Institution: BRUNEL UNIVERSITY (H0113)

Unit of Assessment: 15 – General Engineering

Title of case study: Dynamic Extractions: New Platform Liquid-Liquid Continuous Flow Technology for the Purification and Manufacture of Drugs for Industry

1. Summary of the impact (indicative maximum 100 words)

In recognising the challenges facing a competitive, globalised pharmaceutical industry, the Advanced Bioprocessing Centre team at Brunel University have pioneered the technology and a methodology for speeding up the R&D, purification and manufacture of new drugs.

Already being adopted by market leading pharmaceutical companies, the High Performance Counter-current Chromatography presents a new technological platform to generate significant reductions in development costs; an increase in yield and a greener waste process.

The research supported by eight Research Councils grants totalling £3,557,168 led to establishing a spin-out company, Dynamic Extractions, which today operates a commercial enterprise with £1M turnover in partnership with Brunel.

2. Underpinning research (indicative maximum 500 words)

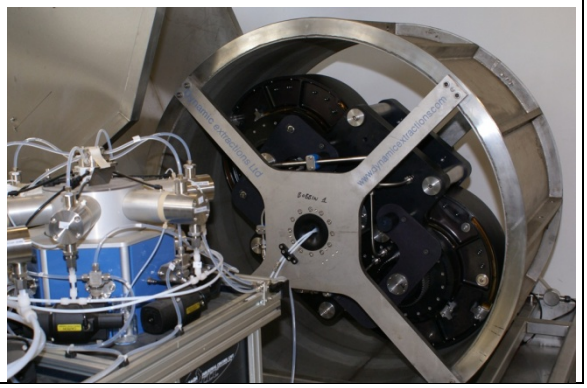
The manufacture of high value pharmaceutical products is critical to underpin industry longevity. R&D into new drugs to tackle increasingly complex conditions is capital intensive, leading 'big pharma' to outsource the complex and time consuming process.

Building on 20-year experience in the field, Sutherland and his team pioneered Counter-current Chromatography (CCC) in the UK; producing the capability of using a two-phase liquid stream to obtain unprecedented yield and solubility with no loss of product. In proving the technology to be reliable, scalable and significantly faster (separation processes in minutes rather than hours), the process has been adopted by some of the world's leading global pharmaceutical brands. [Publications 5 and 6 and Source 5].

First developed in the US in the 1960s, CCC lay dormant until Sutherland and his team improved the performance, reliability and visibility of the technology via establishing the first international conference series in 2000 followed by a spin-out company, Dynamic Extractions (DE), in 2003 under the auspices of the then Brunel Enterprise Centre (BEC). Re-named High Performance Counter-current Chromatography (HPCCC) the process enables efficient commercialisation of the instruments at various scales with a potential 10% penetration into the $1 billion preparative extraction/chromatography market.

A number of grants from the Research Councils have been awarded with notable outcomes: the feasibility of scale up of the technology with a BBSRC/DTI LINK Award with leading industries (Grant 1); the feasibility of scale-down and linking to Mass Spectroscopy (G2); the realisation of process scale-up (G3); the feasibility of further scale-up to industrial scale via an BBSRC-SBRI Grant with Dynamic Extractions (G4)[P1]; the equipping of the new Advanced Bioprocessing Centre (G5) and the building a new 18 L prototype pilot instrument (G5) [P2].

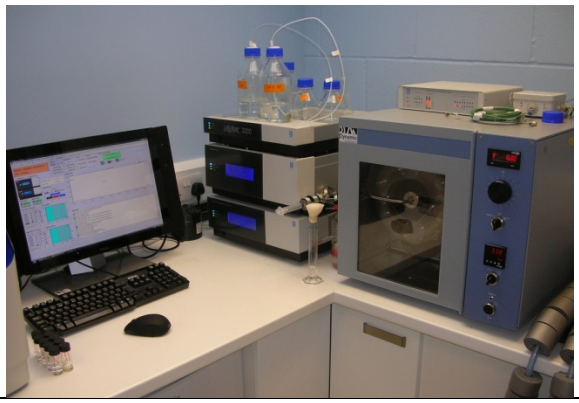
Running from 1998-2006, the equipment development phase culminated in the University investing £1M SRIF money in a new Advanced Bioprocessing Centre (ABC)opened in April 2006, housing large scale hazards and applications laboratories with pilot scale prototypes of 4.6L and 18L capacity (the largest in the world at that time; see opposite).
When DE moved to Slough in 2005, two of the four founder shareholders (Janaway and Wood) moved with them, Hawes retired and Sutherland formed



