Institution: University College London

Unit of Assessment: 12 – Aeronautical, Mechanical, Chemical and Manufacturing Engineering

Title of case study: Ultra scale-down technologies for speeding routes to bioprocess manufacture

1. Summary of the impact

UCL's creation of ultra scale-down (USD) technologies has led to economic benefits by speeding to manufacture next-generation healthcare products. This has resulted in documented savings for pharmaceutical companies in pilot-scale studies (eg ~£280k for a protein therapy) and in manufacturing cost-of-goods (eg ~£200k pa for an antibody). Licensing values realised for USD-facilitated manufacturing processes range from a £10m early-stage payment for an antibody therapy [text removed for publication] to US$1bn for a therapeutic vaccine.

Since 2008 some 40 companies have used UCL USD technologies, which have now also facilitated the formation of a spin-out company and additional job creation. Patient benefits have emerged through the contribution of USD to better bioprocess definition, with USD technologies now helping deliver the US Food and Drug Administration's Quality by Design initiative for biopharmaceuticals, valued at more than US$20bn a year through a 25% reduction in time-to-market and more robust manufacture.

2. Underpinning research

UCL research into ultra scale-down (USD) technologies has demonstrated how to take a projected process sequence for full-scale manufacture and then identify critical regimes such as regions of high stress or the presence of hostile interfaces. Such regimes are then reproduced using millilitre-scale devices so that it is possible, using just small quantities of precious material available at early stages of new product development, to predict full-scale manufacturing performance.

The **underpinning research** focused on the characterisation of the effects of process stress on biomaterials. This was based on original fundamental research into the concept of critical regime analysis [1]. Success was achieved in the creation of mimics of intricate high-stress centrifuge feed zones. These provided new insights into the effects on, for example, mammalian cells [2] and polymer-flocculated cell debris [3]. Rigorous engineering characterisation was used with predictive models to verify hypotheses of how biological structures are affected during processing, e.g. for high acceleration centrifuge feed zones [2] and for high impact centrifuge discharge zones [4, 5].

The research advanced understanding of how mechanical, hydrodynamic and impact stresses that exist during flow in the complex geometries found in manufacturing-scale equipment can affect the structure of delicate biological materials. In this way, such materials, including macromolecules and structured aggregates for biopharmaceuticals and vaccines, and whole cells for therapy, can be characterised in terms of their response to process engineering environments. The potency of USD technology is the ability to address whole bioprocesses and characterise key interactions between process stages. **Key research findings** have included an understanding of how the preparation of the material can affect its response to process stress, and how the material and process environment can be modified to avoid deleterious effects, for example for antibodies [5] and for human cells with defined surface markers for therapy [6].

This research has led to subsequent successes, for example the characterisation of the impact of cell age on robustness to stress and the nature of antibody therapies formed [7], along with the design of processes for the recovery of a next generation fusion protein vaccine candidate [8]. UCL's USD technology has provided the first rigorous engineering basis for whole bioprocess design for such materials.

The research outputs were achieved between 2000 and 2013, particularly through a managed EPSRC Innovative Manufacturing Research Centre (IMRC) programme in bioprocessing from 2002-2007, which was hosted and led by UCL Biochemical Engineering in collaboration with over 40 leading industrial research groups in the biopharmaceutical sector. This programmes focused on developing new fundamentals and applications of USD technologies and increasing the value base for continuing exploitation. Such collaborations allowed fundamental research with high-performance industrial strains and next generation therapies, and enabled access to industrial-

scale manufacturing facilities for verifying USD predictions. This programme successfully created the USD concept from engineering fundamentals to a practical technology for application in the bioprocessing industries especially for macromolecular bioprocessing. The outputs of the research were reviewed four times by the EPSRC, with the 2005 international review and panel visit (York, Cabral, Middelberg) also commenting on industrial impact, eg: *"The programme appears to be well designed to achieve its aim of changing the way bioprocesses are designed and optimized in the future. It is already achieving real benefits for its industrial partners".* The second phase of the IMRC programme (2007-2012) emphasised greater company collaboration to help enhance the value of USD technologies and extend the application to the vaccine, human cell therapy and synthetic biology sectors.

Key UCL academic staff involved in USD development were D.G. Bracewell (Post-doctoral Researcher, now Reader Biochemical Engineering) – new separations and creation of USD formulation and M. Hoare (Professor Biochemical Engineering) – programme director and creation of USD primary recovery. Other staff involved in complementary IMRC research were (Biochemical Engineering unless stated otherwise): F. Baganz (Lecturer now Senior Lecturer) – fermentation;; P.A. Dalby (Lecturer now Professor) – protein engineering / formulation; E. Keshavarz-Moore (Lecturer now Professor) – cell bioprocessing; G.J. Lye (Senior Lecturer now Professor) – microscale engineering; N.J. Titchener-Hooker (Professor) –process modelling; J. Ward (Senior Lecturer Biochemistry now Professor Biochemical Engineering) – cell biology; Y. Zhou (Lecturer now Senior Lecturer)– data handling; D. Nesbeth (Post-doctoral Researcher, now Lecturer) – synthetic biology; Tarit Mukhopadhay (EngD researcher now Lecturer) – vaccine bioprocessing.

