GE Healthcare

Fast Trak Services: Long-term collaboration supports speed to market in single-use biomanufacturing

A case study

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Pfizer, Inc. collaborated with GE's Fast Trak team to accelerate their timeline for delivering biosimilar mAbs to emerging markets. Support services were needed to quickly convert existing stainless steel processes to single-use technologies, generate material for comparability and preclinical studies, and build a flexible mAb biomanufacturing facility in China. While Pfizer's prefabricated KUBio™ facility is being built, ongoing collaboration with GE's Fast Trak scientists for production of toxicology material, full-scale manufacturing runs, and training is expected to facilitate speed to market for these two biosimilars.

Introduction

In their pursuit of developing therapeutics, biopharmaceutical companies face many challenges, including pressure to meet aggressive timelines, reduce risk and cost, and increase speed to market. Addressing these challenges is especially critical for biosimilar manufacturers, who face fierce competition and an expanding footprint in emerging markets (1). The global biosimilars market is growing rapidly and is expected to exceed more than $6 billion by 2020 (2).

In this case study we will demonstrate a successful outcome for one biosimilar manufacturer who leveraged the full capabilities of GE. By working with GE, Pfizer benefited from a global service and technology provider focused on building strong relationships, streamlining process transfer strategies, and implementing both single-use technologies and flexible, deployable manufacturing platforms.

Customer needs and concerns

Pfizer was interested in working with a service provider to reduce risk and increase the speed to market of two biosimilar monoclonal antibodies (mAbs), while working under aggressive timelines. Assistance was needed in designing the scope of work for converting the existing stainless steel processes to single-use technologies while ensuring product titers and analytical comparability of the two target molecules. Fast deployment of a global, flexible, scalable, cost-effective biosimilar manufacturing solution was required to facilitate the goal of being first to market in an emerging region. Furthermore, once the decision was made to purchase a biomanufacturing facility, process transfer and start-up support at the new facility were desired.

Both the conversion to single-use and the process transfer needed to be completed in less than six months for both mAbs. Importantly, the molecules had to be confirmed as biosimilar products according to their critical quality attributes (CQA). Intellectual property (IP) protection was a concern at the start of the project, so initially GE's Fast Trak team did not know the culture media and feed formulation, several process solutions, or the analytical comparability analytics. There were some initial concerns regarding whether the process would require modification or if GE's equipment would have to be modified to accommodate the process. Other concerns centered around communication with, and alignment of, global teams. Specifically, Pfizer wondered whether GE's team was flexible enough to handle real-time scope and process changes as the definition phase progressed.

Customer outcomes

Project scope of work

The initial scope of work consisted of two 10 L process transfer runs for each of two mAbs, known as Product A and Product B, for a total of 4 × 10 L runs in GE's single-use bioreactors. One of these runs would be followed by a downstream run-through. After each run, the process could be optimized if necessary to meet customer targets. All 10 L protocols, solution records, and bills of material would be generated. Another 10 L run, both upstream and downstream, would be performed for each mAb for process confirmation.

