

Report on 10th Annual bioProcess UK Conference

3–4 December 2013, London, UK

The 10th Annual bioProcessUK conference was held in London on 3–4 December 2013, with the theme ‘Biopharmaceutical Innovation: a Vision for the Future’. The event was fully booked and 281 delegates attended, more than in any previous year. The bioprocess industry was well represented, constituting more than 60% of the delegates; more than 10% of the industrial delegates were from overseas. The talks and workshops provided a panorama of innovative developments in the area, and substantial opportunities for networking were provided.

Several intriguing contributions exemplified the current industrial perspective on bioprocessing. An overview of bioprocess development for monoclonal antibodies (mAbs) and next-generation medicines was provided by Kripa Ram of MedImmune. Ram posed the intriguing question of whether bioprocess engineering has its own analog of Moore’s Law in computer engineering, which states roughly that computing capacity doubles every 2 years. Are we, the bioprocessing community, learning quickly enough from our collective experience, and has this common understanding been translated into such an exponential growth? Certainly, the number of approved medicines does not show such a trend, being approximately constant at 20–25 new molecular entities approved every year by the US FDA [1]. But the question is important for the more efficient production of next-generation medicines: how can we leverage what we have learned so far? Which, if any, rate-limiting capabilities are we lacking? MedImmune has refined their mAb platform production process based on a CHO cell-line to achieve titers in excess of 10 g/l while maintaining scalable performance between

3- and 15,000-l bioreactors. Ram stressed that MedImmune’s development portfolio contained a steadily increasing proportion of novel molecular structures, and posed the question of how learning gained in the recent improvement of antibody development and processing could be applied to these new product classes.

Clifton McPherson of Protein Sciences reviewed the development and licensure of a recombinant influenza vaccine, Flublok®, produced in insect cells. The use of a baculovirus expression system reduced the risk of viral infection, since few adventitious agents are known that can replicate in both insect and mammalian cells. The seasonal nature of the product provided another challenge, with at least one vaccine antigen typically changing every year. This variability could affect the performance of such critical unit-operations as the chromatographic steps. After some variability in these steps was attributed to depth-filter performance, the downstream process was successfully validated. The single radial immunodiffusion potency assay preferred by the FDA was adopted to expedite release. Product stability continues to be challenging, with the current approved shelf life being only 16 weeks. The licensure of Flublok is an important milestone in vaccine production, both because it is the first recombinant influenza vaccine to be licensed, and as a high-profile demonstration of baculovirus as a platform for the production of recombinant vaccines and therapeutics. In the spirit of leveraging our community’s understanding, such achievements will no doubt facilitate the development and production of even more complex vaccines in the future.

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Another potentially game-changing technology, continuous processing, was discussed by Konstantin Konstantinov of Genzyme. The FDA's support for continuous processing has been clearly laid out in their Pharmaceutical cGMPs for the 21st Century [2]. However, while continuous processing is the standard for the production of small and specialty chemicals, and is becoming a viable alternative for pharmaceuticals [3], some practitioners wonder if it can cope with the high variability that is intrinsic to the production of biomacromolecules. In this regard, Genzyme's experiences have been useful in demonstrating that critical sequences of unit operations, especially cell culture followed by capture and polishing chromatography, can be stably operated in continuous mode for several weeks. Konstantinov pointed out that, historically, process industries evolve into continuous processing modes, from the production of petrol to wood pulp to casting of steel. In each case, processing difficulties were circumvented by novel designs. Cell culture has already been run in continuous (perfusion) mode for many years, with blockbusters such as Remicade® being produced commercially in this mode [4]. The critical issue is now to operate purification steps, especially chromatography, in continuous modes that can be operated stably when coping with the somewhat variable feeds produced upstream. Using the periodic countercurrent chromatography (PCC) mode [5], two purification case studies were presented. An enzyme was produced continuously by perfusion cell culture of a CHO cell line, and taken through an integrated PCC purification process. The process was shown to be stable over 60 days of production, with viable cell densities in the perfusion system approximately 40 million cells per ml. In the second case study, a mAb was produced in 12-l bioreactors that were again integrated with PCC purification. The entire train of bioreactor and two continuous chromatographic steps, along with viral inactivation, led to the generation of bulk drug substance in 22 h (12 h upstream and 10 h downstream). Over 30 days of continuous operation, all quality parameters, including protein concentration, potency, aggregate level, residual protein A and host cell protein level, were found to be stable. Examples such as these will be crucial in allowing the bioprocess community to evaluate the risk-reward balance, and may well tilt the balance in favour, of continuous processing.

