BioReliance®
Pharma & Biopharma
Manufacturing &
Testing Services

Customer Success Story

Acticor

Development and Manufacturing of a Fab Fragment for Clinical Trials

Balancing Speed and Risk to Meet an Aggressive Timeline

Highlights

- Acticor selected our BioReliance® End-to-End Solutions for process development and GMP manufacturing of an Fab fragment to support clinical trials
- The project timeline allowed only 18 months to get from the cell line to clinical batch manufacturing
- A strategic approach to risk management was leveraged to help meet an aggressive timeline

The Company

Acticor Biotech, founded in 2013 as a spin-off of Inserm, the French National Institute of Health and Medical Research, is advancing an innovative drug for the treatment of the acute phase of ischemic stroke. Glenzocimab (ACT017) is a humanized Fab fragment of a monoclonal antibody. The therapeutic candidate is directed against a novel target of major interest, platelet glycoprotein VI (GPVI) in order to inhibit its action. The target is involved in the growth of the thrombus, but not in physiological haemostasis. This limits the bleeding risk associated with its inhibition.

The Challenge

Starting with a set of CHO-S cell lines, Acticor needed a partner to do clone selection, create the master cell bank, develop an optimized process for producing the Fab fragment and then manufacture GMP batches to initiate a clinical trial – all within 18 months. The future of the company and this therapeutic candidate were dependent on the success of this project.

MilliporeSigma

BioReliance® End-to-End Solutions provided a tailored suite of services to Acticor

Contract Development and Manufacturing Services for Phase I/II:

- Clone selection from a CHO-S cell line, master cell bank manufacturing and characterization
- Analytical methods development and validation
- Upstream and downstream process development, reproducibility,
- Pre-clinical batch for toxicology study (pilot scale, 50L)
- Clinical supply for phase I/II (3 batches, 200L)
- Stability studies (supportive and GMP)

Approach

Strategic Risk Management to Accelerate Timelines

Recognizing the need to move quickly, our BioReliance® End-to-End Solutions team developed an accelerated approach to process development and manufacturing that didn't expose Acticor to additional risk. The overall strategy incorporated a number of key elements including:

- Leveraging the team's extensive expertise in biologics
- Ensuring close communication with the Acticor team and building a relationship based on trust and transparency
- Conducting process development steps in parallel, when possible, to optimize the timeline
- Reducing the number of runs during development and ensuring comfort and confidence in moving forward with a smaller set of data than is typically generated
- At all stages of the project, identification of possible risks and the approach proposed to mitigate those risks were discussed and agreed upon with Acticor.

"We had a very aggressive timeline for this project, and as a start-up it was critical that we were able to deliver against key milestones. We needed a partner that could move quickly but also ensure quality and minimize our exposure to risk.

We found that with the MilliporeSigma team."

Kristell Lebozec
Head of Pharmaceutical and Non-Clinical Development, Acticor

Optimizing the Process for a Fab Fragment

The first step in this project was an effective and efficient transfer of the cell line producing the Fab fragment along with accompanying documents and information. In many cases, creation of a process development cell bank, followed by expansion of cells and creation and characterization of the master cell bank are completed prior to initiating process development. To accelerate the timeline for this project, our team began process development using the process development cell bank while expansion and creation and characterization of the master cell bank were done in parallel.

Conducting these activities in parallel, rather than sequentially, can save up to three months as generation of the master cell bank requires about one month and characterization can take between six and eight weeks. Having extensive experience with CHO cells, our team knew the cell lines received from Acticor were stable and the risk of running these activities in parallel was low.

As glenzocimab is not a full antibody with an Fc region, templated approaches incorporating Protein A as the affinity step during downstream processing were not suitable. As such, the team needed to screen several resins to customize an approach for purification of the Fab fragment.

Accelerating Development

Faced with a highly compressed timeline, our team, in close collaboration and agreement with Acticor, executed a number of activities in parallel and in some cases, reduced the number of runs conducted. In addition to the cell bank and process development steps describe above, other areas in which the timeline was compressed included:

- The drug substance was sensitive to the formulation buffer and shear stress. To address this, the team executed a formulation study in parallel with other development activities. The formulation was selected based on one month of stability data in contrast to the more conventional three-month study.
- A pilot batch was run prior to the reproducibility study to deliver material and start validation of the analytical package earlier.
- Two runs were conducted during the development test rather than three

Enabling Flexibility in the Contract

An important aspect of this program, and for many early stage companies, is the flexibility offered with regards to the contract. In this case, a two-stage program was put in place. The first included non-GMP activities such as development of the fully characterized master cell bank and process development; the second stage was the manufacturing itself. With this approach, a customer doesn't have to commit to a GMP slot that would be needed perhaps a year in the future, without knowing, for example, if toxicity studies will be successful.