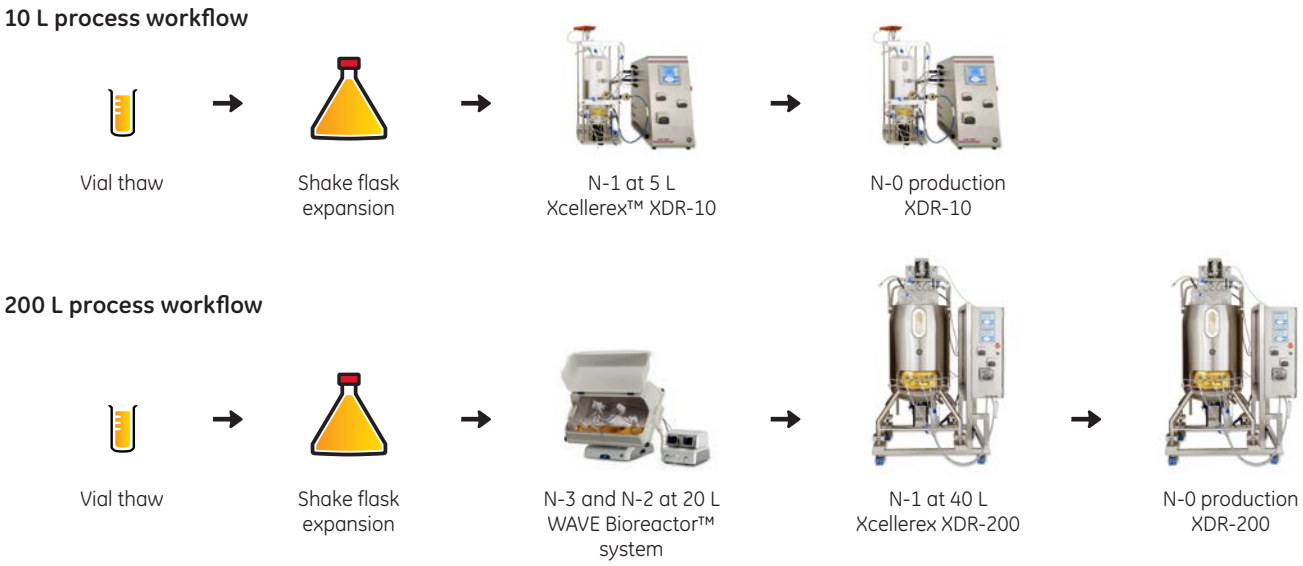

Fig 1. Process flows for 10 L and 200 L upstream processes using single-use bioreactors from GE.

Two proof of concept scale-up runs at 200 L scale would be performed for each mAb, for a total of 4 × 200 L runs, including both upstream and downstream processing. All 200 L batch records, solution records, and bills of material would be generated. The ultimate target is a 2000 L bioreactor for both mAb molecules, but that scale was outside the current project scope.

Fast Trak scientists in the United States would follow GE's standard process transfer standard operating procedure (SOP). That SOP defines the steps, roles and responsibilities, and templated documents required for process transfer. In addition to following the SOP, Fast Trak's scientists would utilize cross-functional teams with process development, pilot plant, and manufacturing staff. All GE team members are current good manufacturing practices (cGMP) trained and work closely with GE's quality assurance (QA) teams.

Conversion to single-use technology and process transfer

Upstream single-use process

The critical process parameters (CPP) for upstream unit operations were identified for process transfer. Some of these parameters included seed train, agitation rates according to power input, pH, dissolved oxygen (DO), sparge pore size, feed, gassing, and bioreactor control strategies. Pfizer's 12 000 L stainless steel process was scaled down and adapted to GE's single-use bioreactors at a 10 L scale (Fig 1). After the 10 L process was worked out for each mAb, a 10 L process confirmation run was performed. The process was then scaled up to 200 L (Fig 1).

Pfizer staff worked on-site and in-plant with the Fast Trak scientists and engineers for all upstream operations. They were also present for any real-time process or equipment changes.

Fast Trak Services

GE's Fast Trak Services are specifically designed to help biomanufacturers increase their process productivity, reduce cost, and enable them to bring their product to market faster through support in process development, cGMP manufacturing, and training. The Fast Trak Services centers are equipped with the latest technologies to accelerate bioprocessing development in an environment and at a scale that closely replicates the real-life industrial setting. For over 30 years, thousands of customers world-wide have been trained by GE's experienced Fast Trak leadership teams, giving customers access to industry expertise encompassing process and analytical development, process scale-up, as well as manufacture of drug substances for use in toxicology studies or phase I and II clinical testing.

The Fast Trak Services centers are located in South Korea, the USA, Sweden, India, and China, with satellite centers in Turkey, Japan, and Singapore.

Table 1. Upstream process results

Product	Scale	Maximum cell density (x 10^6 cells/mL)	Product titer (mg/mL)	Cell density and product titer comparability?	Analytical comparability?
A	10 L confirmation run	17	2.4	Low but acceptable	Yes
	200 L run 1	24	3.3	Yes	Yes
	200 L run 2	20	3.2	Yes	Yes
B	10 L confirmation run	11	3.4	Yes	Yes
	200 L run 1	10	3.4	Yes	Yes
	200 L run 2	11	3.9	Yes	Yes

The cell densities and product titers were determined by GE. The analytical comparability testing was performed by Pfizer after purifying the mAbs using their standard process. The results are summarized in Table 1.

The upstream process results met Pfizer's expectations for cell density, product titer, and analytical comparability.

Downstream single-use process

The downstream process workflow is shown in Figure 2.

