Bioreactor production: Single-use technology and support for solving your biomanufacturing challenges

Successful biomanufacturing demands reliable, high-performance bioreactors and tight process control. Experienced scientists like GE Healthcare’s Thomas Falkman know that all relevant parameters must stay aligned throughout the production run to ensure consistent product characteristics. Single-use technologies such as high-quality rocking and stirred-tank bioreactors are one way to achieve these goals while providing flexibility in scale. In addition, collaboration with GE skilled experts, like Patrick Guertin, can help you identify and solve challenges through Fast Trak manufacturing services or training.

Enhanced bioreactor production

This applications-focused piece is one in a series highlighting the full range of single-use technologies and Fast Trak support services that GE Healthcare offers to help overcome the challenges that you face throughout your bioprocess workflow. Here we will focus on solutions and support services specifically related to enhanced bioreactor production, including your need for reliable, high-performance bioreactors and process control.

The ideal bioreactor production operation

The objectives of bioreactor production are to maximize productivity and efficiency while maintaining product quality. Bioreactor production is a very important step, because it might have taken several weeks to optimize conditions for scale-up suitable for production. At this stage, it is important to ensure that you have optimized cell growth, viability, protein quality, and bioreactor automation parameters before eventually harvesting the cells and initiating the purification process.

In the ideal state, the cells are growing optimally with an accurate feed composition and feed regime, cell viability is high, and both protein quantity and quality are maintained at optimal levels. The process is uniform, and all parameters remain aligned throughout the production run. The bioreactor uses intelligent control software to accurately regulate process parameters such as mixing, gassing, pH, dissolved oxygen (DO), and temperature.

“It is important to keep product characteristics consistent. Product quality activities are critical, and the process needs to be very uniform. All of these parameters must stay aligned.”

Thomas Falkman, Scientist, GE Healthcare
Applications data support – solutions to overcome your bioreactor production challenges

GE works hard to help address bioreactor production challenges. Support for several of these challenges is provided in GE application notes (see references 1–3). One of these pieces is highlighted here, demonstrating biological and physiochemical comparability of a rocking bioreactor mAb production process to a larger-scale process in a stirred-tank bioreactor [1].

Overview

“This particular application note and the underlying study address the importance of having reliable and adequate process equipment, as well as process control. One example of what can happen if equipment and processes are not sufficient is that, during scale-down and scale-up studies, you will face issues with unreliable models and inconsistent results. This lack of reliability will then influence the overall process reproducibility and product yield.

In this study we also wanted to address the question many users ask themselves, which is how comparable a stirred-tank bioreactor and a rocking bioreactor really are. With substantial process understanding and thorough process optimization, the process performance and outcome of mAb production in Xcellerex and ReadyToProcess WAVE bioreactors were very comparable.”

Thomas Falkman, Scientist, GE Healthcare

---

Thomas has been with GE Healthcare since 2010. In his current role as an upstream application expert, he supports in-house projects with extensive knowledge and experience in upstream bioprocessing, including cell cultivation. Activities include conducting process improvements and providing problem-solving support for customers around the world. Thomas holds presentations and courses about cell culture bioprocessing and products for both internal and external personnel and is an inventor on two bioreactor-related patents. Prior to joining GE, Thomas spent 10 years as an R&D scientist at AstraZeneca. He managed cell culture bioprocessing in both single-use and conventional stirred-tank bioreactors. Large-scale mammalian and insect cell culturing and large-scale microbial fermentation, cross-flow filtration, protein purification, process optimization, and technical improvements are all in Thomas’ skill set.

“In our labs at GE we have a lot of expertise in both stirred-tank bioreactors (such as the Xcellerex™ XDR bioreactors) and rocking bioreactors (like the ReadyToProcess WAVE™ 25 bioreactor system). An extensive number of fed-batch and perfusion runs have been completed. We frequently work with fed-batch, but continuous manufacturing is gaining more interest throughout the industry, and we are putting more and more efforts into that area.”

---

Media operations

Cell culture scale-up

Bioreactor production

Buffer operations

Purification chromatography

Purification TFF-UF

Bulk storage

Fig 1. Typical biopharmaceutical manufacturing workflow. TFF-UF is tangential flow filtration-ultrafiltration.
**Experimental set-up**

The same mAb production process was run in parallel in the rocking and stirred-tank bioreactor, with as similar conditions as possible using similarities in headspace:liquid ratio, agitation/rocking, and feed ratio together with the knowledge we have with ReadyToProcess WAVE 25 process parameters. A high cell density fed-batch production process was performed using a mAb-producing cell line (CHO-DG44*) and ActiCHO™ media platform. To ensure that starting conditions were as similar as possible, the same inoculum source was used in parallel cultures. Cell growth, mAb production, metabolite content, and osmolality were monitored. Cells were harvested after 13 elapsed days and/or when culture viability was < 60%. The experimental layout is provided in Figure 2.