Results

Acticor came to us with an intensive timeline – go from cell line to clinical batch manufacturing in 18 months. Delivery of the pilot batch for their toxicology study was completed six months into the project. Clinical material and the data necessary for the Investigational Medicinal Product Dossier (IMPD) required for approval of clinical trials in the EU was delivered one month ahead of the 18 month deadline. Acticor completed a Phase I clinical trial in January 2018 and is currently in Phase Ib/2a in six European countries.

"MilliporeSigma respected our timeline and we initiated our clinical trial as planned. The skill and experience of the team was critical in identifying ways to accelerate the project and properly balance speed and risk.

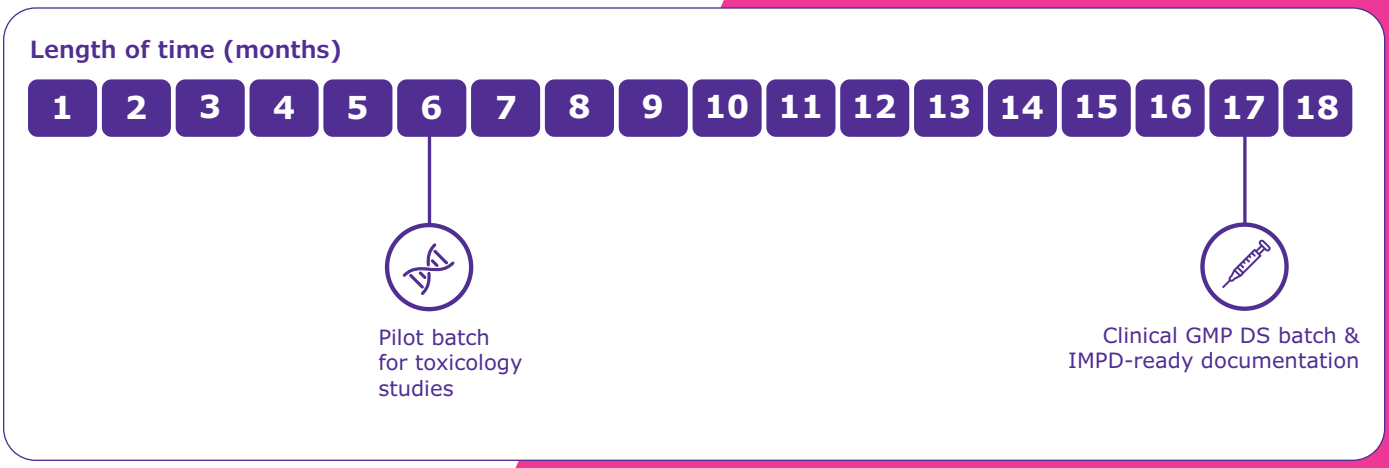
We are excited to continue working with them as Glenzocimab advances in clinical trials."

Gilles Avenard
CEO of Acticor

"We work with many clients who have very tight timelines. Our extensive experience with process development and manufacturing allows us to strike an optimized balance of speed and risk. We know where we can accelerate processes and the associated risks. We also know where we shouldn't move faster. We offer these options and make decisions in close collaboration with our customers to ensure their acceptance."

Sébastien Ribault, Ph.D.
Vice President and Head of
BioReliance® End-to-End Solutions