The academic contributions were also varied and interesting. Ajoy Velayudhan of University College London discussed the development of whole-bioprocess models to capture global trends and interactions in the process trains used for next-generation medicines. A novel variant of the well-established simplex method

for empirical optimization was developed, and shown to be effective in the simultaneous screening of materials (e.g., membrane filters, chromatographic resins) as well as operating conditions in early process development. Once appropriate materials have been selected, and suitable initial operating conditions established, then more fundamental models, based on detailed mass and energy balances, can be used to optimize difficult unit-operations. In particular, models for each unit-operation in sequence can be used to evaluate globally robust operating conditions. An example was presented, in which charged glycoproteins were taken through cell culture, capture, and two polishing chromatographic columns. The impact of cell culture variability was taken into account in optimizing the pair of polishing columns together. Such methods are likely to become more important in the rapid and efficient design of robust bioprocesses. Niall Barron of Dublin City University described the use of miRNAs to improve CHO cell culture productivity, not only with respect to growth rates but also genome stability and glycosylation. These non-coding RNAs control gene expression post-transcriptionally, and seem to play important roles in various disease states [6]. Barron showed that depletion of miR-7 improved the phenotype of CHO in cell culture; that miR-7 improved product levels by approximately 75%; and that miR-34a improved glycosylation. Such studies will ultimately facilitate the development of personalized treatment regimens [7]. Jeremy Lakey of Newcastle University gave an entertaining overview of how surface science could be exploited to develop new biological products. Using protein structures carefully designed to be active at interfaces, a range of interesting and surprising surface effects can be demonstrated. These structures can be engineered to form self-assembled monolayers and provide controlled immobilization of proteins and protein fragments in preferred orientations to deliver improved functionality. His group has developed a biosensor based on a shear horizontal surface acoustic wave that is sensitive to mass, viscosity and elasticity. This sensor could wirelessly transfer its information to a mobile phone, which would send it to a computer to provide an appropriate readout. Such 'mobile diagnostics' could be invaluable in a variety of settings in which a diagnostician is not able to examine a patient directly. The proteins that are used in the biosensor can be immobilized on gold, plastic, glass, and other surfaces. The approach might produce a scaffold for 3D arrays of cells or tissues, which are of great promise in regenerative medicine and in drug development [8].

University College London held a workshop on QbD on the eve of the conference, which was very

popular. The differences in implementation of QbD in large companies as opposed to contract manufacturing organizations were discussed in a lively exchange. Suzanne Farid of University College London chaired a workshop to assess the operational and economic challenges of continuous bioprocessing. A detailed cost-of-goods analysis was made to compare fed-batch to perfusion culture. Various trade-offs were also discussed, including balancing economic savings against flexibility and development time, and combining batch and continuous operations. The discussion that followed clearly illustrated the widely varying perceptions of the benefits that continuous manufacturing currently has to offer and how these are affected by the stage of development of the product and company involved. Workshops by BD Biosciences, BioReliance, Life Technologies, Sartorius Stedim Biotech, and Thermo Fisher Scientific were also well attended.

The introductory and final presentations emphasized the conference's theme of innovation. Nigel Titchener-Hooker of University College London, who gave the opening address, stressed the continued need for innovative manufacturing to deliver economical and timely medicines. Mark Bustard from the Health-Tech and Medicines Knowledge Transfer Network summarized the developments over the past 10 years, over which substantial growth has been achieved. He outlined some pivotal UK funding initiatives to support research and its translation into commercial products. The Biomedical Catalyst Fund has awarded GB£120 million of investment in academic and business led projects to develop solutions to healthcare challenges since its launch in 2011 and has secured further funding until 2015. An important focus of the collaborative efforts of the bioprocess community is the construction of the National Biological Manufac-

turing Centre in Darlington (UK), which is expected to be operational in April 2015 and will be operated by CPI. The Biotechnology and Biological Sciences Research Council (BBSRC) has funded several collaborative Networks in Industrial Biotechnology and Bioenergy, some in collaboration with the Engineering and Physical Sciences Research Council (EPSRC). The BBSRC and EPSRC will work with the Technology Strategy Board to launch the Industrial Biotechnology Catalyst in early 2014; the goal is to support projects from conceptualization through commercialization.

Continuing with the conference theme of innovation, Steve Bagshaw of Fujifilm Diosynth Biotechnologies drew on his organization's legacy of in-house inventions to provide perspective on the topic of innovation over the next 10 years. He stressed the importance of research partnerships and collaborations for addressing future challenges and in particular the critical importance of the availability of people with the right engineering and technical skills. He challenged the audience to engage with this issue to secure the future health of the UK biotechnology sector.

In summary, the conference provided its delegates with timely updates and a substantial number of novel approaches, conceptual and practical, at the frontiers of bioprocessing.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- 1 US FDA data on new molecular entities. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM242695.pdf
- 2 Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan. www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836
- 3 Trout B. Fully automated end-to-end continuous manufacturing of small-molecule pharmaceuticals and implications for biologics. Presented at: *Integrated Continuous Biomanufacturing conference*. Barcelona, Spain, 20–24 October 2013.
- 4 Whitaker SC, Francis R, Siegel RC. Validation of continuously perfused cell culture processes for production of monoclonal antibodies. In: *Validation of Biopharmaceutical Manufacturing Processes*. ACS Symposium Series, Washington, DC, USA, 698, 28–43 (1998).
- 5 Lacki KM, Bryntesson LM. Protein-A Counter-Current Chromatography for Continuous Antibody Purification. Presented at: *American Chemical Society conference*. Anaheim, CA, USA, 21 March–1 April 2004.
- 6 Shi H, Xu J, Zhang G *et al.* Walking the interactome to identify human miRNA-disease associations through the functional link between miRNA targets and disease genes. *BMC Sys. Biol.* 7, 101 (2013).
- 7 Weidhaas J. Using microRNAs to understand cancer biology. *Lancet Oncol.* 11, 106 (2011).
- 8 Tibbitt MW, Anseth KS. Dynamic microenvironments: the fourth dimension. *Sci. Trans. Med.* 4(160), 160ps124 (2012).