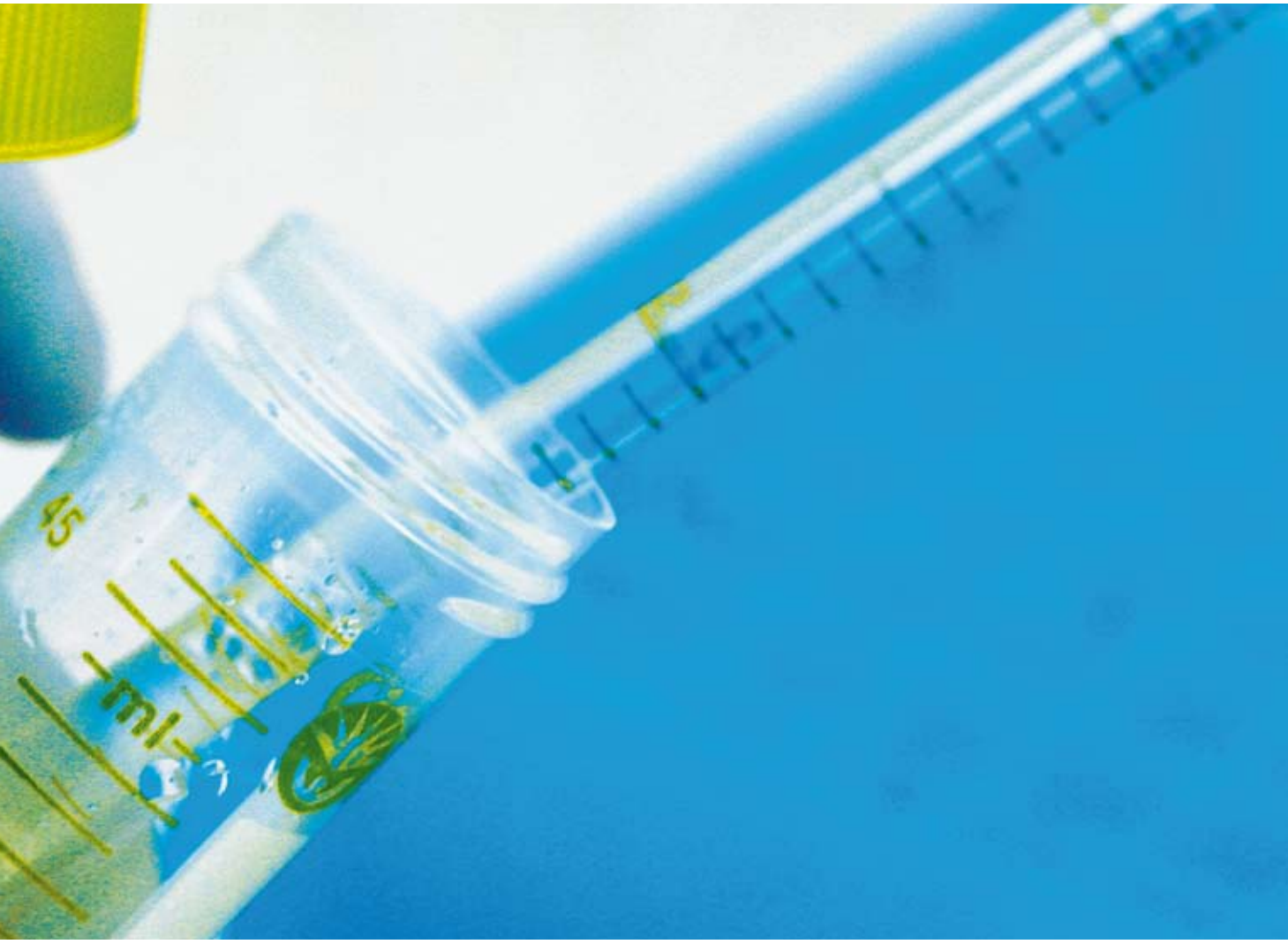
Lonza

GS Gene Expression System™



The GS Gene Expression System™

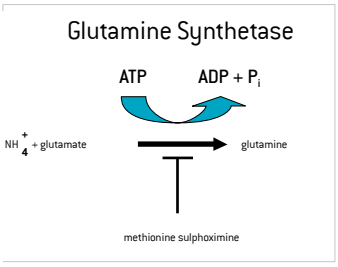
Lonza's powerful proprietary GS System™ uses a robust viral promoter and selection via glutamine metabolism to provide extremely rapid development of high-yielding, stable, cGMP-compatible mammalian cell lines. The GS System™ is successfully used by over 85 global pharmaceutical and biotechnology companies and is familiar to all worldwide regulatory authorities who have already approved 5 licensed products which use the GS System™ including Zenapax® (Roche) and Synagis® (Medimmune).