a new team with Ignatova, Hewitson, Garrard and Fisher covering chemistry, natural products and biochemistry.
While the company focused on instrument development/sales, production and commercial separations, the ABC addressed new technology for the purification of biologics such as proteins [G6, G7, P3], rapid method development and continuous processing.

A feasibility study for the purification of glucosilonates such as glucoraphanin from Broccolis seeds was commissioned by the National Cancer Institute (NCI-P4). The success of the study led to DE being commissioned to manufacture 1kg and 2kg of pure glucoraphanin for clinical trials as an anti-cancer agent.

Taking academic research and turning it into industrial reality [P5,P6] the TSB High Value Manufacturing research programme (G8) funded "Scalable Technology for the Extraction of Pharmaceuticals (STEP)" with GSK and Pfizer as end users and DE as the supply company. In 2012 DE established a laboratory-based robust preparative device capable of 1 kg/day throughput of crude extract. (see opposite – new 24x7 laboratory based automated instrument at Dynamic Extractions Ltd in Slough).



3. References to the research (indicative maximum of six references)

Publications referred to in underpinning research and impact sections

[1]. Ignatova, S., Wood, P., Hawes, D., Janaway, L., Keay, D., and Sutherland, I.A. (2007) Feasibility of scaling from pilot to process scale, J. Chromatog. A., 1151 (1-2), 20-24 http://dx.doi.org/10.1016/j.chroma.2007.02.084

[2]. Sutherland, I.A., Hewitson, P. and Ignatova, S. (2009) A New 18 Litre Process Scale Counter-Current Chromatography Centrifuge, J. Chromatogr. A., 1216, 4201-4205. http://dx.doi.org/10.1016/j.chroma.2008.11.097

[3]. Sutherland, I.A., Hewitson, P. Sieber, R., van den Heuvel, R., Arbenz, L., Kinkel J. and Fisher, D. (2011) Scale-up of protein purifications using aqueous two-phase systems: comparing multilayer toroidal coil chromatography with centrifugal partition chromatography, J. Chromatogr. A., 1218, 5527-5530. http://dx.doi.org/10.1016/j.chroma.2011.04.013

[4]. Fisher, D., Garrard, I.J., van den Heuvel, R., Chou, F.E., Fahey, J.W. and Sutherland, I.A. (2005) The Technology Transfer and Scale-up of a Potential Cancer-preventative Plant Secondary Metabolite – Glucoraphanin, J. Liquid Chromatog. & Rel. Tech., 28 (12-13), 1913-1922 http://dx.doi.org/10.1081/JLC-200063563

[5]. DeAmicis, C., Edwards, N., Giles, M.B., Harris, G.H., Hewitson, P., Janaway, L. and Ignatova, S. (2011) Comparison of preparative reversed phase liquid chromatography and countercurrent chromatography for the kilogram scale purification of crude spinetoram insecticide, J. Chromatogr. A, 1218, 6122– 6127 http://dx.doi.org/10.1016/j.chroma.2011.06.073

[6]. Sutherland, I.A., Thickitt, C., Douillet, N., Freebairn, K., Johns, D., Mountain, C., Wood, P., Edwards, N., Rooke, D., Harris, G., Keay, D., Mathews, B., Brown, R., Garrard, I., Hewitson, P., Ignatova, S. (2013) Scalable Technology for the Extraction of Pharmaceutics (STEP): Outcomes from a 3 year collaborative industry/academia research programme, J. Chromatogr. A., 1282, 84-94 http://dx.doi.org/10.1016/j.chroma.2013.01.049

