

Accelerate Your
Process Development With High-Throughput,
Single-Use, Fully Automated Bioreactors

White Paper

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Introduction



ambr® 250 is a fully automated bioreactor system offering independent, parallel control of 12 or 24 single-use bioreactors

Biopharmaceutical R&D teams everywhere face the same dilemma in the development of biologics and vaccines: they must increase productivity to meet strict budgets and deadlines, while maintaining or improving data accuracy.

In order to meet market demands, biopharmaceutical companies are increasingly turning to bioreactor technology that allows for high-throughput process development and optimization for both microbial fermentations and cell culture processes.

Costly Failures and Slowdowns

Upstream process development can be a lengthy undertaking, with most processes taking 12-24 months to develop. Some of the most common hurdles for developers to overcome are process run failures and operational slowdowns such as long bioreactor turnaround times or downtime caused by scheduling runs around staff availability.

Run Failures Mean Rework

Experimental runs can fail for many reasons, mainly related to human and equipment errors (sensor, agitation motor, and controller malfunctions account for many of those failures). With an industry standard failure rate of 8 to 10%, this represents a major area for improvement for the entire biopharmaceutical process development industry. Bench-top reactors in particular are prone to scientist errors and sensor/probe failures due to intensive setup processes, manual liquid handling, and reuse of probes and sensors.

Operational Limitations

With bench-top bioreactors, testing must be scheduled based on scientists' availability to sample, so the bioreactors sit idle at times when they could be in use and moving development forward. Additionally, bench-top reactor setup can take anywhere from 30 to 90 minutes, with connection of tubing and air lines, probe calibration, etc. Factoring in the additional effort required for breakdown and cleaning after a run, standard bioreactors consume a significant amount of employee hours. When several bench-top reactors must be run in parallel, these inefficiencies are multiplied, taking up scientists' time instead of allowing them to concentrate on the more technical aspect of process development.

Enter the ambr[®] 250



ambr 250's easy connect bioreactors are fully integrated with sensors and filters

Over the past 4 years, automation has gone from a "nice to have" technology to a necessity for maintaining a competitive edge in process development for biologics and vaccines.

The award-winning ambr[®] 250 is a single-use, high-throughput fully automated bioreactor system, available in 12- or 24-reactor configurations. The system, deemed "a major breakthrough in bioprocessing technology," recently won two major BioProcess International (BPI) Awards: Best Technology Application, Upstream and Best Collaboration (between Tap Biosystems and Merck).¹

It is comprised of three parts:

- Easy-connect single-use 250-ml bioreactors (available in both microbial and mammalian configurations)
- Automated workstation
- User-friendly software with audit trail and process control

The ambr[®] 250's single-use vessels come fully integrated with precalibrated sensors and liquid and gas filters, so setup is a streamlined, 3-step process (click to view Setup, Run Mode, and Automated Processing video clips):

1. Place vessel in holder and secure with a clamp
2. Connect pH probe
3. Clamp the vessel liquid manifold to the pump feed port

The automated liquid handler performs accurate media combination and addition, and can be used for automated sampling, inoculation, and even media preparation.

Rise in Productivity

With a setup time as low as 3 minutes and the ability to run and sample any time, the ambr® 250 was designed to change the way your R&D lab operates.

Fully integrated single-use technology precludes the need for time-consuming sensor calibration, setup, and cleaning, while the automated liquid handler helps to reduce failures and contamination, and increase accuracy. Takeda, who evaluated the system for use with stable cell and transient protein production, noted the increased productivity. They found that with the ambr® 250, "experiments can be turned around in 3 to 4 hours versus 1 to 2 days."²

You can perform runs and sampling day or night, as the ambr® 250 is equipped with audit trail and control software. Sampling can be triggered automatically when deviations occur, transitioning your lab to 24/7 operations without 24/7 staff. Dr. Mark Carver, Senior VP of R&D and Innovation at FUJIFILM Diosynth Biotechnologies explains that the new system "... will allow us to produce 'High Throughput Scale Down' data for better process understanding, thereby enabling our customers to proceed more quickly to larger scale manufacture."³

Activity	10 L Scale	Benchtop Scale	ambr® 250
Preparation	1.0	1.0	n/a
Sterilization	2.0	1.5	n/a
Set-up	0.5	0.5	0.1
Inoculation	0.16	0.16	0.03
In-run activities: Sample/induce/feed <small>*Off-shift hours, where employees stay late or return to the lab on nights/week-ends to complete tasks</small>	0.16 (off-shift hours*)	0.16 (off-shift hours*)	n/a
Harvest and/or drain	0.2	0.17	0.2
Kill off/Clean	2.0	1.3	0.12
Total (hours)	6.02	4.79	0.45

Table 1. Summary of time consumed (in hours) by bioprocess run activities in 10 L scale, Benchtop Scale, and the ambr® 250. The ambr® 250's productivity is over 90% higher than that of both the 10 L and Benchtop Scale.

