro 2016 soccer tournament.

Competing against powerhouse teams like England, Portugal, and The Netherlands, a country with a lower population than Wichita, Kansas, managed to win two games, tie two others, and suffer only one loss.

Coincidentally, another event was also celebrated in Iceland in June of 2016—one that might well have a significant and lasting impact on the cost of health care around the world in years to come.

On June 3rd, a ribbon was cut and champagne poured to toast the shiny new Alvotech biomanufacturing facility in Reykjavik. The 13,000 square-meter structure, located on the campus of the University of Iceland, will be at the forefront in creating products known as biosimilars.

Pros and cons of biopharmaceuticals

Biopharmaceuticals have proven themselves to be extremely effective for a wide array of ailments, ranging from infectious diseases, to neurological disorders, to diabetes and arthritis[1]. They not only provide remedies for patients, some of whom previously had few other effective options, but also come with far fewer side effects than conventional chemical-based medications. The side effects from typical, chemical-based medicines can not only add to the misery of an existing ailment, but also increase costs to a patient by way of additional medications and procedures.

The major downside of biopharmaceuticals is, of course, the cost to develop them. The Tufts Center for the Study of Drug Development reported[2] in 2014 that it took $2.6 billion to develop and win approval for a new drug. These expenses are understandable, considering both the time and manpower required to design a new drug, and the clinical trials that are required to test them.

But when a manufacturer finally has a drug approved by the U.S. Food and Drug Administration (FDA) — 51[3] were approved in 2015 — the rewards are lucrative. A biopharmaceutical manufacturer can reap many billions — Gilead Sciences, maker of the hepatitis C drug, Sovaldi, pulled in $24.5 billion in 2014[4] — and patents assure the companies of exclusivity to keep profits rolling in for years.

The massive profits go hand in hand with exorbitant prices that the manufacturers are able to charge for new biopharmaceutical drugs, which often puts the patients who desperately need these medications in an impossible situation. In many instances, health insurance companies will simply not pay for biopharmaceutical treatments. Without the help of insurance, many families have to either choose to let a loved one suffer or die, or go very deeply into debt in order to pay for the medication. Patients in developing countries are often completely shut out from the possibility of obtaining them at all.

Biosimilars arrived on the scene in recent years as an alternative that could offer some promise to patients in this predicament. Sometimes confused with "generic" chemical-based medicines, there is an important difference[5] with biosimilars: generics are identical to their brand-named counterparts, while biosimilars are not. The U.S. Affordable Care Act states that biosimilars have "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."

Biosimilars are developed in the same manner as the original and offer the very same benefits. However, since they are manufactured without the costs of research and development, biosimilar manufacturers can offer the drugs to patients at a fraction of the price of the original drugs.

Alvotech is born

Bringing down the cost of biopharmaceutical products and making them more available worldwide were major motivators for Alvotech's founder, Robert Wessman, and business development executive Emmanuelle Lepine. They felt passionately about getting these medications to not only patients in the West who were priced out of these vital medicines, but also patients in third-world nations, who simply have no access.

Eef Schimmelpennink took the CEO reins in 2016. He noted in his remarks at the facility's grand opening that one of the top-selling biopharmaceutical drugs on the market made $15 billion dollars the previous year, which was equal to Iceland's entire gross domestic product for the year. He felt that this was not a sustainable economic model for a society and was determined to have Alvotech change that trend.

Choosing Iceland

After considering various locations in the world, Wessman and his team settled upon Iceland for the plant's location for a number of important reasons. Iceland happens to occupy a strategic location between the world's biggest markets—the United States and Europe. Alvotech also wanted to avail itself of the attractive pool of talent that Iceland has to offer. The company specifically chose to erect their facility at the University of Iceland, so they could be in place for future collaborations with the university.

The intellectual property (IP) environment was also a factor. Iceland has no IP covering the antibodies that Alvotech planned to develop. That meant that the company could get a valuable six-month head start over its competitors when releasing their products.

Yet another feature that appealed to the founders was the abundance of green energy in Iceland. The island touts the fact that almost 100% of the energy used there is obtained from geothermal energy and hydroelectric power.

Partnering with Finesse

Finesse Solutions entered the picture in 2013, before Alvotech broke ground on the Reykjavik facility. Finesse was making a name for itself in upstream automation and was chosen to design the manufacturing process for the new facility. Dr. Barbara Paldus, Finesse CEO, was brought into the discussion later that year, as was Dr. Fjalar Kristjansson, who would become Alvotech's COO.

The Finesse team examined Alvotech's original process concept design and, over the following months, came up with alternate ideas. Little by little, the small Silicon Valley company impressed the Alvotech executives to the point where an agreement—and then a contract—was signed in summer 2014.

The two companies visited major vendors around Europe to determine which equipment from each vendor would be, as Paldus put it, "Best of Breed." Components were chosen from Thermo, GE and Danaher/Pall to complement Finesse's own products. The resulting plan is a mixture of 1000L and 2000L high-yield disposable fermentation and downstream processes, with a fill-and-finish line for vials and prefilled syringes.

