Institution: University of Hull

Unit of Assessment: B8: Chemistry

Title of case study: Chemtrix - Scalable Flow Chemistry

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

Chemtrix Ltd. was established in February 2006 as a 50-50 joint venture between the University of Hull and Lionix Ltd. In 2008 the company attracted investment from Limburg Ventures BV, Panthera, Technostartersfund, Microfix BV and Hugo Delissen (€2 million) that led to the creation of Chemtrix BV. In 2009 the Company launched Chemtrix USA and a second investment round followed with investors Particon BV. In 2012 ESK Ceramics GmbH & Co. KG, acquired a minority interest (30%) in Chemtrix BV based on a valuation of €5.3 million.

The three products developed and marketed by Chemtix, Labtrix®, KiloFlow® and Plantrix®, are differentiated from competitor products as they offer 'scalable flow chemistry', such that optimised reaction conditions can be easily scaled from R&D to production. In addition to the employees and investors in Chemtrix the main non-academic beneficiaries of the research have been industrial customers such as Janssen Pharmaceutica NV, Edward Air Force Base, Iolitec GmbH and DSM.

2. Underpinning research (indicative maximum 500 words)

In the early 1990s a small number of researchers (7-8 academics) mainly from Europe, the USA and Japan started to develop microfluidic based methodology which built on techniques drawn from the semiconductor industry (in particular photolithography and wet etching) in an attempt to produce so called micro total analytical systems. Professor Haswell, one of these pioneers, published the first micron-scale flow injection analysis system in 1995 and started to develop micro reactor technology.[1] This activity became instrumental in securing a prestigious multi university/industry £5 million Foresight LINK grant in 1999 that in turn was used by the DTI (now TSB) to establish a strategic national focus for the micro- and nano-technology. The research of Professor Haswell since 1993 has lead to over 180 peer reviewed publications and 10 patents in the field which have focused on establishing the fundamental design and operational parameters of flow reactors which gives the methodology significant advantages in the fields of synthetic and analytical chemistry.[2-6] These advantages can be attributed to the unique operating conditions associated with meso/micro flow-reactor devices in which the spatial and temporal control of reagents is achieved under a non-turbulent, diffusion limited mixing regime. Within such systems the control of hydrostatic and other pressure gradients, the immobilization of catalysts (Pd, Pt, sulphated zirconia, zeolites and enzymes) and the monitoring of reactants and products have featured strongly. A range of chemical reaction types have been carried out to demonstrate the advantages meso/micro flow-reactors offer in terms of stereoselective product control, multi-step synthesis and *in-situ* separations. In addition, mathematical models of reactions in meso/micro flow-reactors under electrokinetic and hydrodynamic control have been successfully constructed and validated using *in-situ* measurements of spatially and temporally resolved concentration profiles.

In 2002 a previous postdoctoral fellow of Professor Haswell, Dr Paul Watts (Lecturer, University of Hull; 2002 to 2013) and a former PhD student and postdoctoral researcher Dr Charlotte Wiles (PhD Student, University of Hull; 2000 to 2003 and post doctoral researcher, University of Hull; 2003 to 2005) seized the opportunity to commercially develop the underpinning research carried out at Hull, focusing in particular on the up-scaling (volume increase) of micro-reactor methodology whilst retaining the inherent operational advantages of excellent reaction control and efficiency. In partnership with the University of Hull and Lionix, Chemtrix BV was established to develop micro-reactor based operating systems for industrial applications of flow chemistry. Charlotte Wiles is now the Chief Executive Officer with Chemtrix BV. The research carried out at Hull in the field of micro-reactors has therefore been instrumental in establishing the core technology on which Chemtrix has now developed innovative products that have lead to a significant growth and internationalisation of the business; with industrial customers in Europe, UK, USA, Israel, India, Taiwan, Korea, China and Australia.

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

(1) Development of a micro flow injection manifold for the determination of orthophosphate, R.N.C. Daykin and S.J. Haswell, *Analytica Chimica Acta*, 1995, **313**, 155-159.

(2) Theoretical investigation into the rates of chemical reactions in micro-total analytical systems (µTAS) operating under electroosmotic and electrophoretic control, P.D.I. Fletcher, S.J. Haswell and V.N. Paunov, *Analyst*, 1999, **124**, 1273-1282.

(3) The use of novel microreactors for high throughput continuous flow organic synthesis, G.M. Greenway, S.J. Haswell, D.O. Morgan, V. Skelton and P. Styring, *Sensors and Actuators B*, 2000, **63**, 153-158.