Speedy Integration for Staff and Lab

Designed with scientists in mind, a key benefit of the ambr® 250 is its ease of use: scientists can become proficient with the system – running up to 24 bioreactors – in just 3 days.

With standard bench-top reactors, it can take 2-4 months for a scientist to become comfortable running 10 or more bioreactors at once. Modular software in the ambr® 250 with preprogrammed code allows scientists to build complex processes without prior programming knowledge. A research associate from Takeda stated that the software is intuitive and "both the machine and software were easy to learn and use." These features help your operations move faster upon implementation, but they also pay dividends over time as new employees come onboard.

In addition to the short training time, the equipment can be integrated into new or existing operations without major facility changes. Its relatively small footprint compared to 12 or 24 individual bench-top reactors means it can be placed anywhere in the lab – each system measures 1 meter deep and the 12- and 24-reactor configurations are 2 and 4 meters wide, respectively.

Superior Scalability

Because the ambr[®] 250 is geometrically similar to standard bench-top bioreactors, data obtained from an ambr[®] 250 is comparable to that obtained from the lab or pilot plant. This enables scientists to seamlessly scale-up directly into large pilot scale, bypassing a process development batch size to save valuable time and money in the process development program.

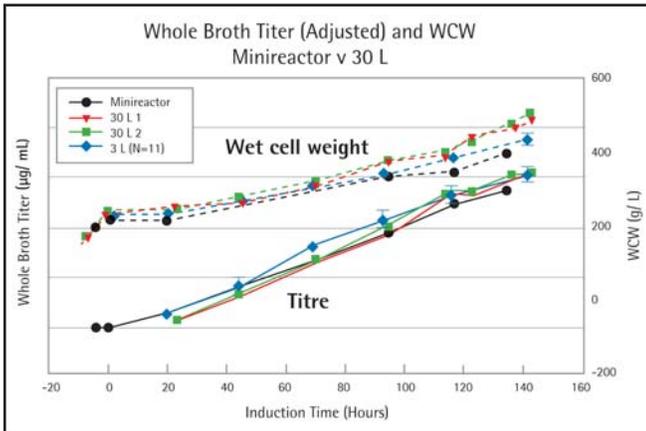


Figure 1. Scale up profile of microbial culture. *Pichia Pastoris* fermentation-0.25 L to 30 L. (Courtesy of Rachel Bareither & David Pollard, Merck Rahway)

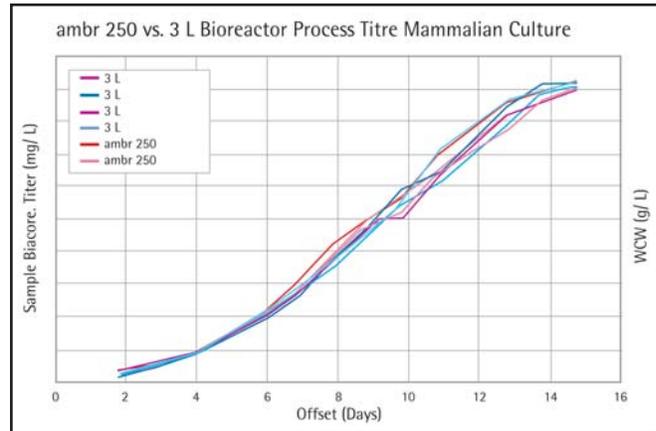


Figure 2. Scale up profile of mammalian culture. ambr[®] 250 vs. 3L bioreactor process titre mammalian culture.

Bottom line: What's the ROI?

The combination of automation and single-use technology has many advantages for biopharmaceutical developers. The most obvious benefit is significantly increased productivity.

While the industry standard failure rate falls between 8 and 10%, the failure rate for the ambr[®] 250 has been shown to be less than 2%, meaning that repeat runs are reduced by up to 80%. The reduction in failures results from:

- Each run using new, precalibrated sensors and probes
- Accuracy from positive displacement pumps
- Liquid handling performed by robots for more accurate additions

With less rework, full automation, and bioreactors that run in parallel, the ambr[®] 250 allows your staff to focus more on development and analysis and less on manual tasks. Additionally, the single-use technology means that resources are not spent on steam-in-place and autoclave equipment for cleaning.