3. References to the research

A total of 45 USD-related publications in leading refereed journals and a master patent (Dunnill P., Titchener-Hooker, N.J, Hoare, M, 2002,"A method and apparatus for producing a biomaterial product", WO2002001303 A3) have been realised.

References [1], [5] and [7] best demonstrate research quality:

1. Boychyn M, Yim SSS, Ayazi-Shamlou P, Bulmer M, More J, Hoare M, 2002, Characterization of flow intensity in continuous centrifuges for the development of laboratory mimics. Chem Eng Science 56, 4759-4770. http://doi.org/csq7kx
2. Hutchinson N, Bingham N, Murrell N, Farid S, Hoare M, 2006, Shear stress analysis of mammalian cell suspensions for prediction of industrial centrifugation and its verification. Biotech Bioeng 95, 483-491. http://doi.org/dwtvdn
3. Berrill A, Ho SV, Bracewell DG, 2008, Ultra scale-down to define and improve the relationship between flocculation and disc-stack centrifugation. Biotech Prog 24 426-431 http://doi.org/fr9dpr
4. Chan G, Booth AJ, Mannweiler K, Hoare M, 2006, Ultra scale-down studies of the effect of flow and impact conditions during *E. coli* cell processing. Biotech Bioeng 95, 671-683. http://doi.org/bkx9qn
5. Biddlecombe JG, Craig AV, Zhang H, Uddin S, Mulot S, Fish BC, Bracewell DG, 2007, Determining antibody stability: creation of solid-liquid interfacial effects within a high shear environment. Biotech Prog 23, 1218-1222. http://doi.org/cksrnw
6. McCoy R, Ward S, Hoare M, 2009, Ultra scale-down studies of the effect of shear on cell quality; processing of a human cell line for cancer vaccine therapy. Biotech Prog 25 1448-1458. http://doi.org/dh982h
7. Reid CQ, Tait A, Baldascini H, Mohindra A, Racher A, Bilsborough S, Smales CM, Hoare M, 2010, Rapid whole monoclonal antibody analysis by mass spectrometry: an ultra scale-down study of the effect of harvesting by centrifugation on the post-translational modification profile. Biotech Bioeng 107 85-95. http://doi.org/cspkgh
8. Lau EC, Kong SY, McNulty S, Entwisle C, Mcilgorm A, Dalton KA, Hoare M, 2013, An ultra scale-down characterization of low shear stress primary recovery stages to enhance selectivity of fusion protein recovery from its molecular variants. Biotech Bioeng 110, 1973-1983. http://doi.org/n5q

The key funded activities (both EPSRC) supporting this research were GR/R 33878/01 "A research programme to change fundamentally the way in which biopharmaceutical processes are

developed", value £3060 k from 2002 to 2007, and EP/E001 1599/1 "An Innovative Manufacturing Research Centre for Bioprocessing at UCL", value £5976 k from 2007 to 2012.

4. Details of the impact

Through adoption of new technologies, UCL's research into USD technologies has led to commercial benefits for companies developing new drugs by **reducing the time to take new products to manufacture**, **with ensuing cost savings**. EPSRC-commissioned reviews of the IMRC programmes have provided overall commentary on the impact of USD technologies [a]; the following provides specific examples of some of the industrial impacts achieved.

New technologies adopted by industry: in 2009 GSK established a GSK-UCL Centre of Excellence in Bioprocessing: *"in recognition of the high value of USD technologies in facilitating bioprocess development, **GSK invested ~ £1.03 million through UCL**. This resulted in the successful development and integration of UCL USD technologies at GSK where they are employed to complement and accelerate in-house activities focused on (i) de-risking of lead molecules (ii) improving process understanding and (iii) abbreviating the critical path into full development. The use of high throughput microscale technologies for such purposes helps **ensure only industrialisable molecules are selected** and accelerated into development. In turn this **can mean the difference between success and failure** for a medicine through clinical trial stages and beyond."* [b]

The independent use by industry of USD technologies is growing. One example is to aid pilot-scale process development. The director of biopharm development at MedImmune said: "A *major benefit is the **increased predictability of cell line development** that results from the use of USD techniques at an early project stage. Since 2010 USD techniques have led to more predictable and better cell line performance when scaled up resulting in **~30% resource saving on each development project** and an **increase in project capacity of also ~30% per year**, both at laboratory and pilot (100-200L bioreactor) scale."* [c]

Similarly, Protherics' application of USD techniques in production of its snake venom antidote in 2009 showed **20% savings in cost of goods** compared to the previous process, saving the company around **£200,000 since 2008**. Subsequently Protherics applied IMRC USD techniques in the development of the process for CytoFab, a new product for sepsis therapy, where USD techniques **cut the development length in half** compared to traditional development techniques, **saving around £200,000**. The process as developed using USD methods was validated at pilot-plant scale for use in 2009-2011 for clinical trials, having "***triggered a stage payment of £10 m to Protherics in 2008.*"** [d]