(4) Micro reactors: principles and applications in organic synthesis, P.D.I. Fletcher, S.J. Haswell, E. Pombo-Villar, B.H. Warrington, P. Watts, S.Y.F. Wong and X.L. Zhang, *Tetrahedron*, 2002, **58**, 4735-4757.

(5) Electrokinetic control of a chemical reaction in a lab-on-a- chip micro-reactor: measurement and quantitative modelling, P.D.I. Fletcher, S.J. Haswell and X.L. Zhang, *Lab on a Chip*, 2002, **2**, 102-112.

(6) Pressure-driven and electroosmotic flows and electrical currents in Lab-on-a-chip micro reactor devices, I. Broadwell, P.D.I. Fletcher, S.J. Haswell, X.L. Zhang, R.W.K. Allen, J.M. MacInnes and X. Du, *Trends in Physical Chemistry*, 2004, **10**, 117-133.

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

Key impacts have been:

- 2 new businesses (Chemtrix BV and ChemtrixUSA).
- 13 jobs created including 4 PhDs, 3 MScs and 4 engineers.
- The development of 3 innovative products (Labtrix® KiloFlow® and Plantrix®) with a growing international industrial and academic customer base.

New businesses: After receiving substantial investment from Dutch investors, the Headquarters of Chemtrix was established in Geleen (Netherlands) in April 2008; and product development and sales actively commenced. Chemtrix Ltd.[A] remains the holding company trading under the name ‘Chemtrix BV’. In 2009 Chemtrix USA was registered to facilitate sales in North America and Canada whilst management and product development/engineering remains in the Netherlands and R&D at The University of Hull where 2 full-time employees (Drs Wiles and Ngamsom, previous Hull postdoctoral workers) develop customer-initiated processes/products related to process optimisation. In total Chemtrix BV employs 11 full time staff (split between the Netherlands and UK) and Chemtrix USA has 2 employees. In addition Chemtrix has sales representatives in Europe, Taiwan, India, Israel, Korea and China; and is actively investigating other worldwide market opportunities with the Asian market developing rapidly.
Instrumental in securing initial investment were two patent families licensed from the University of Hull and two patents licensed from Lionix, BV. Since then, Chemtrix has applied for two patents [B,C] with two more patent applications are in progress, IP generation remains key to the on-going technical development of the Company.

New innovative products: Based on early research conducted at Hull, the commercial advantages of micro-reactor technology, as it relates to organic synthesis under flow conditions, has underpinned the development of new products which now meet previously unfulfilled industry needs [D] (Figures 1-3). Competitor analysis reveals that other micro-reactor companies either specialise in small scale screening equipment (*e.g.* Syrris, Mikroglas, Future Chemistry) or large scale production systems (*e.g.* Corning, Alfa Lafal) and it is not facile to directly translate research from one system to another. Chemtrix believes that it is the only Company currently developing equipment to directly link both markets; specifically using the slogan ‘scalable flow chemistry’.

The first product launched was Labtrix® (2009), a fully automated flow reactor platform (Figure 1a) containing a glass micro-reactor (Figure 1b) (volume 1-20 µL), allowing processes to be optimized using minute quantities of reagent (200 experiments day^{-1} using 10’s mg of material[C]). Furthermore, the equipment enables researchers to conduct organic synthesis more safely[D] as well as generating less chemical waste. Independent evidence is reported by Ley.[E] In addition, Chemtrix is the only micro-reactor supplier to manufacture a reactor (Figure 1c) that enables the incorporation of heterogeneous catalysts.[D]

(a) (b) (c)

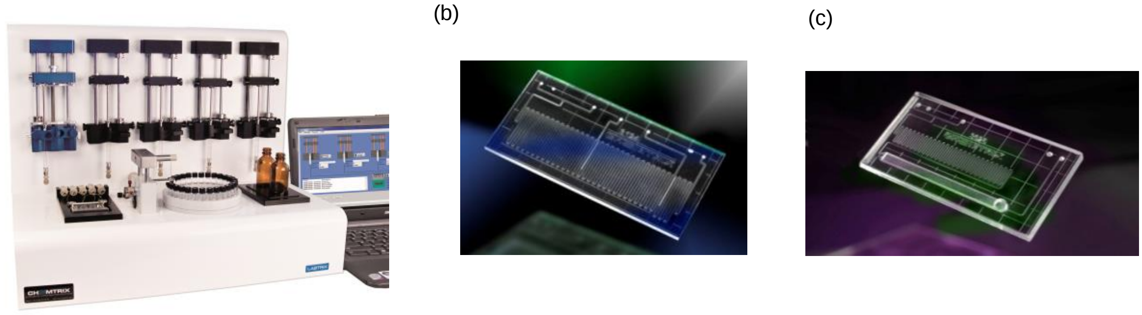

Figure 1. (a) Labtrix® system (launched 2009) and (b/c) micro reactors.