The international use of the GS System™ by both commercial organisations and academic institutions has lead to a large body of published information. New users can draw upon this material to expand their knowledge and skill base and improve their use of the GS System™.

Lonza has itself created over 250 cell lines using the GS System™, many of which have been grown at large-scale and produced product for use in clinical trials and in-market supply. Other GS System™ users have also accumulated experience with a diverse range of products where high yields have been achieved. Many investigators use the GS System™, not only to develop a manufacturing process, but as a tool to create recombinant proteins for biological studies. The reliability of the GS System™, as a consistent means of rapidly generating high-producing cell lines, speeds time to market.

Principles of the GS System™

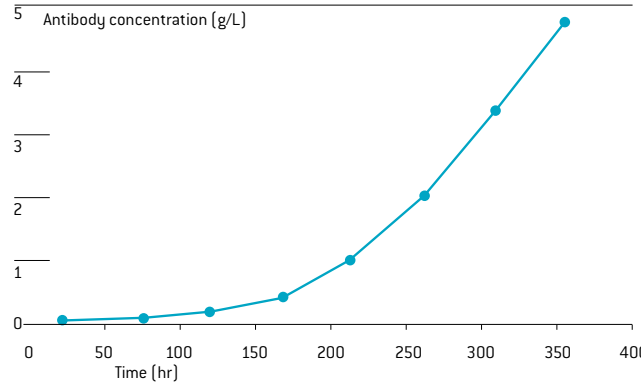
Glutamine synthetase (GS) is the enzyme responsible for the biosynthesis of glutamine from glutamate and ammonia. This enzymatic reaction provides the only pathway for glutamine formation in a mammalian cell.



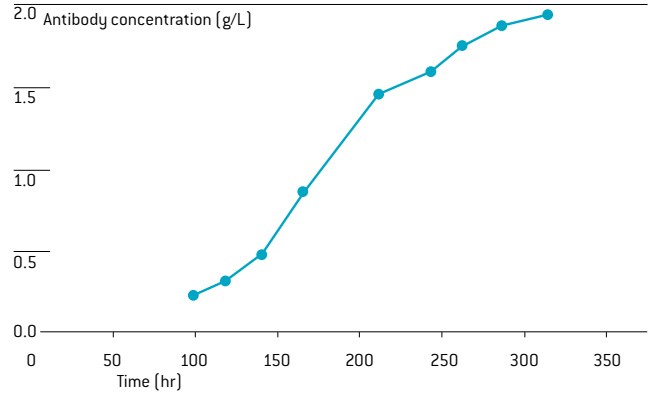
In the absence of glutamine in the growth medium, the GS enzyme is essential for the survival of mammalian cells in culture. Some mammalian cell lines, such as mouse myeloma lines, do not express sufficient GS to survive without added glutamine. With these cell lines, a transfected GS gene can function as a selectable marker by permitting growth in a glutamine-free medium. Other cell lines, such as Chinese hamster ovary (CHO) cell lines, express sufficient GS to survive without exogenous glutamine. In these cases, the GS inhibitor, methionine sulphoximine (MSX), can be used to inhibit endogenous GS activity such that only transfectants with additional GS activity can survive.

Yield The high manufacturing cost of protein products, particularly for therapeutic proteins, means that maximising volumetric productivity is essential if economic processes are to be established. Use of the GS System™ reliably results in high yielding cell lines early in cell construction programmes. Maximum expression levels attainable depend on the product but cell lines producing over 5 g/L of recombinant antibody have been created, with specific production rates in the range of 15-65 pg/cell/day.

Productivity in a chemically defined, protein-free GS-CHO bioreactor process



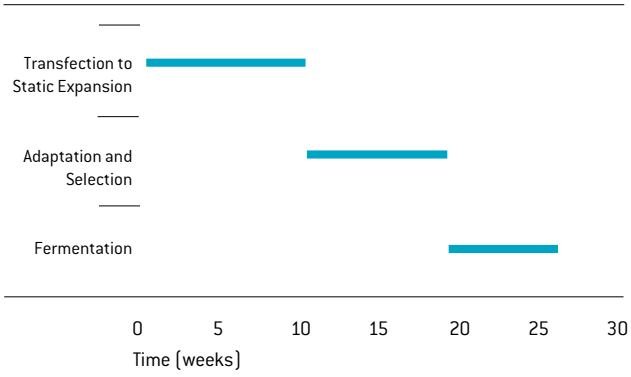
Productivity in a chemically defined, protein-free GS-NS0 bioreactor process



Speed Speed at the development stage of any biotechnology project is crucial to success. The GS System™ allows for rapid selection of high yielding cell lines during the first screen. Even higher yields are achieved through media and process optimization. This significantly reduces the time required to generate a cell line suitable for cGMP manufacture. Construction of full length antibodies with human constant regions is rapid and easy using Lonza's GS constant region vectors which enable the addition of any variable region in a single ligation step.