*Licensed from Celica GmbH, Laupheim, Germany

**Results**

Table 1 and Figure 3 show the cell growth, viability, and yield results. Cell growth and viability were similar for both bioreactors. mAb yields from the parallel productions were 5.0 and 4.9 g/L for XDR-200 and ReadyToProcess WAVE 25, respectively. Similar metabolite and physio-chemical profiles (e.g., CO₂, osmolality) were also achieved (Fig 4, 5, and 6).

“This comparability is the result of great process knowledge and is very impressive considering the two vessels have two completely different geometries and process control.”

Thomas Falkman, Scientist, GE Healthcare

---

**Table 1. Results from the bioreactor mAb production cultures**

<table>
<thead>
<tr>
<th>Culture max. viable cell count (10⁶ cells/mL)</th>
<th>XDR-200</th>
<th>ReadyToProcess WAVE 25 satellite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvest viability (%)</td>
<td>65.3</td>
<td>73.0</td>
</tr>
<tr>
<td>Harvest product concentration (g/L)</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Cell-specific product accumulation (µg/cell/d)</td>
<td>27</td>
<td>28</td>
</tr>
</tbody>
</table>

---

**Fig 3.** Viable cell concentration, viability, and mAb concentration in the two parallel production cultures. Samples were taken just prior to feeding.
Fig 4. Metabolite concentrations in the two parallel production cultures.

Fig 5. Osmolality in the two parallel production cultures. Samples were taken just prior to and after feeding.

Fig 6. Partial carbon dioxide pressure in the two parallel production cultures.

Conclusion

“Although it has very different vessel geometry, the well-controlled rocking (WAVE) bioreactor gave a good reflection of the process in an (XDR-200) stirred-tank bioreactor and generated data that is representative of the outcome of a large-scale process. We have also shown that the ReadyToProcess WAVE 25 system can be an efficient tool not only for scale-up but also for process development work in general. The work demonstrated a great comparison and showed how versatile the WAVE 25 bioreactor is.”

Thomas Falkman, Scientist, GE Healthcare

Evaluating applications data is one way to learn about bioreactors and other technologies that support your complex bioreactor operations. Another option is to collaborate with experts who work with customers like you around the world to solve their bioreactor production challenges by providing manufacturing services or training.
Manufacturing and training services – solutions to overcome your bioreactor production challenges

“We don’t just supply equipment, we support customers along the whole biomanufacturing process. Our Fast Trak Process Development and Bridge Manufacturing services can assist customers in solving specific bioreactor production challenges, for instance, converting from traditional to single-use bioreactors while keeping the process and shear sensitivities in mind. Or we can deliver training targeted to the needs of their staff, so they can help themselves.”

Patrick Guertin, Fast Trak Global Technical Manager, GE Healthcare

GE’s portfolio of services is designed to provide end-to-end process support to help take you from molecule to market in the shortest time possible. For instance, with Fast Trak Bridge Manufacturing Services we can manage your process development through scale-up cGMP manufacturing to deployment and start-up. But our goal at Fast Trak is not just to solve your biomanufacturing challenges. It is to provide full transparency to our scientist engineers and processes so we can empower you to solve them, too. Within Fast Trak, you can also access hands-on training to strengthen your skills in, for example, single-use bioreactor operation.

Fast Trak Bridge Manufacturing—an end-to-end solution for your bioprocessing needs

If you want to add the flexibility, efficiency, and convenience of single-use technologies to a new or existing production line, we can manage this, or parts of it, for you. Our Fast Trak Bridge Manufacturing Services offer a cost-effective solution to decrease time-to-market (Fig 7). For example, the end-to-end process development of a product can be performed in 12 to 24 months at our facilities, and then transferred to your site for clinical and commercial manufacturing. Or we can support certain parts of your process in a much shorter time frame. We also offer operational training and on-going technical support post-installation. Table 2 lists some of our extensive biomanufacturing experience.

Table 2. Examples of the biomanufacturing experience within GE’s Fast Trak Bridge Manufacturing team

<table>
<thead>
<tr>
<th>Product</th>
<th>Cell line</th>
<th>Xcellerex XDR bioreactor scale</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb and mAb fusions</td>
<td>CHO cells</td>
<td>Scales from 10 L to 2000 L</td>
<td>Manufactured clinical mAb material in our Fast Trak biomanufacturing cGMP suite for clinical trials, as an alternative to using a contract manufacturing organization (CMO) Successful EU QP phase III audit First Investigational New Drug (IND) Application that used a single-use stirred-tank bioreactor</td>
</tr>
<tr>
<td>Recombinant proteins, including therapeutic</td>
<td>CHO cells</td>
<td>Scales from 10 L to 1000 L</td>
<td>First 1000 L perfusion culture that was performed in a single-use bioreactor</td>
</tr>
<tr>
<td>enzymes</td>
<td>Human HEK 293 cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccines: subunit, inactivated, and virus-</td>
<td>Insect S2 cells</td>
<td>Scales from 10 L to 1000 L,</td>
<td>Enabled rapid technology transfer First IND Application that utilized microcarriers in a single-use stirred-tank bioreactor</td>
</tr>
<tr>
<td>like particle (VLP)</td>
<td>Vero cells</td>
<td>including 50 L on microcarriers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In Fast Trak Bridge Manufacturing, process development and manufacturing scale up are performed at our facility equipped with similar equipment, instrumentation, and automation that will eventually be deployed to your facility. We offer complete transparency. You are welcome to visit the facility to witness cGMP processing and receive training during the non-cGMP work. This approach saves time by enabling equipment testing and process verification to be performed pre-deployment and reduces costs and risk by minimizing the number of process changes required post-installation.

