Lonza

Mammalian Cell Culture

Process R&D Services

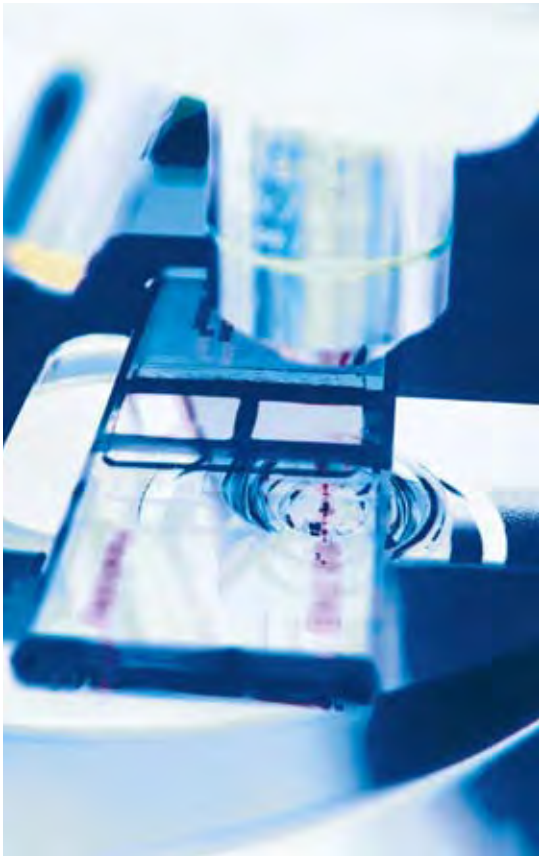
Lonza's global R&D center for mammalian cell processes is based in Slough, UK (near London's Heathrow airport) alongside our custom manufacturing facility. Lonza undertakes highly specialized development and manufacturing services for the pharmaceutical and biotechnology industries. This is based on over 25 years of experience in mammalian cell culture and development of proprietary technology for small- and large-scale manufacture of innovative biopharmaceutical products.

Lonza is able to offer a complete range of R&D Services and an array of technologies and skills to best match our customers' requirements for all stages of product development. This includes assisting in product design for manufacturability, creating cell lines and developing processes through to commercial-scale manufacture. Lonza's services are flexible and are created through close interactive partnerships with our customers who may request Lonza to perform a complete development program or individual work packages based on Lonza's or customers' technology.

In addition to providing services, the R&D center is also actively engaged in developing new technology and services to meet our customers' future needs. Our aim is to maintain technical leadership through in-house innovation and by collaboration with academic and commercial partners. We have recently acquired the AggreSolve™ screening technology from Zyentia Ltd. and have partnered with BioWa to introduce its Potelligent® technology into CHOK1SV cells. We encourage potential collaborators with innovations in the area of bioprocessing to discuss their ideas with us.

Project Management

At Lonza, we are committed to our customer's success, so it is our mission to ensure your product reaches its full potential. We pride ourselves on delivering high-quality, flexible service that is both responsive and pro-active. Every program at Lonza is assigned a dedicated Customer Project Manager who anticipates and resolves unforeseen challenges while leading the project team to deliver results. This internal advocate coordinates all activities associated with your project and ensures you are continually updated on its progress. Ther goal is to drive the project to make sure the agreed upon activities, timelines, and budget are met to your complete satisfaction.



List of R&D Services

As you would expect from a contract manufacturer with over 25 years experience, Lonza offers a full set of process and analytical development, optimization and validation expertise. A non-exhaustive list of such activities is provided below:

- AggreSolve™ technology
- GS Gene Expression System™ and CHOK1SV cell line
- Vector construction
- Cell line construction and cloning
- Cell bank preparation and characterization
- Cell line stability assessment
- Genetic characterization of the cell line
- Cell culture process development
- Cell culture process optimization
- Purification process development
- Purification process optimization
- Virus reduction studies
- Development of specific analytical procedures
- Importing customer's assay(s) and qualification at Lonza
- Formulation studies for simple liquid formulations
- Extinction coefficient determination
- Product stability studies
- Reference standard creation and characterization
- Product comparability (e.g. for earlier reference standard or product lots)
- Process scale-up
- Process and assay validation required for product license applications
- Providing information for regulatory documentation

AggreSolve™ Technology

Lonza has recognized the need to support product design for manufacturability and has expanded its offering to include tools for predicting the tendency of a product to misfold and aggregate. AggreSolve™ is a comprehensive in silico protein analysis platform that can be applied to solving the problems posed by protein aggregation and low stability.

