Tech Brief

Lay the Proper Foundation for Upstream Success

Decisions made early in clinical development may impact the journey of your molecule and ultimately, success of the commercial strategy. Among these decisions are the selection of a partner for development of upstream processes. You need speed, quality and regulatory compliance – all appropriately balanced.

Our experts have decades of bioprocessing experience and work in close collaboration with biopharmaceutical companies of all sizes to overcome even the most challenging upstream development and processing challenges. Our upstream ecosystem – comprised of cell line and media platforms, cell line development, cell line and product characterization services, single-use bioreactors and mixers, process development services, and next generation processing programs – gets upstream development right the first time.

Figure 1. Our upstream ecosystem, featuring products, services, and expertise for upstream development and manufacturing.

The Life Science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Millipore®
Preparation, Separation, Filtration & Monitoring Products

SAFC®
Pharma & Biopharma Raw Material Solutions

BioReliance®
Pharma & Biopharma Manufacturing & Testing Services

Success Starts Here: Cell Lines, Cell Culture Media and Raw Materials

The CHOZN® Expression Platform for High Productivity and Scalability

The CHOZN® expression platform is built on Chinese Hamster Ovary (CHO) cells genetically engineered for fast and easy production of monoclonal antibodies and other recombinant proteins. This platform allows for easy selection of stable clones producing high levels of recombinant proteins with proven scalability from R&D to Clinical scale production. The CHOZN® GS-/- cell line has had endogenous glutamine synthetase (GS) genes deleted using CompoZr® Zinc Finger Nuclease (ZFN) technology, and is auxotrophic for L-glutamine. The platform is provided under flexible licensing terms and no royalty obligations.

This glutamine auxotroph cell line is designed to be used with an optimized expression vector that contains the GS gene and expression cassettes. This allows for easy insertion of your gene of interest or antibody heavy and light chain cassettes into the platform vectors. Importantly, our cell lines have been part of the regulatory dossier with multiple regulatory agencies including those in the US, Japan, China and the EU.

Learn More

Application Note:
The Combination of Ubiquitous Chromatin Opening Element (UCOE®) Expression Technology with the CHOZN® Platform Reduces Resources and Cell Line Development Timelines

Webinar:
Accelerate Delivery of High Producing Cell Lines

Cell Culture Media Tailored to Your Needs

Selection of the right media is critical for optimizing upstream operations and setting the stage for successful clinical and long-term commercial production. This is no small task. Media formulations are complex with many components to consider and must be tailored to the cell line, molecule and process. Every chemical within the formulation can have an impact on the production process, titer and product quality; determining whether a component is included in the formulation, and if so, at what concentration, can be a laborious and time-consuming exercise that can pull resources from other mission critical activities.

We offer a proven, ready-to-use cell culture media portfolio for fed-batch and perfusion applications supporting your needs from expansion to production scale. We have supplied the biopharmaceutical industry with media for upstream processes for 40 years and our media are used in seven of the top 10 biologics based on revenue.

Our Cellvento® 4CHO and EX-CELL® Advanced media platforms are optimized for CHO cell expression. For fed-batch applications we offer a set of feed designs that can be combined with our media or other basal media as well.

We've also pioneered advances in cell culture technology in upstream processing. Cellvento® 4Feed is a highly concentrated feed that includes our new modified amino acids and compaction technology. EX-CELL® Advanced HD Perfusion medium is specifically designed for perfusion application and Cellvento® 4CHO-X is designed to enable seed train intensification (N-1) addressing the different nutrient demand in perfusion. All products are proven to contribute to superior cell growth and productivity and are designed to support flexibility in production and increase of capacity.

If you need a custom formulation, our media development services range from rapid screening projects to comprehensive exploration of formulations development using high throughput technologies and multi-variant analysis. These services combine our extensive portfolio of off-the-shelf and custom cell culture products and a best-in-class team of experts with a proven track record of success working with a diverse set of biologics and process requirements. This multi-disciplinary team brings together the unique combination of expertise, experience and project management skills required to anticipate the challenges presented by each project, understand client objectives, exceed expectations and deliver long term success.

Case Study:
Optimizing a Media Formulation to Deliver Higher Titers

Challenge: The company sought an expert partner to develop a single cell culture media formulation that could be used in production of a monoclonal antibody about to enter Phase II clinical trials. The current process required three media formulations, each sourced from a different supplier and contained animal-derived products. It was essential that the new formulation delivered an increased titer while preserving critical quality attributes (CQAs).