**Solutions for process development**

With over 100 years’ collective experience among the process development leadership team, we know that quality, reliability, and cost are major considerations for your project. Early collaboration with our experts provides you access to the in-depth practical skills of our highly trained bioprocess technicians, as well as the broader experience and insight essential for developing a strong and sustainable biomanufacturing strategy for your facility. For instance, we perform bioreactor process optimization to help maximize cell line yield.

**Solutions for upstream**

Our upstream manufacturing teams have significant experience in scaling up single-use biopharmaceutical processes for clinical manufacturing. With expertise in batch, fed-batch, perfusion, suspension, and adherent techniques for mammalian, microbial, and vaccine manufacturing projects, we can work with you to help optimize conditions for even very challenging cell expansions, such as adherent cells on microcarriers. As an example, we have successfully scaled up the process for vaccine-containing Vero cells from flasks to an Xcellerex XDR stirred-tank bioreactor platform.

**Solutions for downstream**

Our specialist scientists and engineers are qualified in chromatography process development supporting mammalian, bacterial, virus, virus-like particles (VLP), and recombinant protein purification. They have extensive experience with purification platforms and filtration systems for bulk formulation of drug substances.

**Comprehensive training for your specific needs**

To further empower you, we provide detailed hands-on training and education, both on-site at our facility and off-site at your facility, whether for training existing staff or new equipment operators. Fast Trak training and educational courses can also be held at Fast Trak regional centers around the globe. Our standard courses cover areas such as cell culture, filtration, chromatography, design of experiments (DoE), and high-throughput process development (HTPD). We also offer customized courses to support you in the optimization and troubleshooting of existing unit operations specific to your process needs, for example.

---

**GE technical expert spotlight – Patrick Guertin, MSc, biochemistry**

Patrick Guertin has been with GE Healthcare since 2006. He is currently a Fast Trak Global Technical Manager (GTEM) who works closely with customers from biopharmaceutical companies, CMOs, and government labs to solve their specific upstream biomannufacturing challenges. Patrick brings more than 25 years of industry experience and substantial expertise in upstream process development, pilot plant operations, and cGMP manufacturing for mAbs, recombinant therapeutics, and vaccines.

Among his skill set are:
- scale-up and scale-down procedures in microcarrier, fed-batch, and perfusion modes
- process optimization in traditional and single-use mammalian and microbial bioreactors
- development of animal-derived component free (ADCF) media and feed
- technology transfer, process design, and data analysis

“One of the things customers value most when working with us is our collaborative nature. We look at customers’ data carefully and collaborate with them to formulate conditions that optimize their cells and final molecules. We are attentive to the process sensitivity, whether they are using traditional or single-use technology. Something that we do really well is scalability. For example, when converting from stainless steel to single-use technology, we can scale down a customer’s 10,000 L run to 10 L for process development, then scale back up in one of our larger single-use bioreactors.”
These courses will help you build your bioprocessing skills and give you access to our experts, our knowledge, and our experience on specific technologies and practices. When asked what they like best about our courses, participants often answer that the blend of lecture- and lab-based training is just right, instructors are very knowledgeable of many different industrially relevant processes, are patient, and easy to understand, and what they learn is highly relevant to their work at biomanufacturing organizations around the world.

If you are interested in learning more about process development and evaluation, scale up, and bioengineering in animal cell culture, we recommend the following course:

Fast Trak Advanced bioreactor cultivation technology

### Customer objectives
- Convert process from conventional to single-use workflow
- Structured technology transfer
- Scale up from 10 to 200 L. Ultimate target: 2000 L bioreactor for two mAbs
- Deploy global biosimilar manufacturing platform with aggressive timelines

### Project challenges
- Demonstrating molecule comparability after conversion
- Process and shear sensitivities
- Process and equipment design
- Communication with global teams
- Real-time scope/process changes
- Timeline challenges

### Outcome of working with GE
- Reduced customer’s process development timeline by 13 months
- Developed 200 L bioreactor process in 5 months
- Transplanted project to local region for further development and ultimate technology transfer

### References

### Summary

Biomanufacturers interested in maximizing productivity and minimizing costs can benefit from GE’s single-use bioprocess solutions and support services that span the entire process. Whether you need one piece of single-use equipment, an integrated platform, an entire single-use facility, or technical expertise and support for a specific manufacturing challenge, GE can deliver. Our technical experts are on hand to provide Fast Trak Process Development, Bridge Manufacturing and training courses that will help propel your organization to success.