GLOBAL WATCH MISSION REPORT

Microfluidics for the development, production and delivery of high-volume products – a mission to the Netherlands and Germany

APRIL 2006

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– a mission to the Netherlands and Germany

REPORT OF A DTI GLOBAL WATCH MISSION
APRIL 2006

CONTENTS

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1 EXECUTIVE SUMMARY AND RECOMMENDATIONS

1.1 Executive summary

The DTI Global Watch Mission on the development, production and delivery of high-volume products in the Netherlands and Germany was organised to increase the awareness of commercial benefits of the application of microfluidics technologies in UK industry. During the course of the mission in April 2006 the UK team held five days of meetings with over 22 academic and industrial groups in the Netherlands and Germany involved with the commercialisation of microfluidics technology.

The mission concentrated on chemical, pharmaceutical, household goods and personal care sectors where it was felt that the UK may be slow to take advantage of this new technology in comparison to the countries visited. Sectors where microfluidics is already established or close to commercialisation, such as ink-jet printing and medical devices, were not included. During the course of the mission the team encountered significant evidence of commercial activity in the medical device sector in both Germany and the Netherlands.

Both the Netherlands and Germany have world-leading activities in the commercialisation of microfluidics. The Netherlands has advanced activities in biotechnology-related areas, food processing and instrumentation. Germany has a strong position across a number of areas; particularly notable are chemicals, pharmaceuticals and biotechnology.

The technology supply chain in both countries is fully populated with organisations including academic groups, research institutes, device foundries and numerous product and system development companies. As befits a larger economy, there is a higher level of activity in Germany which has led to a community of dynamic product and system development companies. In addition the mission team observed significant end-user engagement in the German chemical industry.

The chemical sector is one area where Germany has a strong lead in applying microfluidics. Two companies (CPC/Synthacon and Ehrfeld) offering integrated reactor systems and process development services were visited. Benefits of using a microreaction approach have been identified for hazardous reactions, the production of high-value chemicals and where it is difficult to obtain high yields in conventional equipment. The next five years will be critical for microfluidics in this sector in determining how widely the technology will be adopted by chemical companies.

There is activity in microfluidics in the pharmaceutical sector in both the Netherlands and Germany. There are a number of areas where application is gaining acceptance. In drug discovery and testing, microfluidics is being developed for a number of key processes such as protein crystallisation and cell-based testing of drug candidates. Another area of application is drug delivery and patient monitoring where a Dutch group is developing chips that can monitor lithium levels in patients. Microfluidics could also benefit the scale-up to manufacturing of drugs; however, limited evidence for this was seen on the mission.

Microfluidics in the household, personal care and food sectors is still in the early stages. One or two specific examples of microfluidic applications were noted. The German company Bartels Mikrotechnik GmbH has produced a micropump that is suitable for delivering small volumes of fluids. One potential application for this device is in domestic steam irons. High-end packaging has been developed using microfluidic nozzles to deliver very fine droplets for cosmetic applications. Membrane systems are under development for applications such as filtration and emulsification. Aquamarijn, a Dutch company, is working with a large Dutch beer-brewing company to field-test filtration membranes in a pilot filtration plant installed in a high-volume production plant.

Both the Netherlands and Germany have put significant investment into microtechnologies and some of it has been very successful. The Netherlands has a well integrated national infrastructure for innovation. There is a strong focus on the generation of an entrepreneurial environment starting with universities. Notable in this area is the University of Twente and the MESA+ Institute which is uniquely focused on commercial activity and has been successful in creating spin-outs with a high survival rate.

The mission visited IMM in Germany which has been successful in creating numerous spin-outs over the last 15 years. These have received considerable help from IMM during the early stages of their development and many are now successfully establishing themselves as commercial companies.

Microfluidics technology is still developing and many new technologies are emerging. Much of the innovation is being driven by the needs of new products. As the application of microfluidics in many areas is still immature, it is likely that there will continue to be a stream of new technologies and product innovations for many years to come before specific approaches become widely accepted as the standard for a given application.

1.2 Recommendations

While microfluidics is still an emerging technology, there are many indications from the Netherlands and Germany that it could produce some degree of disruption in the sectors studied in this report. UK companies in chemical, pharmaceutical, household, personal care and the food industries need to start the process of engaging with this technology, if they are not already.

