Biologics

Quality at scale

Reducing risk and Improving outcomes through digital insight, regulatory readiness, and execution discipline

Case study

De-risking late-stage scale-up for an Fc-fusion program

Challenge

A customer needed to transfer an established Fc-fusion protein process from Brisbane to a new site and rapidly redevelop it for late-stage clinical supply and commercialization. Goals included consistent, reproducible seed-train growth and a 14-day process achieving a 1–1.5 g/L titer, all under tight timelines and within a limited design space, without impacting critical quality attributes (CQAs).

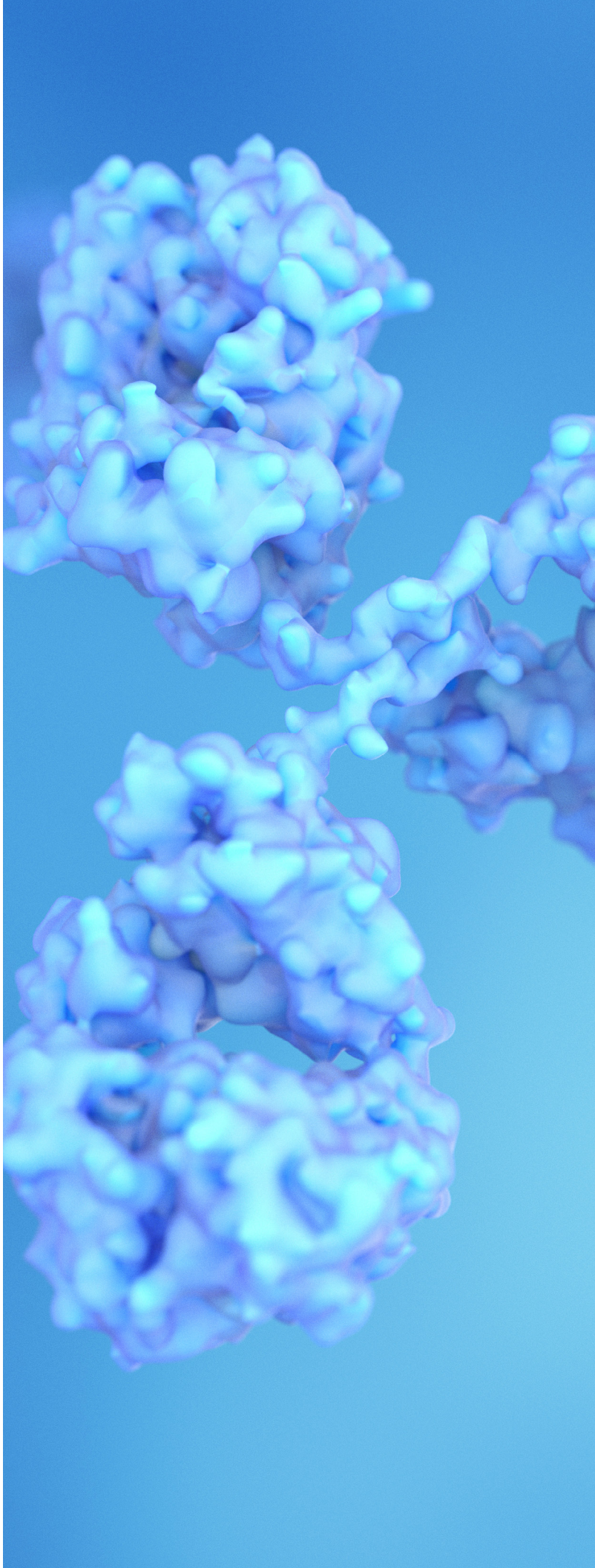
Solution

We executed a structured, stage-gated tech-transfer and optimization plan. Parallel Advanced Micro Bioreactor (Ambr) screening refined media and feed strategies while stress-testing seed-train robustness, leveraging prior data; a second Ambr round confirmed optimal conditions. Four-by-four bench-scale bioreactor runs then fine-tuned parameters to increase titer and consistency without compromising CQAs, supported by integrated Analytical and Formulation Sciences (AFS) and Downstream Processing (DSP) teams to ensure analytical continuity and downstream fit.