Pfizer has adopted the use of USD techniques as part of the toolbox in its process development activities to help improve liquid-solid separation in cell culture processing. In particular, the techniques were used to help understand the flocculation behaviour of high cell density lysates and develop an improved separation process using flocculation and centrifugation [text removed for publication] [e]. In the area of formulation processes for conjugated vaccines Pfizer have adopted USD techniques, therefore **avoiding large-scale evaluation studies, which are costly and use industrial capacity for non-commercial production** [e]. As of 2013, savings associated with the non-utilization of facility capacity are $280k/product transfer/site and the improved process understanding via USD characterisation may also lead to better risk mitigation with scale-up, technology transfer and rapid root-cause analysis for process-related issues.

UCL's research has helped achieve a Quality by Design (QbD) agenda – a US Food and Drug Administration (FDA) initiative for the development of new therapies. This requires companies to work in new ways to achieve regulatory approval and validation status for their products, and offers major cost-saving potential. One USD collaborator comments, "***A key feature of USD technologies** is their role in **helping biopharmaceutical companies to deliver a Quality by Design agenda** via the early quantification of Critical Processing Parameters which determine Critical Product Attributes, eg the early indication of the impacts of process shear stress on the process streams involved in the Protherics studies. The FDA Quality by Design agenda is already valued at more than US$20bn to the overall biopharmaceuticals sector eg through a 25%*

reduction in time to market and delivery of more robust processes." [d]

Next generation products developed by industry: One major impact has been via collaborative programmes focused on technology transfer into new sectors such as next generation recombinant vaccines. Over £1m of industrial funding has been gained to support studies in the supply of novel vaccines and the use of USD to devise de novo bioprocesses eg in 2010-2011 for novel fusion proteins with ImmunoBiology, which the company described as "extremely valuable" for its business activities [f]. In the period 2004-2008 BioVex, a UK biotechnology discovery company, were able to use USD to investigate the processing of a major vaccine candidate therapy, a Herpes Simplex virus engineered to kill cancer cells specifically. This understanding of the manufacturability of the virus product enabled BioVex to demonstrate and ultimately realise the value of their product through an **up to US$1bn acquisition in 2011 by the US company Amgen.**[g].

A second key emerging industrial sector has been the **provision of human cells for therapy** via the development of USD technologies for whole bioprocess design. A £1.8m company-TSB programme (2007-11) allowed UCL to explore the role of USD in speeding the development of allogeneic cell-based therapies. For example, for one of the partners, ReNeuron, the Chief Scientific Officer observed how USD tools helped them "*identify ways in which robustness and acceptable yields may be retained,"* and that "*The increased insight and understanding helps **enhance the quality of process information** to be used by the Contract Manufacturing Organisation (CMO) to inform scale up and also to **help inform regulatory bodies with respect to meeting Quality by Design standards***." [h]

Creation of spin-out company: USD studies were an essential research technique in the development of novel adsorbent materials for bioprocessing, which UCL filed as a patent in 2013. A UCL start-up, Puridify, was established in 2013 to develop the new technology, which offers a **ten-fold increase in purification productivity over existing reagents**, with a **lower lifetime cost**. This will broaden patient access to drugs through reducing prices. In May 2013, the company won a £100k OneStart award to take the venture forward with the establishment of 25m^2 of bioprocessing laboratories and the engagement of 3 expert bioprocess scientists/engineers [i].

5. Sources to corroborate the impact

[a] The Economic Impact of the Innovative Manufacturing Research Centre, DTZ for EPSRC, 10 May 2011, (http://www.epsrc.ac.uk/SiteCollectionDocuments/Publications/reports/EconomicImpactOfTheIMRCs.pdf) See pages 20, 36, 42, 46, 53 for reference to general economic impact of ultra scale-down technologies.

[b] The impact of collaboration on GSK's product development is corroborated in the statement from the Head of Biopharm Process Research, GSK. Available on request.

[c] For the impact on MedImmune, refer to the statement from the Director of Biopharm Development at MedImmune. Available on request.

[d] For the savings at Protherics and commentary on value of Quality by Design, see the statement from the previous Chief Scientific Officer, Protherics. Available on request.

[e] For the savings at Pfizer, see the statements from Pfizer, available on request.

[f] Manufacturing of low-cost, high-efficacy vaccines (ImmunoBiology) – Technology Strategy Board BD203C end of grant report with independent industrial comment, 2011, pp. 6-10. Available on request.

[g] For the contribution of USD to Biovex's acquisition, see the statement from Biovex's SVP Development (now also VP Clinical Operations, Amgen). Available on request.

[h] A discovery tool for bioprocessing of human cells for vaccines/ human cell therapies (OnyVax, ReNeuron). Technology Strategy Board TP/7/BIO/6/I/M0011G end of grant report with independent industrial comment, 2011,pp. 35. Available on request.

[i] OneStart award to Puridify 2013 (www.oxbridgebiotech.com/onestart); Patent filing number: WO2013068741.