Because the ambr[®] 250 is a fully automated and highly parallel bioreactor technology that is now integrated with Umetrics MODDE Design of Experiment (DoE) application, a costly DoE experiment

can be performed in one run, in some cases reducing the completion time of a process development program from 3-6 months (with standard bioreactors) to 3 weeks.

Overall, implementing the ambr[®] 250 lets you accomplish more with your existing resources and prepare for scale-up much more quickly. Unlike development with standard bioreactors (which can take 6-12 months or more), process development with the ambr[®] 250 can be completed in as little as 1-2 months, or over 80% faster. Adopters are already seeing the benefits, making decisions based on more reliable data and eliminating bottlenecks in early process development that hinder their time to market. Even with the higher cost associated with single-use vessels, the drastic reduction in rework saves a considerable amount of money, making the system a worthwhile investment. An ambr[®] 250 user recently stated in a presentation at a Sartorius upstream meeting that after purchasing the 12-reactor ambr[®] 250, their investment was returned in just one year.

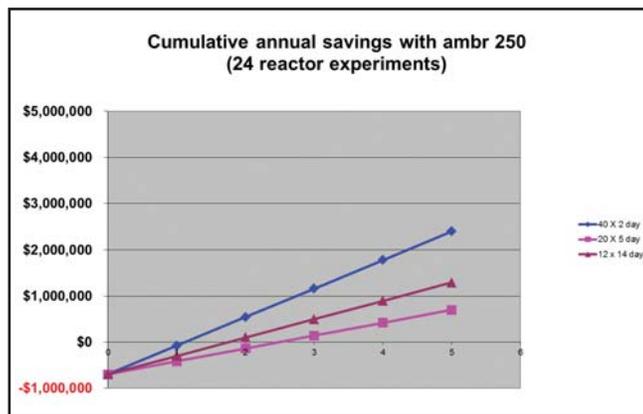


Figure 3. Return on investment using the 24-bioreactor configuration, through year 5.

Conclusions

As the R&D climate for biologics and vaccines becomes more competitive and budgets are driven down, you must take advantage of technologies that allow for rapid process development and optimization.

The ambr[®] 250, currently in use at several major biopharma companies such as Merck and Fujifilm, has been proven to accelerate process development and provide more reliable data. By saving time and money and enabling better decisions, customers are using the single-use, automated bioreactor technology to ultimately get drugs to market faster. As Dr. Simon

Dewar, Head of R&D Upstream Operations at FUJIFILM Diosynth Biotechnologies notes, "The ambr[®] 250 is at the forefront of microbial fermentation technology. In my 25 years as a fermentation professional, it is the only scale-down fermenter system I've seen that is so well-executed that it changes everything."⁴

¹TAP Biosystems And Merck & Co. (MRK) Double Triumph At BPI 2014 Awards. Biospace.com. 2014 October 27. Web. 12 Apr. 2015.

²Carpio M, et al. Evaluation and Characterization of the ambr250™ System for Use with Stable Cell and Transient Protein Production. Poster session presented at Cell Culture Engineering XIV, ECI Conference Series; 2014 May 4-9; Quebec City, Canada.

³FUJIFILM Diosynth Biotechnologies. FUJIFILM Diosynth Biotechnologies continues expansion of R&D facilities including addition of latest high throughput equipment. 2014. Web. 30 Mar. 2015.

⁴Fujifilm Diosynth Biotechnologies Chooses ambr250 System For Optimizing Microbial Fermentation. Biospace.com. 2014 September 16. Web. 30 Mar. 2015.

A profile of Sartorius Stedim Biotech

Sartorius Stedim Biotech is a leading provider of cutting-edge equipment and services for the development, quality assurance and production processes of the biopharmaceutical industry. Its integrated solutions covering fermentation, cell cultivation, filtration, purification, fluid management and lab technologies are supporting the biopharmaceutical industry around the world to develop and produce drugs safely, economically and in a timely manner. Sartorius Stedim Biotech focuses on single-use technologies and value-added services to meet the rapidly changing technology requirements of the industry it serves. Strongly rooted in the scientific community and closely allied with customers and technology partners, the company is dedicated to its philosophy of "turning science into solutions."

ambr[®] systems are designed and manufactured by TAP Biosystems (now part of the Sartorius Stedim Biotech Group) a leading global provider of automated cell culture and fermentation systems for life science research, development and production. ambr systems are widely used for cell line development and process optimisation at pharmaceutical, biotechnology and academic laboratories. They are proven to provide a reliable model and consistent scalability to a range of upstream processes.

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