Outcome

Scalability was confirmed through 12 L, 250 L, and 2,000 L batches. Bridging studies aligned legacy and new processes to minimize transition risk, while range-finding and robustness assessments validated performance across operating ranges—delivering a commercialization-ready process that met titer and timeline targets while protecting product quality.

We assist customers at any phase of the workflow with smooth, efficient technical transfer processes.



Introduction

Flexible solutions to bring your biologic to market faster

Whether you're starting with a DNA sequence or looking to add additional capacity for an existing process, our experienced global teams can help. We have produced more than 886 biologics batches and manufactured 12 commercial molecules between 2019 and 2024. Our teams leverage the latest equipment, established processes, and templated documentation to efficiently deliver results.

With networked manufacturing sites across Asia, Europe, and the United States, we help you reproducibly deliver your molecule on time while meeting high quality standards. Our sites feature global centers of excellence in cell line development and single-use technologies. To bring your IgG1/4 or bispecific molecule to market faster—in as few as nine months—several of our sites offer our Path to IND program.

From 2018 to 2024, our biologics sites have completed:

116 process, performance, and qualification (PPQ) batches

385 clinical batches

384 commercial batches

Contents

Cell line development

At our Bioprocessing Collaboration Center (BCC) in St. Louis, Missouri, we have a dedicated team that can create and optimize a cell line for you—or optimize your cells from a research cell bank. Improving protein expression increases yields, saving both time and money.

At the DNA level, we utilize artificial intelligence and machine learning (AI/ML) technologies to drive gene optimization and vector construction. Plasmids are transfected into the CHO-K1 host cell line or other selected cell lines. The CHO-K1 cell line incorporates transposase technology, which enhances gene integration and can achieve titers of up to 11 g/L*. It has been used in more than 43 IND/IMPD submissions to date.

Finally, high-throughput process development leverages the Beacon™ Optofluidic System to identify and select top-expressing cell clones.

*Terms and conditions: Titer levels provided are estimates based on n-1 process intensification techniques only and may vary based on molecule type.

Cell line development services:

- Enhanced optimization through AI- and ML-based gene sequence optimization and vector construction
- Transposase-based technology in the CHO-K1 cell line helps to increase speed to IND
- State-of-the-art, automated high-throughput equipment, including the Beacon™ system, Ambr® 250 system, and Tecan™ platforms
- Platform seed train, fed-batch production, and harvest processes
- Custom cell line development using custom or commercial cell lines, including CHO, myeloma, hybridoma, and PER.C6™ cells
- Simple cell line licensing agreements that avoid royalties or restrictions
- Regulatory guidance and support
- CGMP-compliant cell banking services

Cell line development at the St. Louis, Missouri, US site.

Process development capabilities, upstream and downstream

We apply our deep process development expertise to significantly increase batch yield and reduce processing time for your molecule. By applying Design of Experiments (DoE) methodology to both upstream and downstream processing, we define critical process parameters (CPPs) and critical quality parameters (CQPs) that enable robust processes, maximize yields, and optimize throughput.

Upstream process development

With more than 30 years of experience working with over 200 molecules, we specialize in the development of monoclonal antibodies (mAbs), bispecific antibodies, Fc-fusions, enzymes, recombinant proteins, and other complex molecules. Our end-to-end upstream capabilities are designed to address your unique challenges, accelerate your path to market, and deliver robust, scalable, and tailored production solutions. For upstream process development, we utilize the Sartorius Ambr® 15 and Ambr® 250 system platforms, as well as 0.5 L, 1 L, and 10 L single-use bioreactors, to define optimal feed strategies and processing conditions.