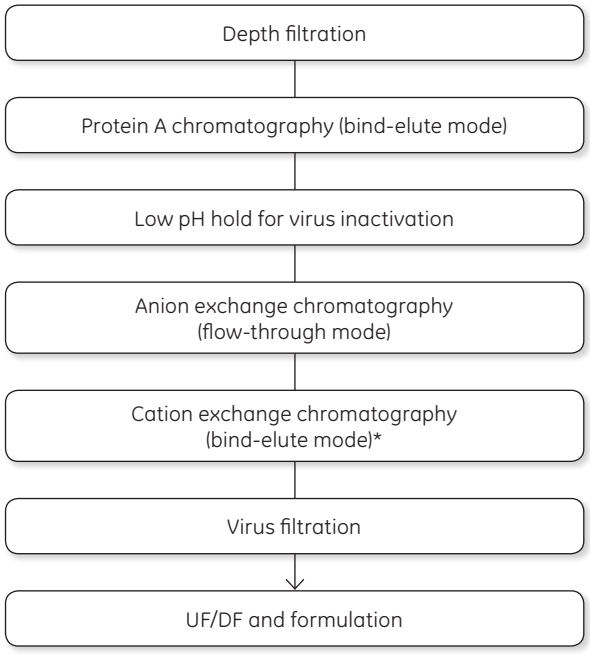

Fig 2. Downstream process workflow for mAb products A and B. UF/DF was performed using TFF. UF = ultrafiltration, DF = diafiltration. *Product B only.

The original downstream mAb process was performed in large stainless steel centrifuges, tangential flow filtration (TFF) systems, chromatography systems, and buffer tanks. The CPP for downstream process transfer were identified, including linear velocities, loading and binding capacities, collection criteria, flux rates, temperatures, pressures. pH, conductivity, hold times, and storage conditions. The stainless steel downstream process was scaled down and adapted to GE's single-use TFF systems, depth filtration systems, chromatography columns, buffer systems, bags, tubing sets, and sensors.

The recovery at each step and the total process recovery were calculated. Analytical comparability testing was performed by Pfizer. The results are summarized in Table 2.

The downstream process met Pfizer's expectations for recovery and analytical comparability.

Process transfer

The upstream and downstream processes were successfully converted from conventional stainless steel to single-use technology and scaled up from 10 L to 200 L. The project was finished in five months, including completion of 6 × 10 L batches and 4 × 200 L batches, as well as generation of more than 50 process documents and four complete bills of material. An estimated 6 to 12 months were saved based on Pfizer's original timeline for a similar scope of work. Pfizer's expectations were met for both upstream and downstream results, including analytical comparability.

Based on the successful outcome of the first phase of the project, Pfizer decided to purchase one of GE's flexible manufacturing solutions, which would be located at their future manufacturing site in Hangzhou, China.

Table 2. Downstream process results

Product	Scale	Clarification (% recovery, step)	Protein A + VI (% recovery, step)	AIEX (% recovery, step)	CIEX (% recovery, step)	UF/DF (% recovery, step)	Total process recovery (%)	Recovery comparability?	Analytical comparability?
A	10 L confirmation run	86	93	89	NA	95	68	Yes	Yes
	200 L run 1	88	102	86	NA	98	76	Yes	Yes
	200 L run 2	88	91	99	NA	97	73	Yes	Yes
B	10 L confirmation run	85	98	86	78	94	53	Yes	Yes
	200 L run 1	91	100	97	86	92	67	Yes	Yes
	200 L run 2	93	95	93	79	96	65	Yes	Yes

VI = virus inactivation; AIEX = anion exchange chromatography; CIEX = cation exchange chromatography; NA = not applicable

Choice of flexible manufacturing technology

The FlexFactory™ biomanufacturing platform is a cGMP-compliant option that provides a complete production train, from cell culture to drug formulation, that can be installed in 12 months. GE's KUBio biomanufacturing facility is a prefabricated cGMP-compliant facility for biosimilar mAb production. It can be built, assembled, qualified, and ready-to-run within 18 to 24 months. FlexFactory single-use platforms are included in KUBio facilities. After considering the options, the decision was made to move forward with a KUBio facility. GE's Fast Trak and Enterprise Solutions teams worked with Pfizer to ensure appropriate selection of equipment and consumables.

Process training

While the KUBio is being built, it is critical for Pfizer to maintain the clinical timeline for both mAbs. Therefore, Pfizer is continuing to work with GE's Fast Trak teams for Bridge Manufacturing Services and other support until the process can be transplanted to their new KUBio facility in China (Fig 3).