The Key capabilities of the AggreSolve™ platform:

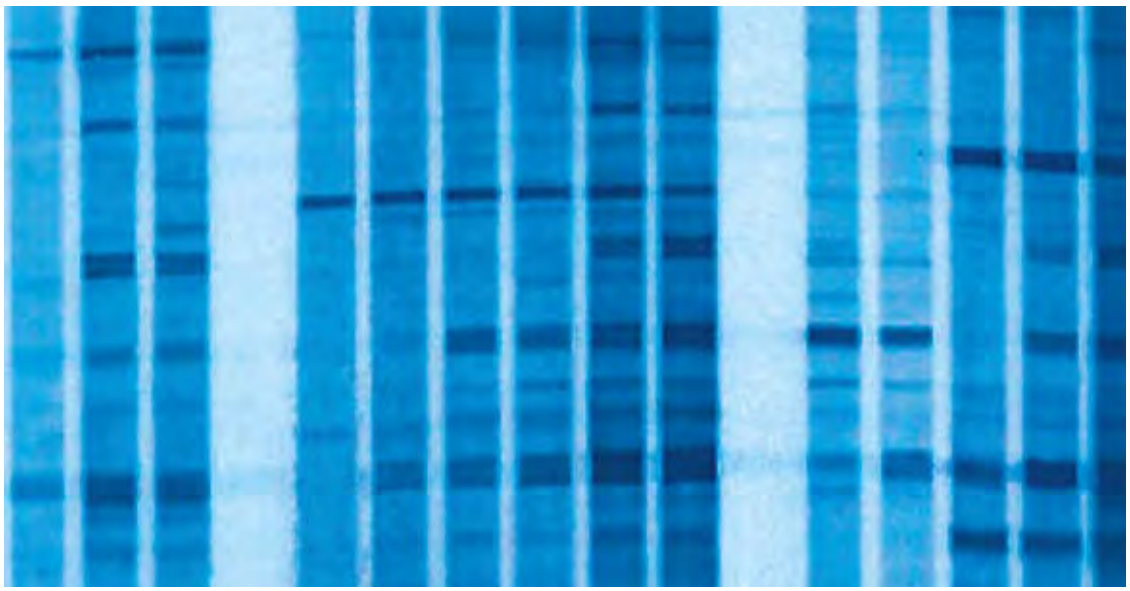
- Assessment of product development potential based on its aggregation and stability profiles
- Screening of protein variants to select those with optimal stability
- Identification of sequence changes likely to reduce aggregation
- Design of aggregation inhibitors and stabilizers

GS Gene Expression System™

Lonza's powerful proprietary GS Gene Expression System™ (GS: glutamine synthetase) is used internationally by over 95 global pharmaceutical and biotechnology companies and by over 75 academic laboratories to provide rapid development of high-yielding and stable mammalian cell lines. Cell lines with the GS Gene Expression System™ are being used to make 5 licensed products and many more products that are in development. Many investigators also use the GS Gene Expression System™ as a tool to generate recombinant proteins for research purposes. The GS Gene Expression System™ is complemented by the CHOK1SV cell line, a variant of the CHO-K1 cell line that grows in suspension culture using chemically defined, animal component-free medium.

Additional offerings include:

- Constant region vectors – pConPlus vectors
- Host cell protein Western blotting assays
- Host cell protein ELISA assays
- Methionine sulphoximine assays