Upstream process development services:

- Clone and media/feed screening and process development/ optimization using the Ambr® 15 and Ambr® 250 systems
- Master cell banking
- Fed-batch, perfusion, and XD™ cell culture processes
- Use of high-density mammalian cell culture technologies, including proprietary XD™ technology
- Cell culture process modeling, metabolite analysis, and amino acid analysis
- Single-use scale-up and scale-down models
- Upstream process intensification
- Technology transfer support
- Process characterization and validation studies
- Process robustness studies

Downstream process development services

Downstream process development presents unique challenges, particularly when transitioning from benchtop stages to CGMP production and manufacturing. With more than 30 years of experience developing purification techniques for complex molecules, Thermo Fisher Scientific's end-to-end downstream capabilities—including open analytical testing and seamless technology transfer support—are designed to minimize risk and overcome challenges. We help accelerate your path to market while delivering high-yield, tailored solutions—all without sacrificing quality.

Downstream processing capabilities:

- Design of Experiments (DoE)
- Process development, transfer, and optimization
- Scale-up from benchtop to commercial scale
- Chromatography at pilot and benchtop scale (Protein A, cation/ anion exchange, viral filtration, ultrafiltration/clarification)
- High-throughput screening and filtration
- Open-lab analytical testing
- Material generation for studies
- Viral clearance studies
- Process characterization and validation studies
- Process robustness studies

Upstream process development at our Lengnau, Switzerland site.

Downstream processing at our St. Louis, Missouri, US site.

Analytical and formulation development capabilities

Creating robust analytical methods and drug substance/drug product (DS/DP) formulations that meet your therapeutic criteria is essential to the success of your biologic—from demonstrating efficacy to achieving clinical adoption. Analytical methods include key tests to verify protein or antibody identity, assess potency, detect product- or process-related contaminants, and characterize post-translational modifications (PTMs). By incorporating an Analytical Target Profile (ATP) into enhanced quality attribute monitoring, we ensure that our methods are aligned with your specific therapeutic goals and regulatory requirements, providing a clear framework for your process control strategy.

Equally important in biologic drug substance development is formulation. By developing DS/DP formulations that address patient needs and optimizing key attributes such as ionic strength, pH, shear forces, and surfactants, stability can be enhanced, storage conditions improved, and delivery options expanded. Product stability is critical, as it confirms shelf life and efficacy over time, ensuring consistent performance and patient safety—both essential in the pharmaceutical industry.

Method development

- **Identity:** Peptide mapping (UV), imaged capillary isoelectric focusing (icIEF), ion exchange (IEX)
- **Purity:** Capillary gel electrophoresis (CE-SDS), size exclusion chromatography (SEC), imaged capillary isoelectric focusing (icIEF)
- **Activity and potency:** Binding ELISA, enzymatic activity
- **Characteristics:** Appearance, pH, osmolality, Protein A titer, A280/SoloVPE, protein concentration
- **Impurity and excipients:** Residual DNA, residual host cell protein (HCP), residual Protein A
- **Characterization:** Multi-attribute method (MAM), N-linked glycan profile, sialic acid

Method establishment

- **Risk assessment:** Evaluate if client's method is suitable for its intended purpose in quality control
- **Method establishment and PD support:** Implement methods to support PD development
- **Method quantitation:** Establish the performance characteristics of methods
- **Method transfer:** Establish qualified or validated methods and assist with transfer to the QC lab

Formulation development

- **Range-finding DoE:** Identify optimal pH, excipient types, and ranges to assess DoE robustness
- **Surfactant screening:** Evaluate surfactants, agitation, and freeze/thaw stability
- **Robustness DoE:** Response surface methodology (RSM) used to optimize pH and excipient levels
- **Forced degradation studies:** Gain an in-depth understanding of degradation pathways

Stability testing

- **Short-term:** Six or more months to evaluate final formulation
- **Accelerated:** Use established parameters to estimate long-term stability
- **Stressed storage conditions:** Evaluate formulation stability at higher temperatures, etc.

Process characterization and validation

Understanding how process parameters affect the quality of your final biologic drug product is critical on the path to commercialization. A clearly defined, well-understood process can prevent costly missteps, such as batch losses and time-consuming rework, which often lead to manufacturing delays. This knowledge base enables better decision-making around common challenges throughout the product lifecycle and minimizes batch-to-batch variability.