While very knowledgeable in all aspects of the technology, the Finesse team was nevertheless in uncharted waters. At that time, Alvotech's plant was to be the largest single-use facility project of its day—a complete, end-to-end upstream/downstream automation and Manufacturing Execution System (MES), which even some of the industry's largest manufacturers did not produce at the time. Finesse had even developed two completely new software platforms for the downstream portion—TruPur and TruChrom.

Fortunately for Finesse, they had earned the trust of the Alvotech team, who preferred smaller, more agile companies with whom they could work closely. Finesse already had engineers and support personnel who could supplement Alvotech's small, but growing team, obviating the need for them to hire staff more quickly than they had intended.

Major challenge for both companies

The road to the ribbon-cutting was not a smooth one, however, for either company.

For Finesse, one of the biggest challenges was creating a manufacturing process for products that were just taking shape at the time. Because Alvotech's production plans were still being finalized, Finesse assembled an aggregate of experts together to try to develop generic processes for generic cell lines.

While it seemed a monumental task, the directive to devise a flexible, agile process allowed the Finesse team to devise a rather impressive product. They created a biomanufacturing system that would be so adaptable that it could be used for any process that Alvotech could conceive.

On the Alvotech side, construction of the very modern and high-tech facility was on an ambitious schedule and the progress, at times, did not appear to be fast enough to meet it. Schimmelpennink visited the building site in October 2015, recalling that it seemed to be just a set of walls and floors, with nothing else built in. Kristjansson, however, was confidently predicting opening the facility a mere eight months later.

Combining the traditional Icelandic "Þetta reddast!" attitude (the saying translates to "it will all work out okay!"), along with dedicated work by his construction team and some good fortune, Kristjansson followed through and the facility did open as scheduled. Alvotech now has six drug products in its pipeline, with production expected to start at the end of 2016.

Alvotech's design for success

The design of the Reykjavik plant was made to be completely streamlined. Components are received on the basement floor and then proceed upwards in the building to be processed. Quality control tests are completed in the basement and are sent up to the first floor lab for production. On the first floor, upstream processing scales the cell material from 400ml up to 2000L, and then sends it directly to downstream processes, such as protein affinity purification and diafiltration. On the third—fill-and-finish—floor, the product is mixed with buffer material, sterilized, and then placed in vials and syringes. The third floor activities also include inspection, cold storage, packaging and final quality control.

Schimmelpennink cites the integrated structure of his company for his optimism for success. Alvotech has built this new state-of-the-art headquarters and manufacturing facility in Iceland, and has established five other locations around the world. Two Alvotech sites in Germany—in Jülich and another site currently being acquired in Hanover—are focused on R&D and, among other functions, perform cell line development, analytics, and protein characterization. Clinical and regulatory project management development is done in the Zürich facility.

Beauty as well as function

Walking into the Reykjavik facility is not the experience one would expect when entering a manufacturing plant. When he planned the building, Wessman devoted significant attention to aesthetics. Part of this came from having the structure on the campus of the University of Iceland; it was expected to be an attractive building, especially sitting next door to a well-known landmark, The Nordic House.

Wessman is, himself, an art aficionado and it is said that he has a significant collection in his own home. So, Wessman and his architect, Pálmar Kristmundsson, commissioned the Paris-based painter, Erro, to create large colorful paintings that cover 40 square meters of walls throughout the offices and common areas in the building.

Additionally, world-renowned Icelandic sculptor Sigurður Guðmundsson was brought in to create works of his own that are featured prominently inside and outside the facility. One of the structures adorning the atrium is made of polished steel and stands six meters high. The other artwork, which stands in the water feature in front of the building, is called "Data Pool." It consists of two stone monoliths, which appear to be modernized versions of the Easter Island "Moai."

Future for Alvotech and the biosimilars industry

As commercial production takes off, Alvotech plans to fit its second active pharmaceutical ingredient (API) suite, already constructed, with another production line that would accommodate commercial needs. This line would be built in the other half of the Reykjavik facility.

In the long term, Paldus sees Alvotech as having a significant effect on the industry, potentially changing the biosimilars landscape. More importantly, she feels that Alvotech will play a large role in expanding the availability of biopharmaceuticals in emerging markets.

Alvotech's sister company, Alvogen, covers over 35 markets, worldwide, including the U.S., Central and Eastern Europe, and Asia-Pacific. With such a distribution network, they stand a chance to change the paradigm of how drugs are manufactured and sold in emerging countries. By getting the products to an affordable price point, Alvotech might well prove that Iceland can, in fact, provide affordable drug products to the rest of the world.*

Endnotes

1. http://www.fromhopetocures.org/advancing-science/fighting-disease

2. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

3. http://www.forbes.com/sites/bernardmunos/2016/01/04/2015-new-drug-approvals-hit-66-year-high/#220367411044

4. http://www.fiercepharma.com/special-report/top-15-pharma-companies-by-2014-revenue

5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

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