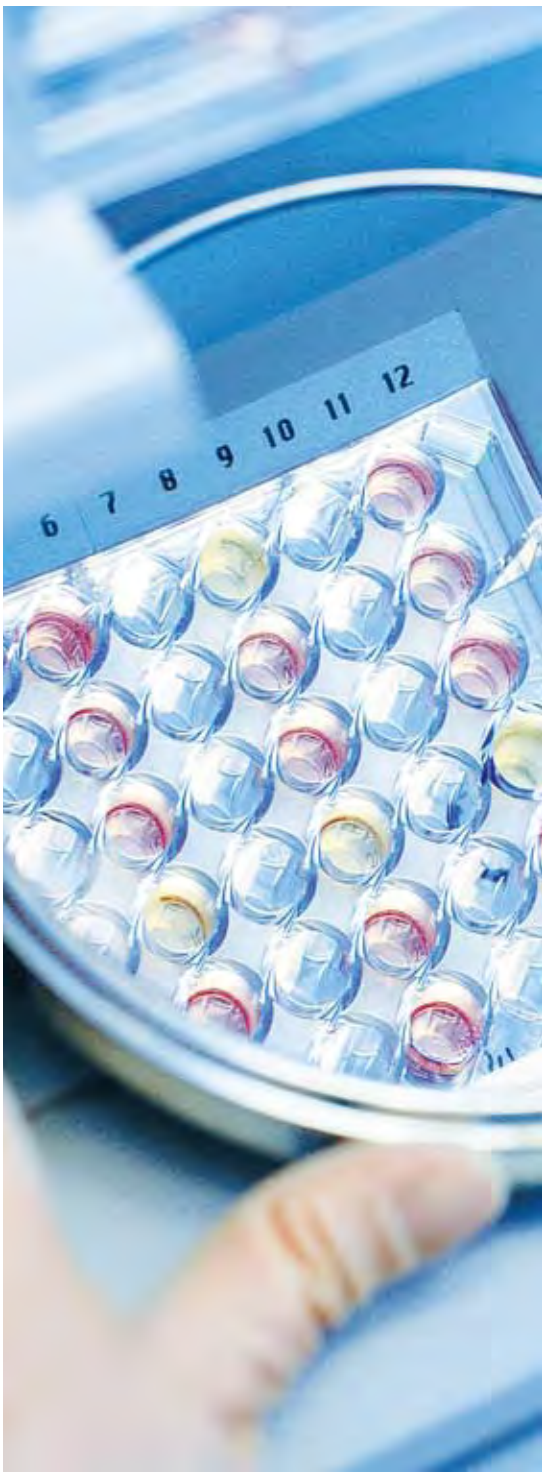


Cell Culture Process Development

Following the creation of a new cell line, or receipt of an existing cell line from our customer, a program of development and scale-up work can be undertaken to establish a cell culture process that is suitable for manufacturing purposes. Typical studies at this stage would include selection of a culture medium, definition of an inoculum expansion and fermentation production process, including feeding strategies, and cell line stability studies.

Lonza has experience developing a wide range of scaleable processes for a variety of expression systems and cell lines including CHO, mouse myeloma, hybridoma and a variety of human cell lines. This includes the optimization and scale-up of processes received from our customers and transferred to Lonza's manufacturing facilities.

Lonza has made a considerable investment in the development of proprietary culture media and feeds for cGMP manufacturing, which are chemically defined and animal component-free. In the case of antibodies produced by GS-CHOK1SV cell lines titers of 2 to 4 grams per liter are typically obtained using a platform process that allows rapid progression into manufacturing. Further optimization can be undertaken for individual cell lines. For antibodies and other proteins, titers of up to 7 grams per liter have been achieved. Such cell line-specific optimization programs are often performed in parallel with the manufacture of early material for clinical trials using one of Lonza's platform production processes.



Cell Line Creation

A key factor in reducing the production costs of biopharmaceuticals for our customers is the development of cell lines producing a high product titer. For recombinant monoclonal antibodies (MAbs) and other proteins, Lonza can create vectors to express product using the GS Gene Expression System™ technology with either the CHOK1SV or the NS0 host cell lines. The selection strategy has been designed to identify cell lines that are highly productive and have the ability to grow well in suspension culture in state-of-the-art, fed-batch fermentation processes. In the case of antibodies, titers of 2 to 4 grams per liter are routinely achieved. In addition for other proteins, titers of up to 4 grams per liter have also been achieved.

Lonza recognizes the economic importance to our customers of speed in process development. Cell line creation is particularly important in this respect and the GS Gene Expression System™ offers significant time benefits. Creation of GS cell lines at Lonza typically takes 12 to 18 months from DNA to provision of cGMP material, depending on the specific needs of the project. Early (non-GMP) development material (up to 20 grams per batch) can be provided from transfected pools of cells, typically within 3 months.

Cell Banking

A dedicated cGMP unit within our licensed UK manufacturing facility is used to create cell banks appropriate for manufacturing use. The cell banks are characterized with consideration to ICH guidelines. For safety and security considerations, dual-site storage can be provided at our US and UK facilities.

Purification Process Development

Lonza has extensive experience in the development and validation of purification processes for the large-scale manufacture of a wide range of therapeutic proteins. These include recombinant monoclonal antibodies, antibody fragments, fusion and chemically conjugated proteins, hormones and enzymes. In addition to developing processes, Lonza is also experienced with transferring customers' processes into our facilities. To ensure the successful development and transfer of an integrated process, and to minimize the development timeline, purification development activities are performed in parallel with fermentation and assay development. Additionally, to enable other development studies to be initiated, the provision of early (non-GMP) development material can be met using one- or two-step platform purification methods. Target specifications for non-GMP and GMP product are defined with our customer at the outset of the project.