Through discussions with industry it was identified that although process chemists are content using fully automated computer controlled equipment, many bench chemists prefer manual equipment. Consequently, reacting to market demand, Chemtrix in 2010 launched Labtrix® Start (Figure 2). Sales of this product have been particularly high, both within academia and industry (independent evidence reported by Kappe[F]) with more than 40 units of this type sold to date ~ 40:60 academic to industrial end users.

Figure 2 Labtrix® Start (launched 2010).

Scale up production from Labtrix® using 'meso' scale reactors (KiloFlow® launched 2011, 3 installed and 2 in production) which consists of mm-size channels (Figure 3a). Through carrying out detailed ongoing research into available static mixer technology, the Company has developed the ability to translate the reaction conditions identified in micro-channels to meso-channels, where combination of these modules (Figure 4b) affords access to production-scale quantities (g-kg's) within a standard laboratory fume cupboard.[G,H] A partnership with ESK has enabled Chemtrix to develop silicon carbide reactors capable of achieving production rates at the tonne-scale (Figure 3b) which will service a growing industrial market estimated to be € 50million.[I] This partnership was strategic in giving Chemtrix access to larger production units and ESK access to the continuous flow reaction knowledge of Chemtrix.

(a) (b)

Figure 3. (a) KiloFlow® system (launched 2011) and (b) Plantrix® system.

Chemtrix is working closely with major international pharmaceutical and fine chemical companies (under CDAs and NDAs), with publicised examples including Sanofi-Aventis (Hungary),[J] DSM Pharmaceutical Products (NL), Janssen Phamaceutica NV (Belgium) and Iolitec GmbH (Germany) who presented results at a Symposia held at CPhI 2011 and Flow Chemistry Europe, Munich, 2011. The work focuses on access to new processing conditions (higher temperatures & pressure) with simplified synthetic processes that can be transferred from R&D to production. In one example, a new route for an API was identified at the lab-scale, resulting in an increase in product purity which upon transfer to the production plant led to significant cost savings due to a reduction in the complexity of the downstream separation process. In addition to the publicised work, Chemtrix are currently working on multiple projects with industrial partners focussing on the translation of batch processes to continuous flow, with the aim of developing sustainable, cost effective production processes. Chemtrix maintains its links to the University of Hull, collaborating in the development of new chemical processes beyond those initially identified as having commercial interest; this includes for example the synthesis of inorganic nanoparticles with Dr Grazia Francesconi.[K]

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

[A] www.chemtrix.com/company-profile (corroboration of the establishment of Chemtrix BV and ChemtrixUSA)

[B] Patent Application - ‘A microfluidic system and the use thereof’ EP2010/002777.

[C] Patent Application – ‘A new design microfluidic device, a kit of parts comprising such microfluidic devices and a modular system comprising such microfluidic devices’ EP10008784.0.

[D] Microreactors as tools for high-throughput synthesis, C. Wiles and P. Watts, *Speciality Chemicals Magazine*, 2009, 40-41.; The evaluation of the heterogeneously catalysed Strecker reaction conducted under continuous flow, C. Wiles and P. Watts, *Eur. J. Orgc. Chem.*, 2008, 5597-5613.

[E] The flow synthesis of heterocycles for natural product and medicinal chemistry, M. Baumann, I. R. Baxendale and S. V. Ley, *Mol. Divers.*, 2011, **5**, 613-630.

[F] The microwave to flow paradigm: Translating high-temperature batch microwave chemistry to scalable continuous flow processes, T. Glasnov and C.O. Kappe, *Chem. Eur. J.*, 2011, **17**, 11956-11968.

[G] Chemtrix’ KiloFlow: The turn-key kilo-lab in your fume hood, C. Wiles, *Chem. Today*, 2011, **29**, 32-33.

[H] Flexible Durchflussreaktoren für das schnelle Scale-up von Produktionsprozessen, C. Wiles and M. Seipel, *Process*, 2012, **1**, 42-44.

[I] Innovative solutions to fulfill the flow chemistry potentials in Europe, L. Pichon, 4th Symposium on continuous flow reactor technology for industrial applications, 2012, Lisbon.

[J] Formation of aromatic amidoximes with hydroxylamine using microreactor technology’, Voros, Z. Baan, P. Mizsey and Z. Finta, *Org. Proc. Res. Dev.*, 2012, **16**, 1717-1726.

[K] The preparation of magnetic iron oxide nanoparticles in microreactors, M. Simmons, C. Wiles, V. Rocher, M. G. Francesconi and P. Watts, *J. Flow Chem.*, 2013, **3**, 7-10.