After the initial phase of work, the single-use upstream and downstream processes for both mAbs were transferred to GE's Fast Trak China team, which is generating material in-country for toxicology studies, again working together with Pfizer on-site and in-plant.

In addition to providing manufacturing and training support, GE is providing support for other needs in the region where the KUBio is being built. For example, GE is helping with sourcing appropriate and compliant raw materials in the emerging region. GE's Fast Trak team, along with GE Global Operations (GGO), supported customer meetings with local government and regulatory officials. Another service provided by GE is single-point project management throughout the project.

When Pfizer's KUBio manufacturing facility is ready, The Fast Trak team will support process transfer, equipment training, and facility start-up activities at the new site.

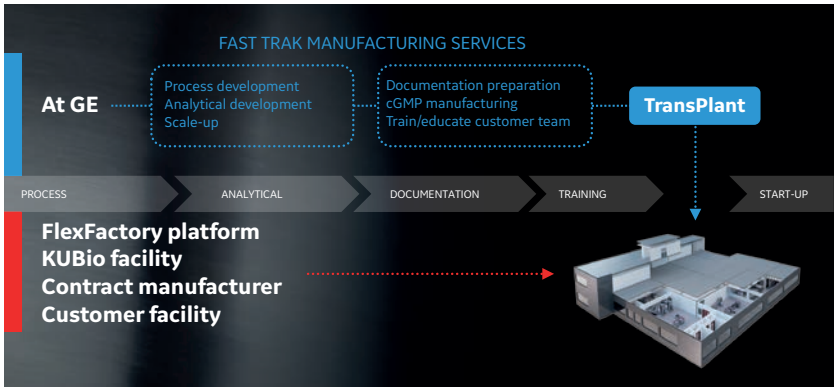

Fig 3. Fast Trak Bridge Manufacturing Services gives you access to process experts and enabling technologies in single-use, and provides you additional manufacturing capacity while you are waiting for your facility to be built. Upon completion we transplant your process back to your teams with complete transparency and training. This not only ensures your process timeline continuity but also facilitates speed to market. cGMP = current good manufacturing practices.

Conclusion

By working closely with GE's Fast Trak team, Pfizer converted their stainless steel upstream and downstream processes to single-use technologies up to 200 L scale. Notably, both mAbs in the study met Pfizer's expectations for analytical comparability. Process transfer, including process documents and bills of material, were completed in five months, saving an estimated 6 to 12 months compared with internal timelines. This outcome led to Pfizer deciding to also invest in a GE KUBio facility, which will be deployed on a site in China.

While the KUBio is being built, assembled, and validated, GE's Fast Trak China team will prepare toxicology batches with Pfizer staff on-site. The toxicology batches will allow Pfizer to submit their drug application earlier than would have been possible with a traditional stick-built facility, which would have required facility completion before starting the first phase of the application process. To further accelerate their timeline, Pfizer is continuing to collaborate with GE's Fast Trak Services to prepare the full-scale (2000 L) cGMP batches required for their drug application in China. Pfizer anticipates that they will be able to get these mAbs to market faster as a result of GE's Fast Trak support in USA and China, working in parallel while their KUBio facility is being built.

Acknowledgements

We thank Pfizer inc., for kindly providing us with permission for use of this body of work as a demonstration of our Fast Trak Services.

"When tasked with the challenge of building a biologics plant in China, Pfizer Inc. sought a solution that would ensure speed to market and also be capable of manufacturing complex mammalian cell culture processes. Traditional stainless steel stick-built projects generally have significantly long completion times making them unattractive for emerging markets. GE Healthcare's KUBio provides an elegant solution to this challenge by leveraging GE's single use technology and pre-fabricated KUBio modules, creating a drug substance facility that can be seamlessly integrated with a more traditional CUB and warehouse facilities.

Ensuring comparable results of a process in different facilities is paramount. A change in technology from stainless steel to single use bioreactors presented a challenge to the project. Should Pfizer invest in a new technology without any prior experience of running the mammalian processes in the XDR single use system? Working closely with GE Healthcare, a small cross-company team of scientists and engineers worked with lightning speed to transfer two processes to the GE Marlborough facility for proof of concept runs, first at 10 L scale and then at 200 L. The data produced helped forge an informed decision to proceed with a single use biologics facility in China. The partnership with GE Healthcare continues with supporting runs in their GE Shanghai facility."

John Coyne
Pfizer Bioprocess R&D, Sr. Manager Pilot Plant, Andover, MA

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