Process characterization (PC) studies are important for several reasons:

1. Establishment of the commercial process control strategy
2. Definition of product and process specifications
3. Enablement of successful process performance qualification (PPQ), manufacturing campaigns, and regulatory filings
4. Support for flexibility and robustness of the commercial process
5. Our workflows incorporate risk-based and knowledge-based quality by design (QbD) approaches to systematically link process design and control to a product's critical quality attributes (CQAs)

Our process characterization studies include:

- **Unit operation studies** that explore parameter optimization, performance, and impacts on critical quality attributes (CQAs). Each unit represents a step in the manufacturing process, including cell expansion and purification.
- **Clearance studies** for process-related reagents and impurities, such as DNA, residual chemicals, and host cell contaminants, including evaluation of detection methods and optimization of impurity removal and product purification strategies.
- **Cell line stability studies** that monitor genetic and phenotypic stability and evaluate cell line performance over extended time periods and multiple passages.
- **Buffer and media hold studies** to assess chemical and physical stability under different storage conditions and their effects on product quality.
- **In-process biochemical holds studies** focused on the stability of intermediates or in-process materials during manufacturing.
- **Hold time evaluations** to assess the impact of hold times on the stability and quality of in-process materials. This includes biochemical stability and strategies to minimize the impact of hold time effects.

Clinical and commercial manufacturing

Robust manufacturing that scales with your needs

Clinical and commercial manufacturing are crucial final steps in bringing your life-changing biologic product to patients in need. Accurately anticipating and meeting demand can be challenging, even when your process is well-established. An insufficient supply can delay clinical trials and market adoption, while excess production can lead to wasted resources and increased costs.

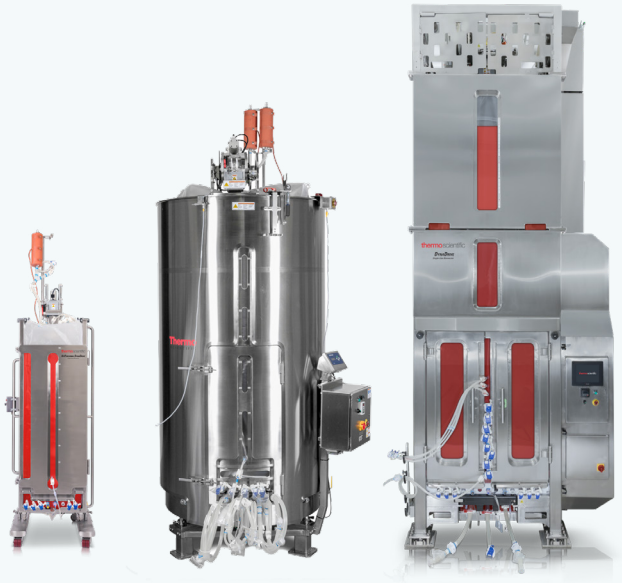
Clinical biologics manufacturing starts at 500 L, with commercial manufacturing supported at batch sizes of up to 10,000 L (when utilizing a multiplex concept). Several intermediate production sizes are also available to best meet the needs of your project. As part of the project, you will also receive:

- CGMP materials
- End-of-production cell banks
- References standards

This enables reproducible production.

Commercial manufacturing of biologics in Brisbane, Australia.

Our facilities utilize single-use technology (S.U.T.)*



500 L **2,000 L** **5,000 L**

500 L, 2,000 L, and 5,000 L Thermo Scientific™ DynaDrive™ Single-Use Bioreactors

Single-use bioprocessing equipment incorporates disposable (single-use) bags, liners, and tubing to prevent samples from coming into direct contact with equipment. This minimizes contamination risks and enhances production efficiency. Single-use bioreactors (S.U.B.), such as the Thermo Scientific DynaDrive 5,000 L S.U.B., enable efficient and scalable manufacturing, allowing you to adapt to market demands with flexibility.

