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Biopharmaceuticals from Mammalian Cells

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Abstract. The advent of genetic engineering and monoclonal antibody technologies has made possible the manufacture of a wide range of pharmaceutical proteins. Many of these proteins are made in mammalian cell culture. This has required the development of novel gene-expression systems as well as technology for the large-scale culture of cells and for the isolation of proteins to exacting standards of purity. *Lonza* has established facilities in the UK and the USA for the contract development and manufacture of these proteins.

Lonza Biologics, formerly *Celltech Biologics plc*, is the world's leading contract manufacturer of monoclonal antibodies and recombinant proteins from mammalian

cells. In 1996, it became a member of the *Lonza* group. The company, which employs over 300 people, undertakes highly specialised development and manufac-

turing services for the pharmaceutical and biotechnology industries based on its extensive experience in mammalian cell culture and on proprietary technology for the large-scale manufacture of these innovative pharmaceutical products. The company is able to offer a complete development package, taking a product from the laboratory through to full scale manufacturing and providing the regulatory data packages and support for clinical trials and in market supply.

Therapeutic Proteins from Animal Cells

Advances in recombinant DNA and monoclonal antibody technology have

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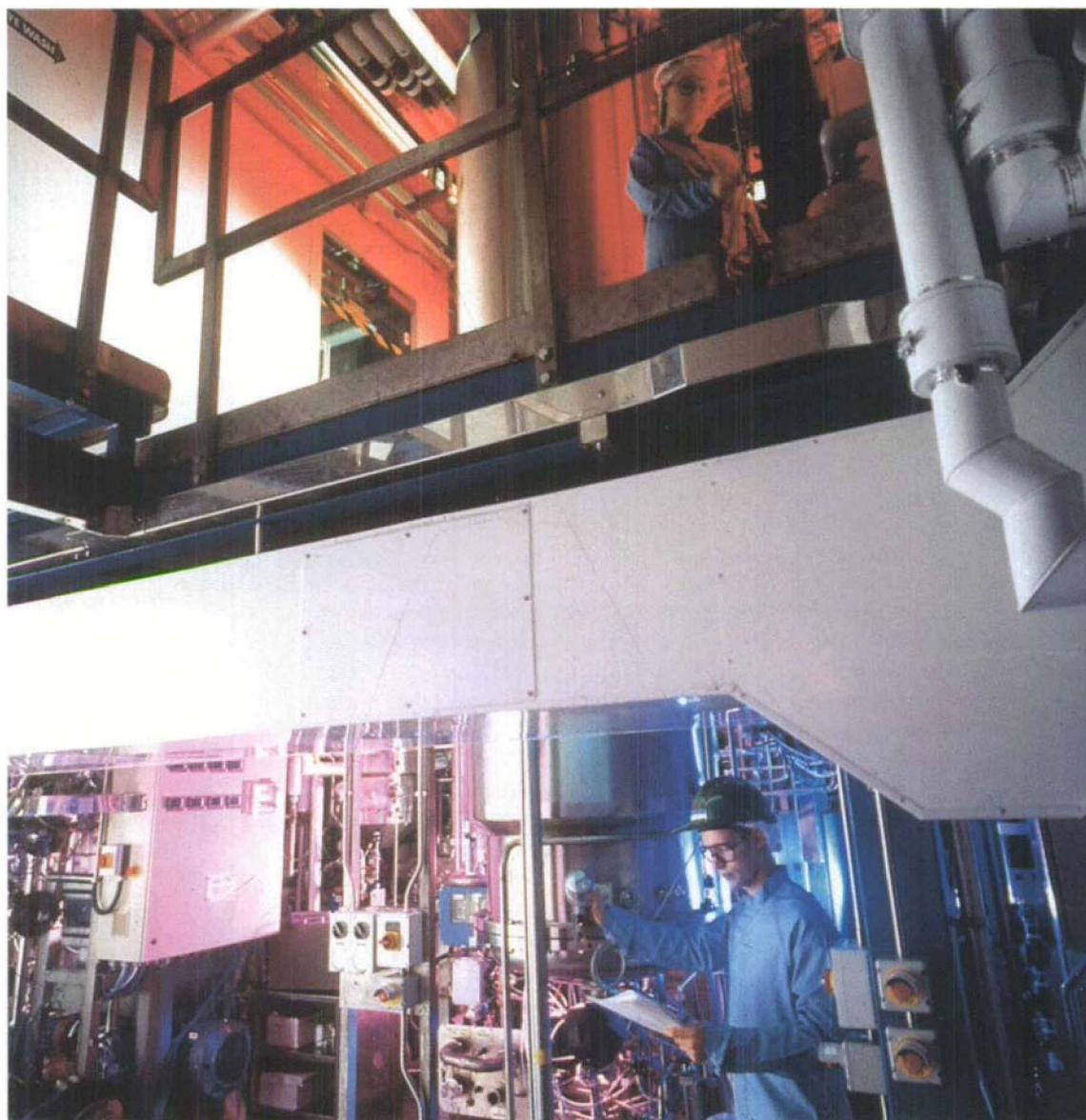


Fig. 1. A 2000-l fermenter in *Lonza's* UK manufacturing facility



Fig. 2. Lonza Biologics' facility at Portsmouth, New Hampshire

made possible the production of a wide range of proteins (antibodies, hormones, blood proteins, vaccines) with therapeutic utility. Some tens of products are now licensed and several hundred more are in clinical trial [1]. These proteins are typically made in microbial or mammalian cell culture. Mammalian cells are essential for the production of large multi-chain proteins and particularly those glycoproteins where authentic mammalian glycosylation is required for biological activity. The most commonly used cell types are Chinese Hamster Ovary (CHO) and mouse myeloma or hybridoma cells.

Genetic Expression Technology in Animal Cells

The cost-effective production of proteins from mammalian cells using genetic engineering technology requires highly efficient gene-expression systems. Lonza has developed a proprietary technology (the GS System™) based on the use of gene vectors containing, in addition to the product gene of interest, powerful viral promoters and a glutamine-synthetase gene which acts as a selectable marker [2]. This system is widely used especially for the

production of genetically engineered monoclonal antibodies, which have been produced at concentrations up to 1g/l in batch culture [3].

Production Process using Mammalian Cell Culture

In addition to effective gene-expression systems, the production of therapeutic proteins also requires efficient large-scale culture technology. At Lonza, cells are grown as suspension cultures in batch airlift reactors ranging in size from 100 to 2000 l [4] (Fig. 1). Highly productive culture media have been designed for use in these reactors. Because the products are intended for therapeutic use, very high levels of purity are required and a variety of chromatographic procedures have been developed for the isolation of particular proteins, in addition to a wide range of analytical methods to characterise protein structure and purity. The company has over 15 years experience of manufacturing many different proteins from a range of mammalian cell types. Manufacturing is carried out to current Good Manufacturing Practice (cGMP) in a 40 000 square feet facility at Slough in the UK and in a

76 000 square feet facility at Portsmouth, New Hampshire in the USA (Fig. 2). In view of the extensive regulations governing the manufacture of biological drugs for use in humans, the company has built up an extensive quality system encompassing regulatory affairs, documentation, quality control, and quality assurance to ensure successful approval for its clients' products.

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