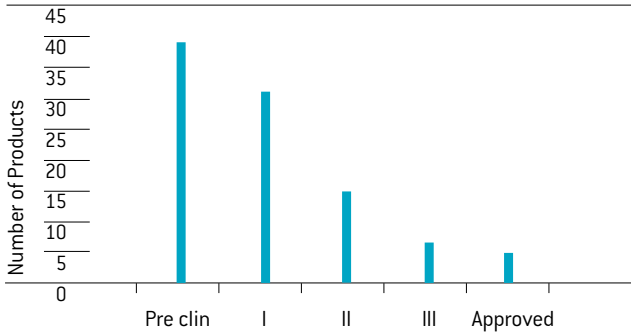
Lonza's proprietary CHOK1SV host cell line facilitates the adaptation to protein-free suspension culture compared to standard CHOK1 processes.

Timeline of steps performed to select high yielding non-clonal GS-CHO cell lines adapted to chemically defined, protein-free medium.



Regulatory Familiarity The GS System™ is well established with over 85 companies using the technology worldwide. Currently there are over 50 products in clinical trials and 5 products in-market that use the GS System™.

Phase of Clinical Trial



Accessing the GS System™

The GS System™ can be easily accessed by contacting the GS team at GSLonza@lonza.com and obtaining a GS Research Evaluation Agreement.

GS Research Evaluation Agreement

A GS REA allows the user to carry out a pre-clinical evaluation of GS with an unlimited number of products.

Standard GS Package

The current standard package of GS materials to which the user has access with a GS REA are:

- GS vectors and sequence data
- Vials of GMP host cell bank NS0
- Vials of GMP host cell bank CHOK1SV
- Transfection medium system
- Comprehensive technical operating manuals
- Cell bank characterization reports to support regulatory submissions
- Access to technical support from Lonza's GS experts
- GS newsletters
- Technology updates

Optional GS Packages

GS customers can augment their standard GS REA package to purchase other proprietary components together with associated know-how. The current optional packages of GS materials to which the user has access are:

- pConPlus vectors
- Serum-free medium system
- Protein-free media systems
- Host Cell Protein Western Blotting Assays
- Host Cell Protein ELISA Assays

GS License Agreement

GS licenses can also be obtained to allow clinical development and commercialization of a product produced using the GS System™. However, users will often continue to hold a GS REA, even with a GS License, to allow for continued evaluation of new products in the laboratory.

Services

In addition, Lonza can create and select GS cell lines as a service for customers and can manufacture cGMP product if required. The advantage of this approach is that Lonza brings years of accumulated GS experience to the project.

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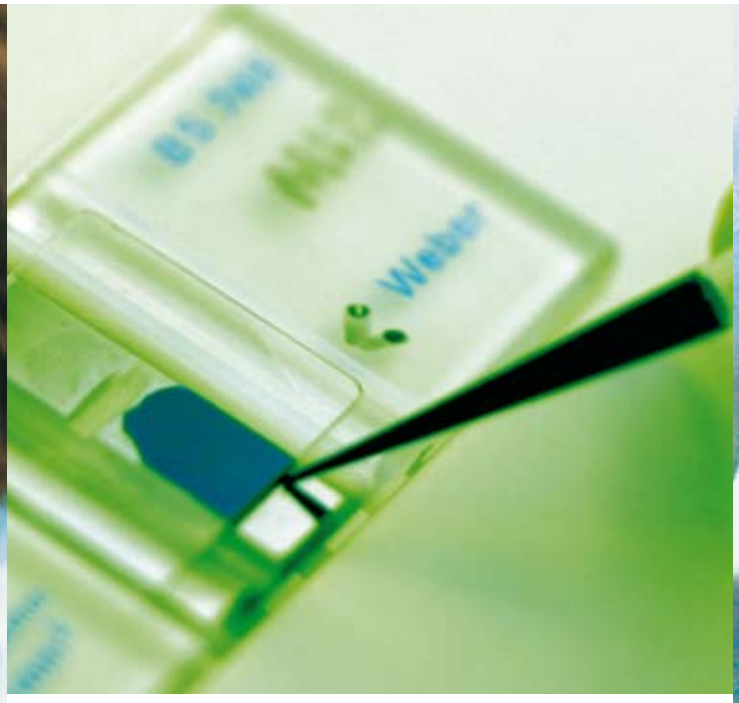

Contact
To access the GS System™, please contact:
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More details can be found at:
www.lonza.com/geneexpressions.html