Advantages of single-use technology (S.U.T.):

- **Reduced labor risk and improved space utilization:** A high turndown ratio of 20:1 reduces seed train requirements and increases facility space efficiency.
- **Lower upfront and operational costs:** Single-use systems reduce cleaning expenses, and the ability to scale efficiently also helps lower start-up costs.
- **Greater flexibility:** Quick, easy technology transfer between bioreactors and sites. Thermo Scientific DynaDrive bioreactors are designed for seamless scale-up, with bioprocessing bags made from the same Aegis5-14 film.

Technical transfer

Whether you begin with us or are looking to expand capacity for an existing commercial process, we can help. Our global technical transfer team—comprised of experienced Manufacturing Science and Technology (MSAT) professionals—works closely with clients to build flexible processes grounded in quality standards, accelerated timelines, and opportunities for

Highlights of our technical transfer process:

- **Custom facility fit assessment:** Using customer-provided information, our MSAT team adapts your procedures to our equipment. They perform hundreds of process assessments each year and often identify opportunities for cost savings.
- **Standardization across sites for global manufacturing flexibility:** We provide consistent customer support, chemical supplies, and error prevention across sites. Leveraging our global network enables robust supply chains and economies of scale for critical chemicals and consumables.
- **Clear communication:** We use stage-gate planning and detailed procedures to quickly identify, communicate, and ideally mitigate production delays. We also leverage RACI charts—a project management tool that clarifies roles and responsibilities—to ensure accountability and streamline communication for efficient project execution.

Path to IND for biologics:

Conquer key challenges in biologics development to obtain clinical packaged material in as little as nine months*

What is Path to IND for biologics?

Path to IND for biologics is a one-of-a-kind biologics development platform that delivers titer levels of up to 8 g/L* for mAb, bispecific, or Fc-fusion molecules. Leveraging Thermo Fisher Scientific's state-of-the-art equipment, advanced software, and full access to the depth and breadth of our resources—including raw materials and CRO services—this platform does more than develop your biologic. It enables simultaneous IND/IMPD submission and initiation of Phase I clinical trials, funding and all, with a ready-to-use drug product in as few as nine months.*

- **Engineered for success:** Leverages AI/ML-driven vector and gene construction, high-yield CHO-K1 cell lines, and afucosylated and transposase technology
- **Proven performance:** Multi-attribute method (MAM), leveraging liquid chromatography-mass spectrometry (LC-MS), to obtain glycan profiling, purity, and charge variant data
- **Faster timelines:** Advance from DNA to Phase I clinical trials in as little as 9 months* with an integrated CDMO and CRO partner
- **Higher titers:** Achieve unprecedented titer levels of up to 8 g/L* across complex molecules, including Fc-fusions and bispecifics
- **Regulatory support:** Benefit from our deep understanding of regulatory requirements to help ensure compliance and mitigate risks
- **Preclinical manufacturing:** Assured high quality and regulatory compliance throughout cell line development, production, and toxicology testing
- **Analytical testing:** Comprehensive testing services to help ensure the safety, purity, and potency of your biologics

Table 1. Path to IND for biologics: Timeline and options by molecule type IgG1- and IgG4-based biologics

Timeline	What you provide	What we use	What we do	What you get
Option 1				
DNA to drug product (DP) release in as few as 9 months*	DNA sequence/gene	• Transposase technology in CHO-K1 GS knockdown cell line system, along with platform process, formulation, and analytics using commercially available raw materials.	• Cell line development	• **Early non-GLP toxicology material** • **Released drug substance** • **Released drug product** • **Stability data for IND Templated quality-reviewed reports** • **Clinical trial packaging and labeling**
Option 2				
Research cell bank (RCB) to drug product (DP) release in as few as 12 months*	RCB of stable pool or final clone	• Your cell line RCB, media/feed strategy*, and cell stability data. • Our platform process, as well as formulation and analytics development.	• Evaluation of our platform process • Platform formulation • Analytical methods • Toxicology batch • cGMP batch at any scale • Validation and characterization study • Stability testing	