Solution: Using the customer's cell line, our media development team screened a variety of media formulations and optimized a single formulation that enabled the antibody titer to more than double while maintaining equivalent CQAs. Additionally, moving to a chemically defined platform, increased process robustness and mitigated regulatory concerns. The entire screening and optimization process, followed by a tech transfer of the formulation to the customer, required only seven months.

Emprove® Dossiers to Fast Track Qualification, Risk Assessment and Process Optimization

Cell culture media drives the productivity of upstream processes and helps ensure critical quality attributes of the final drug product. Because of this key role in manufacturing, along with increased regulatory focus on raw materials, it is recommended that media be included in drug product risk assessments.

A number of cell culture media are now included in our Emprove® program to enable fast track qualification, risk assessment and process optimization. The program provides comprehensive information in the form of dossiers to help select and qualify our CHO media platforms. The dossiers eliminate the time- and resource-intensive compilation and provide support throughout the stages of your operation.

Three types of dossiers are available:

- Material qualification – accelerates media qualification and supports preparation for regulatory filing
- Risk assessment – provides information on the quality management system applied, the supply chain and media stability data
- Process optimization – contains information on typical levels of trace elements, information on origin of raw materials and analytical procedures

Contract Testing Services at Every Phase

Our BioReliance® contract testing services supports every phase of the testing, development, and manufacturing process with a comprehensive and integrated package of services.

Upstream, we perform cell line characterization as required by the regulatory bodies to confirm the species origin and history of the cell line. Tests are typically conducted on cell lines, working cell banks (WCB), and master cell banks (MCB). Upstream biosafety tests are implemented on both raw and bulk materials. Our product characterization services include stability testing, product and reference standard characterization, and comparability and lot release testing.

Support for all phases of drug development

Service	Pre-clinical	Phase I	Phase II	Phase III	Commercial
Cell banking & testing	●	●	●	●	●
Raw materials testing	●	●	●	●	●
Lot release testing	●	●	●	●	●
Clearance validation		●		●	
Virus manufacturing	●	●	●	●	●

Learn More

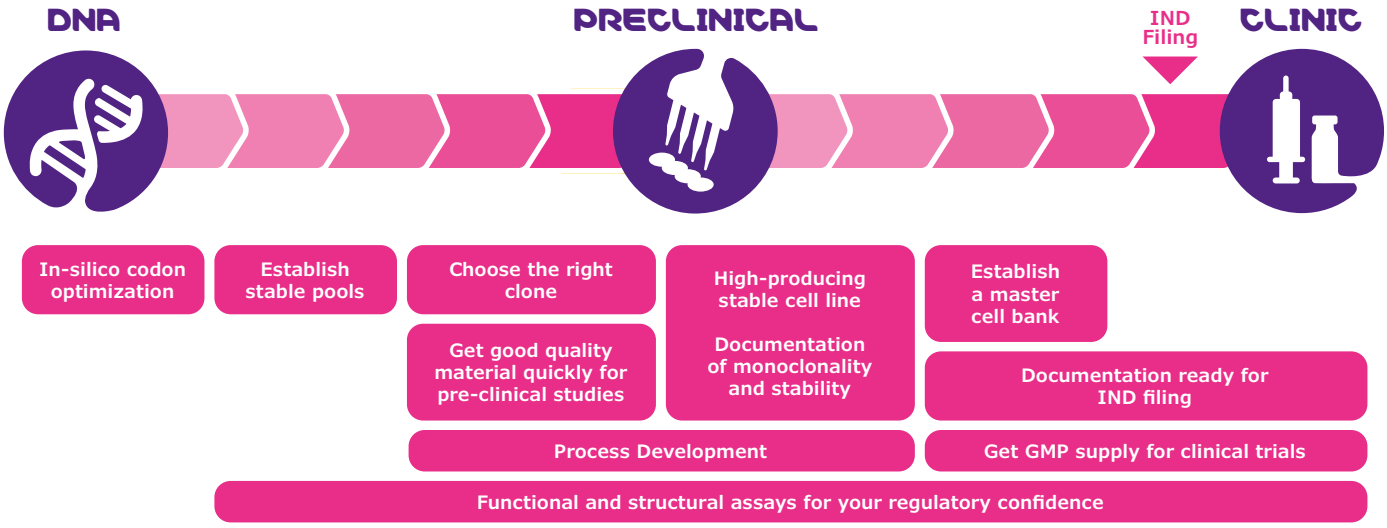
Article:
Viral risk mitigation – a regulatory perspective