Antibody Purification
Lonza has developed purification processes for over 100 different antibodies. For most antibodies Lonza can implement a well-established platform process based on Protein A affinity chromatography followed by ion-exchange separation. Nanofiltration and low pH hold steps are included in the purification process as specific virus reduction steps.

Recombinant Protein Purification
Lonza has developed purification processes for a large number of non-antibody recombinant proteins using a wide variety of chromatographic operations.

Analytical Capabilities

Lonza has analytical capabilities and expertise that encompass a wide range of technologies to support all stages of product and process development. These have been applied to monoclonal antibodies, antibody fragments, fusion proteins, chemically conjugated proteins, hormones and enzymes.

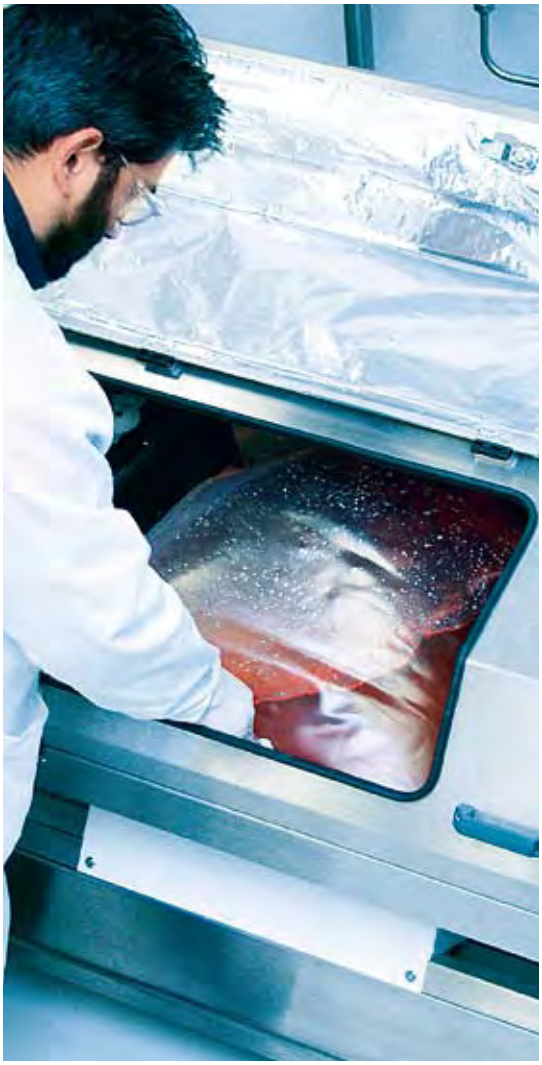
Validated analytical methods are available to support release of early phase clinical material. These methods have also been successfully used to support license applications following product specific validation.

Our analytical experience is applied to support a range of services including:

- Analytical method development
- Analytical method validation and transfer
- Bioassay transfer and validation
- Product characterization and biochemical comparability
- Process development
- Process characterization
- Reference standard characterization
- Elucidation of structure
- Biochemical comparability
- Product isoform characterization
- Product stability studies
- Pre-formulation studies
- Drug substance stability studies
- Drug product stability studies
- Forced degradation studies
- Impurity assay testing
- Process impurity testing
- Product related impurity testing
- Cleaning validation

Process Transfer

Lonza development scientists work closely with process transfer specialists within our worldwide manufacturing and quality groups, together with our customers' experts, to define and document all new processes to create robust manufacturing procedures. Development staff maintain a close collaboration with the manufacturing groups throughout a project lifetime.



Process Validation

For later phase clinical development, Lonza has extensive experience with regulatory agencies worldwide and has validated a large number of processes. The scope of studies performed is dependant on our customers' needs based on the regulatory guidelines. R&D support within a process validation program may include the following activities:

- Characterization of cells at the limit of *in vitro* cell age
- Cell line stability assessment
- Genetic characterization of the cell line
- Additional cell bank characterization
- Process limits studies
- Product specific assay validations
- Process performance consistency studies
- Biochemical comparability
- Reference standard characterization and elucidation of structure
- Reference standard stability study
- Evaluation of virus reduction
- Evaluation of DNA reduction
- Evaluation of resin re-use
- Stability of process intermediates
- Justification of in-market specification

Lonza

Lonza Ltd
Muenchensteinerstrasse 38
CH-4002 Basel, Switzerland
Tel +41 61 316 81 11
contact@lonza.com

Lonza Inc
90 Boroline Road
Allendale, NJ 07401
Tel +1 201 316 9200
contact.allendale@lonza.com

www.lonza.com