

BusinessAwareness

ISSUE 5 2009



The GS Gene Expression System™ – the Cornerstone of Lonza’s Mammalian Cell Culture Business

A biopharmaceutical or biological drug, by definition, is a drug produced by using biotechnology and its product types can range from large molecules such as antibodies and proteins, to much smaller moieties such as nucleic acids (RNA or DNA).

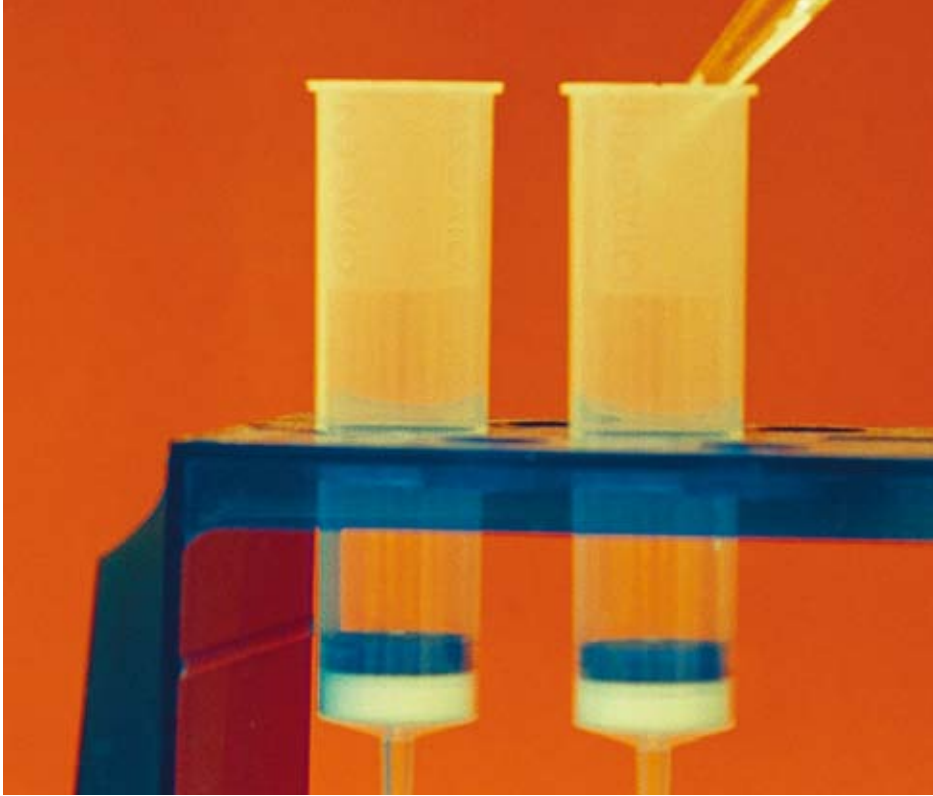
Lonza’s Custom Manufacturing APIs (active pharmaceutical ingredients) division is particularly involved in the biopharmaceutical business segments that require cell culture and fermentation technologies using mammalian and/or microbial expression systems. Lonza’s mammalian cell culture production sites are currently located in Slough (UK), Porriño (ES), Portsmouth NH (USA) and Tuas (Singapore). The latter will be online by 2010. Whereas Lonza’s microbial fermentation sites are located at Kouřim (CZ), Visp (CH) and Hopkinton MA (USA).

The commercial success of biopharmaceuticals, particularly the therapeutic use of monoclonal antibodies (Mabs) for difficult-to-treat indications such as cancer and autoimmune diseases, has spurred the demand and development for economic and robust mammalian cell culture processes over the past two decades.

The market size of biopharmaceuticals is recorded at approximately USD 110 billion in 2008 (Evaluate Pharma, IMS data). The mammalian cell culture products sales are estimated at USD 64 billion out of the total biopharmaceutical market – in which 60% of these sales are generated from antibody based products.

The need to drive down production cost and to increase the efficiency of manufacturing processes have largely contributed to the vast improvements seen in

Life Science Ingredients	Custom Manufacturing API's	Bioscience
<ul style="list-style-type: none"> Nutrition Ingredients Microbial Control Performance Intermediates 	<ul style="list-style-type: none"> Development Services & Biologics R+D Chemical Manufacturing Biological Manufacturing 	<ul style="list-style-type: none"> Therapeutic Cell Solutions Testing Solutions Research Solutions



the productivity of cell culture processes, which have improved 200-fold in the last 15 years. Lonza, aligned with these industry needs, has long been at the forefront in establishing a reliable, predictable and robust platform towards high productivity.

For over a decade, the growth of Lonza's custom manufacturing services for mammalian cell culture has been largely driven by our proprietary technology – the GS Gene Expression System™ (GS: glutamine synthetase). The GS Gene Expression System™ came to Lonza through the acquisition of Celltech in 1996 (now Lonza's site in Slough, UK). Since then it has become the cornerstone of our mammalian cell culture business.

The GS Gene Expression System™, fully owned and licensed by Lonza, is used for the production of therapeutic recombinant

proteins and monoclonal antibodies. Over 100 biotechnology and pharmaceutical companies and 75 academic laboratories worldwide have successfully used the GS Gene Expression System™ which has established itself as the industry standard. This system is characterized by its speed and ease of use.