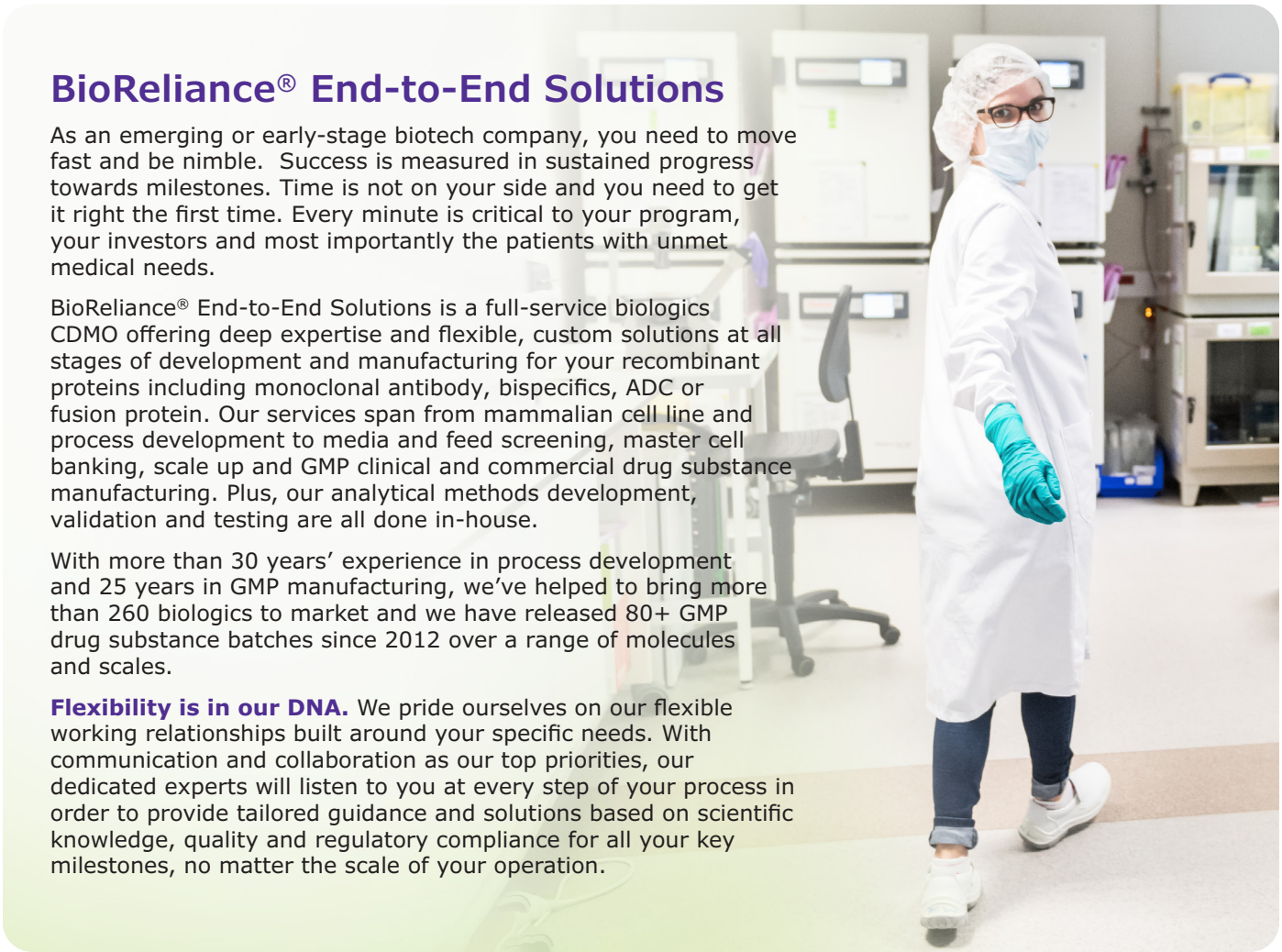
From Cell line to GMP Clinical Drug Substance



Customer Benefits

The BioReliance® End-to-End Solutions team's flexible approach provided strong support across all aspects of this project including:

- **Establishing an acceptable balance of risk and speed** in order to meet the aggressive timeline
- **Developing a robust and optimized process** that successfully addressed challenges with affinity purification, host cell protein removal and formulation
- **Streamlining the transfer of the CHO cell lines for development and the overall process to GMP production,** in an efficient and seamless manner
- **Preparing clinical material and data for the Investigational Medicinal Product Dossier (IMPD)** to support approval of clinical trials in the EU
- **Leveraging expertise and capabilities** of a team with more than 30 years of bringing molecules to market and decades of bioprocessing experience



BioReliance® End-to-End Solutions

As an emerging or early-stage biotech company, you need to move fast and be nimble. Success is measured in sustained progress towards milestones. Time is not on your side and you need to get it right the first time. Every minute is critical to your program, your investors and most importantly the patients with unmet medical needs.

BioReliance® End-to-End Solutions is a full-service biologics CDMO offering deep expertise and flexible, custom solutions at all stages of development and manufacturing for your recombinant proteins including monoclonal antibody, bispecifics, ADC or fusion protein. Our services span from mammalian cell line and process development to media and feed screening, master cell banking, scale up and GMP clinical and commercial drug substance manufacturing. Plus, our analytical methods development, validation and testing are all done in-house.

With more than 30 years' experience in process development and 25 years in GMP manufacturing, we've helped to bring more than 260 biologics to market and we have released 80+ GMP drug substance batches since 2012 over a range of molecules and scales.

Flexibility is in our DNA. We pride ourselves on our flexible working relationships built around your specific needs. With communication and collaboration as our top priorities, our dedicated experts will listen to you at every step of your process in order to provide tailored guidance and solutions based on scientific knowledge, quality and regulatory compliance for all your key milestones, no matter the scale of your operation.

For more information, please visit: **EMDMillipore.com/adaptive-CDMO**

To place an order or receive technical assistance, please visit **EMDMillipore.com/contactPS**

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