Grants referred to in underpinning research:

1. The Industrial Scale up of Countercurrent Chromatography. BBSRC/DTI LINK Award Ref: 100/BCE08803, PI Ian Sutherland, Feb 98 - Jan 00 (£322,668)
2. EPSRC Instrument Development Grant No GR/M48345, "A New Rapid Centrifugal Liquid-Liquid Chromatography Separation and Detection System for Multiple High-Resolution Purification without Sample Loss or Degradation" PI Ian Sutherland, Apr 99 - Mar 02 (£623,244 with Dai Games co-I, Swansea University)

3. EPSRC IMI Responsive Processing, Grant Ref GR/R03143/01, "Realisation of Process Scale Countercurrent Chromatography" PI Ian Sutherland with Gary Lye co-I UCL, Dec 2000 – Aug 2003 (£392,175)
4. BBSRC-SBRI Grant 192/SBRI9675 for Dynamic Extractions Ltd, "Industrial Scale up of Countercurrent Chromatography (CCC): the feasibility of scaling from pilot to process scale", PIs Philip Wood, Svetlana Ignatova & Ian Sutherland Aug 2003 – July 2005 (£125,000)
5. BBSRC Research Equipment Initiative, "Dynamic Rapid Extraction And Manufacture of Pharmaceuticals (DREAM-Pharma)", PI Ian Sutherland, co-I Ian Garrard,, Ref BBD524583/1 (£198,499)
6. BBSRC Grant Ref BB/C506364/1, "An innovative dynamic extraction/chromatography manufacturing process for purifying bioactive proteins (DEM-PRO)" PI Ian Sutherland, co-I Derek Fisher, Sept 2004 – Aug 2007 (£333,129)
7. BBSRC-Tools and Resources Programme Grant Ref. No. BB/E012949/1– "A New Dynamic Extraction Centrifuge with Independent Control of Mixing and Settling Suitable for Separations Involving Viscous Fluids of Similar Densities", PI David Hawes, co-Is Svetlana Ignatova and Ian Sutherland (£83,419) Feb-Oct 2007.
8. Technology Strategy Board High Value Manufacturing Competition, Scalable Technology for the Extraction of Pharmaceuticals (STEP), August 2009 – July 2012 (£1.46m with GSK (lead Keith Freebairn - £503k); Pfizer (£75k), Dynamic Extractions (£438k) with £441k coming to Brunel – PI Ian Sutherland; co-PIs Peter Hewitson and Svetlana Ignatova). Grant No: TP14/HVM/6/I/BD506K – Sept 2009 – Aug 2012

4. Details of the impact (indicative maximum 750 words)

This impact case study demonstrates a pioneering approach to simplifying the process and thus reducing the cost of bringing new drugs to market. A spin-out company, Dynamic Extractions was established in 2003: its business is split approximately 50:50 between instrument sales and contract separation work for industry. With the instrument sales it is developing a global market with 30% of sales in Europe, 20% in North America and 50% in the rest of the world. The company has been operating profitably for 10 years now with 7 staff and a turnover approaching £1m today. 60% of all sales of the new technology are directly to industry, of these 83% are semi-preparative and preparative and being used for preparation of materials for clinical trials and toxicity studies. In an unprecedented move by industry, Dow (USA) recently published a comparison between preparative column chromatography (HPLC) and HPCCC [P5]. The HPCCC process produced a two-fold higher throughput and consumed approximately 70% less solvent than preparative scale RP-HPLC. They were so pleased with the technology they returned a number of times for repeat kg scale separations (***Dr David Rooke).***