Web:
MerckMillipore.com/virus-prevent-detect-remove

Take a Plug and Play Approach: Upstream Development Service

Our Plug & Play Upstream Development Service is designed for emerging biotechnology companies needing to advance confidently and efficiently toward key milestones, with the assurance of complete regulatory compliance. Our success in developing processes that ultimately lead to IND filings and beyond is a testament to our broad expertise and enabled by decades of experience.

Our contract development and manufacturing services, delivered through BioReliance® End-to-End Solutions effectively and strategically balance speed, risk and cost. We have over 30 years in process development experience, greater than 270 biologic projects completed. We do this through flexible solutions, by leveraging our bioprocessing technologies and process development expertise, and by allowing our clients to transfer their process and knowledge to their end point at any step of their drug development.



Learn More
MerckMillipore.com/plug-play-upstream

Case Study:
Increasing the Titer of a Difficult to Express Molecule

Challenge: A customer came to us with a protein sequence and a goal of developing a high-producing cell line capable of delivering the necessary titer of molecule to support clinical development. A single transfection of our proprietary CHOZN® GS-/- cell line, the first-ever commercially available glutamine synthetase (GS) knock-out CHO cell line, had delivered a final low titer performance after generation of stable pools. This initial titer was considered insufficient to support clinical studies, possibly putting the development program in jeopardy.

Solution: Many factors can impact molecule expression including the cell line, signal peptide, the DNA sequence of the gene of interest and copy number. To increase titer, a number of approaches can be explored including assessment of alternative signal peptides, copy number increase by super-transfection (repeat transfection of already-transfected cells) in combination with L-methionine sulfoximine (MSX) selective pressure and MSX addition screening.

Our BioReliance® End-to-End Solutions team utilized these approaches to boost titers. Use of alternative signal peptides failed to improve the titer. Our team was able to leverage super-transfection, combined with the use of MSX selective pressure, and increased the molecule titer nearly 4-fold after generation of stable pools. The increase of the gene of interest copy number was expected. The MSX addition screening enabled a 6 fold increase in titer for some mini-pools.

Case Study:
End-to-End Services from DNA Sequence to GMP Manufacturing

Challenge: The customer, for whom we performed the media screening and optimization for a different project, sought to convert a current cell line to the CHOZN® platform, followed by process development and GMP manufacturing. The company was already working with a CDMO and wanted to transfer their program to a well-established CDMO, able to effectively balance speed and risk, without sacrificing quality and compliance.

Solution: The company engaged our BioReliance® End-to-End Solutions team for cell line development through GMP manufacturing. Key factors driving this decision included the previous, positive experience with the media development team, the reputation of our organization in the region as well as our local experience, including that with regulatory agencies. The documented history of success of the CHOZN® cell line in industrial production of monoclonal antibodies coupled with previous success with cell culture media development services from us was also a critical factor.

Our BioReliance® services team conducts cell line (master and working cell banks and production cell line) and product characterization, as well as biosafety testing.

Integrating Products and Services

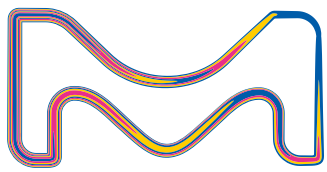
A successful solution requires integrated products and services. The capabilities and case studies presented within this Tech Brief demonstrate how we combine industry-leading products and customer-focused services to deliver state of the art solutions and support for customers developing innovative therapies. Technical, regulatory, and quality consulting experience underpins the value we bring to product development and the regulatory review and submission process. From media development to delivering clinical material, our project management is key in providing an unmatched customer experience, and ultimately accelerating development of your molecules.

Learn more

MerckMillipore.com/plug-play-upstream
MerckMillipore.com/upstream

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

For additional information, please visit **www.MerckMillipore.com**
To place an order or receive technical assistance, please visit **www.MerckMillipore.com/contactPS**



Lit. No. MK_WP8271EN Ver. 0.1
03/2022