Table 2. Path to IND for bispecific and Fc-fusion-based biologics

Timeline	What you provide	What we use	What we do	What you get
Option 1				
DNA to drug product (DP) release in as few as 13 months*	DNA sequence/gene	• Transposase technology in CHO-K1 GS knockdown cell line system, and our platform processes and analytics with commercially available raw materials.	• Cell line development	• **Early non-GLP toxicology material** • **Released drug substance (DS)** • **Released drug product (DP)** • **Stability data for IND** • **Templated, quality-reviewed reports** • **Clinical trial packaging and labeling**
Option 2				
Research cell bank (RCB) to drug product (DP) release in as few as 14 months*	RCB of stable pool or final clone	• Your cell line RCB, media/feed strategy*, and cell stability data. • Our platform processes and analytics with commercially available raw materials.	• Evaluation of our platform process • Formulation development • Platform analytical method development • Custom analytical method development • Toxicology batch • cGMP batch at any scale • Stability testing	

Figure 1. Path to IND services start at our St. Louis, MO, US site and are then scaled up in Groningen, the Netherlands. Sterile fill-finish is completed at our Ferentino or Monza, Italy sites.

Path to IND capabilities	St. Louis, MO, USA	Groningen, NL
Cell line development	✓	
Process development	✓	
Analytical and formulation development	✓	
Preclinical-scale production	50-250 L	
Clinical-scale production		500-2,000 L

Figure 1. Capabilities of the Path to IND for biologics. Cell line development through clinical-scale production process development, as well as analytical and formulation development, are completed at our state-of-the-art facility in **St. Louis, Missouri**. The process is then transferred to the **Groningen, Netherlands facility** for clinical-scale production up to 500–2,000 L. Lastly, it moves to the **Ferentino** or **Monza, Italy site for sterile fill-finish**.

* Terms and Conditions: Titer levels provided are estimates based on third-party results and may vary depending on molecule type or other factors. Timelines from DNA to drug product and start of clinical trials for all Path to IND for biologics options may vary based on molecule type or other factors and are estimates to be finalized after third-party cell line development dates are available and confirmed. The nine-month timeline may incur additional risk.

Global network of biologics sites

Our global network of four biologics sites can help you scale production when needed, supported by the latest equipment and expert teams. Learn more about our sites.

St. Louis, Missouri, US

The **St. Louis, Missouri site** spans over 525,000 sq. ft., with 105,000 sq. ft. allocated to CGMP production.

- Center of excellence for bioprocessing and single-use technology
- Home of our Bioprocessing Collaboration Center (BCC), where we create and optimize cell lines (from in-house or provided cell banks)
- Batches completed (2018–2024): 295 commercial, 198 clinical, and 82 PPQ

Brisbane, Australia

The **Brisbane, Australia site** is a state-of-the-art facility with 118,403 sq. ft. of manufacturing space and 43,055 sq. ft. of warehouse space.

- GMP capabilities for Phase I, II, and III clinical manufacturing
- 100% single-use bioreactors
- Batches completed (2018–2024): 24 commercial, 97 clinical, and 22 PPQ

Groningen, Netherlands

The **Groningen, Netherlands site** is an 18,000 sq. ft. facility dedicated to CGMP manufacturing and includes more than 3,700 sq. ft. of space for analytical testing.

- Center of excellence for new product introductions (NPIs)
- Clinical production site for Path to IND program
- Batches completed (2018–2024): 65 commercial, 90 clinical, and 12 PPQ

Lengnau, Switzerland

The **Lengnau, Switzerland site** is a 1.5 million sq. ft. facility with 174,400 sq. ft. dedicated to CGMP manufacturing.

- Single-use suite featuring 5,000 L DynaDrive Single-Use Bioreactors
- Stainless steel bioreactors, including two large 12,500 L bioreactors
- Newer site with 1 PPQ batch completed in 2024

Choose the right partner

Contact us to learn more about our biologics development and manufacturing capabilities.

Learn more at thermofisher.com/patheon