Interest from industry and academia has been marked; ***Professor Joachim Kinkel*** (Source 6), when commenting on Brunel's work, as chairman of the scientific committee at the Symposium on Preparative and Industrial Chromatography and Allied Techniques (SPICA) said that "liquid-liquid chromatography will be the future new technology for the pharmaceutical industry with its ease of integration in production lines, ideal clean-up of systems and efficient method development". ***Professor Lijuan Chen*** of Sichuan University, when commenting on developments from our early Honokiol work, reported: "In the past two years, we signed a cooperation agreement to develop one novel drug using HPCCC combined with HPLC for treating lung cancer with Chengdu Jiye Bio-Tech Co. Ltd. An agreement has recently been made to develop an anti-cancer drug sharing similar mechanism to taxol in collaboration with Yangtze River Pharmaceutical Group. Honokiol has now passed the on-site verification for drug registration and applied to conduct a clinical trial in China". "They are producing the bulk of the Honokiol drug using two MIDI-CCCs - turning the hope behind our original paper (Chen et al, The Rapid Purification and Scale-up of Honokiol and Magnolol using HPCCC, J,Chromatogr.A., 1142 (2007) 115-122) into reality". (Professor Lijuan Chen – Source 4). From Sutherland's research with GSK there are four new business case studies currently being developed: pharmaceutical and clinical development; virgin manufacture of API; toll refining of API from crystallisation liquors and the use of telescope processing for the manufacture of early development materials (Dr Keith Freebairn, source 5 and Michael Carroll, source 7).

There is a thriving Chinese industry building the traditional CCC instruments with long separation

times, but six key laboratories in Chinese Universities are bucking the trend; investing in the new HPCCC technology (China-25% of DE sales). High quality publications on the fractionation of new compounds from ginsenosides are being published by Tsinghua University, new analogues as new anti-cancer drugs from Honokiol, new anti-tumour agents from Sichuan University and new compounds as anti-depressant drugs from Changchun Normal University.

Dissemination - Training workshops on the use of the technology are being rolled out and an outreach programme placing instruments for collaborative research in the Universities of Geneva, Barcelona, Lyon and Rio de Janiero and also Sichuan University in China where Sutherland has a visiting professorship.

Pivotal to the outreach impact has been establishing a conference series on counter-current chromatography (CCC). The 1st International Conference on Counter-current Chromatography (CCC2000) was launched at Brunel in 2000 and has been hosted in Beijing, Tokyo, Bethesda (USA), Rio de Janiero, Lyon and Hangzhou, also in China. It will return to Brunel in 2014. The technology has also had an impact on the Symposium for Preparative Chromatography and Allied Techniques (SPICA) where talks in 2010 resulted in a special liquid-liquid extraction session and workshop in 2012.

Environmental Benefits - Waste and its disposal continue to be economically and environmentally challenging issues across the pharmaceutical industry. New, greener, business opportunities are arising from the recovery of product from waste streams (up to 15%) making the waste stream more economical to dispose of (***Keith Freebairn, GSK-see above***)

Awards for the research - highest cited paper in JCA in 2009 ("role of counter-current chromatography in the modernisation of Chinese herbal medicines" -JCA1216(2009) 740-753) and SPICA2012 prize for "API recovery from pharmaceutical waste streams" (2012)

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Dynamic Extractions http://www.dynamicextractions.com
2. The Advanced Bioprocessing Centre: http://www.brunel.ac.uk/bib/bioprocess-engineering/abc
3. The Chairman of Dynamic Extractions (UK) can be contacted for the impact of the research on the establishment of a spin-out company, Dynamic Extractions; all sale information has been provided by the contact.
4. Letter received from Vice Director, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, China: The contact confirmed how Sichuan University and Chengdu Jiye Bio-Tech have developed a novel drug for treating lung cancer, using HPCCC.
5. Director, Second Generation Process Department, GSK Research & Development, Stevenage, UK: The contact can corroborate 4 new business case studies in development and the environmental benefits of HPCCC.
6. Chairman of SPICA Scientific Committee and Faculty of Applied Sciences, Georg Simon Ohm University of Applied Sciences, Nuremberg, Germany
7. TSB Final report from the TSB High Value Manufacturing Research Programme, "Scalable Technology for the Extraction of Pharmaceutical", TSB project monitor, available from Brunel.