The GS Gene Expression System™ has proven its commercial viability and is currently being used to make 7 licensed products, along with many others that are in the preclinical and clinical development. These licensed products are Zenapax™, Synagis®, Soliris®, three other non-disclosed monoclonal antibodies and a fusion protein.

Alongside the GS expression vectors the system also includes host cell lines suitable for use in manufacturing processes: NSO (murine derived) and CHO (hamster

derived). Of these, the CHO cell line predominates as an industrial production cell line. Since acquiring the GS Gene Expression System™, Lonza has put enormous effort into increasing the performance of its CHO cell line and improving its suitability for use as a production cell line. In 2002 the CHOK1SV variant, which is pre-adapted to suspension culture and chemically defined, animal component-free medium was released. CHOK1SV derived cell lines show improved productivity and growth compared to those derived from its parent CHOK1 and today CHOK1SV is the host cell line of choice for over one hundred global pharmaceutical and biopharmaceutical companies.

Together with the extensive know-how and experience built around the GS Gene Expression System™ for the creation of high yielding cell lines, Lonza has also developed platform production processes that take our customers through all development stages from the creation of a cell line to cGMP manufacturing. The platform processes are designed for high-yielding protein manufacturing and include cell line selection protocols, optimized biore-

How the GS Gene Expression System™ Works

The GS Gene Expression System™ is based on the principle that cells have an absolute requirement for glutamine in order to survive, this glutamine must either come from the growth medium or be synthesised by the cell from glutamate and ammonium, using the enzyme glutamine synthetase (GS). The GS Gene Expression System™ works by providing the cell with this enzyme thus allowing it to grow in glutamine free medium.

actor processes through improved media and feeding strategies, improved product recovery and purification and are complemented by supporting analytical packages.

Reinventing values with cell line engineering in mind

Lonza continues to strengthen and reinvent its proprietary technology in order to provide higher value, technologically advanced offerings with enhanced cost efficiency to customers. On 12 October 2009, Lonza and BioWa Inc unveiled POTELLIGENT® CHOK1SV, a new host cell line for manufacturing recombinant antibodies. The new cell line combines the power of BioWa's engineered glycosylation POTELLIGENT® Technology with the advantages of GS Gene Expression System™ and Lonza industry-leading cell line CHOK1SV.

The new cell line is a result of the successful collaboration between Lonza and Biowa and it is now available to customers either through our mammalian cell culture and process development services or through non-exclusive, three-way licensing.

The new product brings together cell line engineering (increased antibody potency) and manufacturability (high productivity cell line). The high productivity and enhanced antibody potency are expected to further drive production cost efficiency for an antibody based drug using POTELLIGENT® CHOK1SV. The primary use of POTELLIGENT® CHOK1SV antibodies will be in the treatment of cancer and certain autoimmune conditions. At present, anti-cancer antibodies make up more than 50% of all antibodies in development. There are several POTELLIGENT® antibodies currently in development and we have been

receiving promising interest and uptake for the new cell line within the short time since its launch.

We work with passion using advanced technologies to transform life science into new possibilities for our customers. The GS Gene Expression System™ is one fine example of how Lonza's mission is implemented. By continuously strengthening and reinventing our proprietary technology, Lonza remains closely connected with our customers and show our enterprising and influential spirit while providing higher value, technologically advanced offerings with enhanced cost efficiency to our customers.

How POTELLIGENT® CHOK1SV works

It has been demonstrated that an antibody with a reduced fucose content exhibits much higher levels of antibody dependent cellular cytotoxicity (ADCC) activity compared to a normally fucosylated antibody. ADCC is one of the most important mechanisms by which an antibody can destroy its target cell (e.g. tumour cell) and is triggered by the antibody binding the target cell through its variable domains whilst the constant domains bind the receptor FcγRIII found on natural killer cells which are a part of the immune system. Antibodies without fucose have an increased affinity (ability to bind) for FcγRIII and so cause a much enhanced response. [See Figure 1]

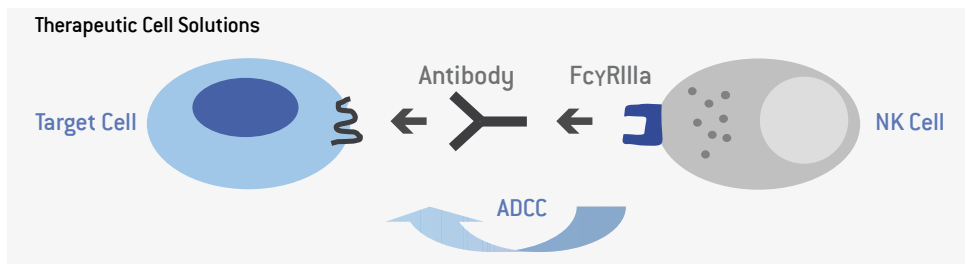


Figure 1: Increase of antibody affinity to the receptor (FcγRIIIa) will enhance ADCC activity. Whereby the ADCC mechanism will lead to the destruction of target cells (e.g. tumour cells) by the human immune system cells called natural killer (NK) cells.

Lonza entered a collaboration with BioWa to create a CHOK1SV cell line with the gene responsible for fucose addition (FUT-8) knocked out. The new POTELLIGENT® CHOK1SV cell line has demonstrated similar properties to the parental CHOK1SV cell line and has been shown to produce entirely fucose-free antibodies with the expected ADCC enhancement.



Lonza