Editorial

Pharmaceutical BIOPROCESSING

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From the mold in Dr Florey's coat to blockbuster drugs

»"The launch of the journal *Pharmaceutical Bioprocessing* can be welcomed as a new forum for the dissemination of information and scientific advances in this area of biopharmaceutical production."«

Michael Butler
University of Manitoba,
Department of Microbiology,
418 Buller Building, 66 Chancellors
Circle, Winnipeg, Manitoba,
R3T 2N2, Canada
Tel.: +1 204 474 6543
Fax: +1 204 474 7603
E-mail: butler@cc.umanitoba.ca

I write to welcome the launch of the new journal, *Pharmaceutical Bioprocessing*, which is intended to bring insights into the latest design and development of production systems and processes for the generation of pharmaceutical products. *Pharmaceutical Bioprocessing* intends to look forward to novel methods and approaches of bioprocesses that will secure the availability of new biological entities in the future. However, it can be valuable to look back a few decades to see how we arrived at our position today, with our range of biopharmaceuticals produced from near platform technologies of stirred tank bioreactors inoculated with high-producer cell lines.

Although the work of Fleming in 1928 discovered the possibility that secretions from a *Penicillium* mold could inhibit the growth of bacteria in a Petri dish, it was the difficult and persistent work of Florey, Chain and Heatley that led to the design of a bioprocess that could at least provide material for some animal tests, and later clinical trials. It is instructive to read the well-documented and heart-warming book by Eric Lax [1], '*The Mold in Dr Florey's Coat*', to appreciate the early experiments conducted at Oxford University, UK during a time of war and with the imminent threat of foreign invasion. In particular, Norman Heatley produced improvised bioreactors made from bedpans and biscuit tins for the surface growth of the vital *Penicillium*. It was his later trip to the USA with Florey that engaged the help of industrial collaborators who were able to make improvements in upstream processing with better producer cell lines, adaptation to deep fermentation bioreactors and improved isolation techniques.

By modern standards, the methods used were crude. There was little in the way of process control, quality by design or analysis of critical quality attributes. There was considerable skepticism that the bioprocess would be economically viable compared with a synthetic process that would be possible following the elucidation of the structure of penicillin. Nevertheless, this work led to a bioprocess production strategy that survived the test of time, and led to the large-scale production of penicillin as one of the most valuable pharmaceuticals of the last century.

Although these reflections on earlier times highlight the difficulties and uncertainties associated with the design of bioprocesses, the methods and strategies that were developed certainly persist today. Now we can be more systematic about the design of high-producer cell lines by the use of genetically designed vectors rather than the use of random mutation. Selection strategies can be automated in a way that would have been inconceivable to the early pioneers of penicillin production. Careful control and monitoring of the culture bioprocess ensures batch-to-batch consistency of complex biological entities that can be scaled-up to meet the required global needs. Analysis of the critical quality attributes of these biologics ensures that the molecular profile of the final product matches the desired clinical efficacy.

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In the early 2000s there was a threat from a global shortage of bioreactor space given the number and quantitative demand for therapeutic glycoproteins [2]. This was perceived as 'the capacity crunch' in which the pipeline of biotherapeutic products was expanding more rapidly than the global capacity for cell culture production. This came about as a result of a number of bioproducts approved in 2000 that were required at relatively high clinical doses. Even though this trend of an expanded pipeline of biotherapeutics has continued, the crunch has been avoided by a careful study of bioprocess technology, and the implementation of strategies for enhanced production by the use of well-designed feeding strategies. Fed-batch cultures that can maintain low glucose and glutamine levels can maximize metabolic efficiencies of producer cells, minimize metabolic by-product formation and allow cells to grow to high densities, and importantly, remain at high viabilities for extended time periods. The extended culture periods allow continued productivity of secreted products, thereby exceeding the equivalent product concentrations from batch cultures by at least an order of magnitude. The profiles of typical batch and fed-batch cultures over the period of a decade are well illustrated in Wurm [3].

At present, the growth of biopharmaceuticals outstrips all other sectors of the pharmaceutical industry. Global sales of biologics are now reported to be US$120 billion per annum with an expected increase to $150 billion by 2015 [101]. Mammalian cell culture technology has led the way for the production of complex glycoproteins that can be used as biopharmaceuticals for unmet medical needs. It is undoubtedly the introduction of humanized monoclonal antibodies that has trailed an unstoppable path for these biopharmaceuticals with around 30 approved therapeutic antibodies, six of which can be classified as blockbusters (>$1 billion annual sales). The global sales of monoclonal antibodies in 2011 were estimated at $44.6 billion and are predicted to increase to $58billion by 2016 [102].

The launch of the journal *Pharmaceutical Bioprocessing* can be welcomed as a new forum for the dissemination of information and scientific advances in this area of biopharmaceutical production. The number of scientists and process engineers working in this field has increased enormously in recent years and this calls for novel platforms for communicating new developments in bioprocessing. Regular biennial meetings of societies such as the European Society for Animal Cell Technology, Cell Culture Engineering and Protein Expression in Animal Cells have secured a niche for oral communication, commercial displays and personal contacts between practitioners of bioprocess technologies in the mammalian cell culture field, as has the Society for Industrial Microbiology for fungal and bacterial bioprocessing. The rapid interest in the associated technologies can be evidenced by the numbers attending these meetings. The European Society for Animal Cell Technology, which was established by far-sighted technologists such as Bryan Griffiths and Ray Spier in the late 1970s and originally saw only a handful of interested vaccine-related scientists, now hosts up to 1000 delegates with both commercial and academic interests.

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It surely must be emphasized that the value of these societies has been to further the cause of ensuring collaboration between universities and industry, as well as between practitioners of different backgrounds including chemical engineering, biochemistry and molecular biology. It is anticipated that *Pharmaceutical Bioprocessing* will serve as a new engine of activity for presenting and exchanging ideas in a written form, continuing the collaboration between bioprocessing scientists and technologists. This type of collaboration secured the success of penicillin production in the late 1940s, and it can now secure the continued success of novel biological entities in the 21st century.

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