A new focus on systems integration is now enabling the acceleration of microfluidics commercialisation which has hitherto been hindered in the Netherlands and Germany. The UK should recognise that many end-user corporations, particularly in bulk materials manufacture, require complete turnkey solutions (not curiosity chips) if the potential of microfluidics is to be realised. Means to stimulate the development of complete systems should be sought.

The evidence from the microfluidics companies clustered around or associated with Twente University and IMM suggest that affordable, direct, hands-on access to microfabrication tools is a key requirement for encouraging a dynamic industrial microfluidics cluster, where start-ups and spin-outs are the principal commercial entities.

Microfluidics is an area where the UK has already had some success through the Cambridge ink-jet cluster and some medical device companies. The UK should continue to capitalise on its skills in engineering and product development to expand the range of applications for microfluidics to other areas.

2 INTRODUCTION

2.1 Background to the mission

Microfluidics is the manipulation, processing and measurement of fluids on a micro scale. A sense of the scale involved can be obtained by considering that the channels and other active features of microfluidic devices are typical less than 100 µm across. Such dimensions are similar to or smaller than the dimensions of a human hair. By processing fluids on such microscopic scales it is possible to obtain novel processing regimes.

Important features of these processing regimes include:

- The potential for processing very small volumes of fluids – important in many biochemical applications where often very little of the sample is available
- Processing takes place in a laminar flow regime which means that mixing is by extremely well controlled and predictable diffusion processes
- Temperature control for exo- and endothermic reactions can be significantly better than in bulk processing technologies
- Many different process stages can be integrated onto a single chip

Such features can lead to many benefits – small sample size, very precise control of processing and reaction conditions, which enables yields and process times to be greatly improved, greatly increased safety for potentially explosive reactions and the ability to produce a complete 'lab-on-a-chip' disposable device that can perform an integrated function such as sample preparation, reaction and measurement. Such devices can be small enough to be the basis for hand-held diagnostic and monitoring tools that open up the prospect of future applications in healthcare, environmental monitoring, industrial monitoring, security and defence.

As a result of its exciting potential, microfluidics represents one of the fastest growing sectors of micro- and nanotechnology (MNT) exploitation with present-day applications and commercialisation in life sciences, drug testing and discovery, industrial monitoring and the chemical industry. Future application areas are as diverse as consumer products, food, agriculture, environmental monitoring, fuel cells and for cooling high-performance computer chips. In fact there are potentially many new applications waiting to be discovered for this exciting new technology.

Microfluidics has already achieved one very notable success as the cornerstone for ink-jet printing technology. The print heads in this technology are built around arrays of nozzles that are capable of ejecting very small – tens of picolitre (pl) – quantities of liquid in an accurately controlled pattern onto the substrate that is to be printed on.

Longer term, microfluidics could impact a very diverse range of markets spanning food, household products, personal care products, healthcare products and pharmaceuticals, offering the opportunity to develop smart and intelligent products at low cost. Applications could include automated product delivery, bespoke drug delivery systems and smart packaging. Many of these applications will be effected through integration into product packaging, with the dividing line between pack and product being very blurred.

2.2 Mission coordinating body

Faraday Packaging Partnership (FPP), jointly funded by UK government and industry, is the largest innovation support and development network within the packaging arena, helping to deliver a new dimension in packaging design and innovation. FPP works with some of the world's 'elite' in the creation and supply of fast-moving packaged consumer goods (FMCG) and is also a specialist applications node of the recently launched Materials Knowledge Transfer Network. Technology for Industry (TFI) Ltd organised and led the mission on behalf of FPP (further information on TFI is given in Appendix B.10).

2.3 Microfluidics in the UK

As noted above, ink-jet printing is a global market for microfluidics, and the UK has been one of the leaders in the development of this technology. A significant cluster of companies has formed in the Cambridge region based around ink-jet printing including companies that develop high-perfomance ink-jet print heads and novel applications for such tools including printable displays and electronics. Companies involved in this cluster include Xaar, Domino, Inca, Xennia, Linx, Cambridge Display Technology and Plastic Logic.

The UK has strengths in a number of application areas that can use microfluidics, for example speciality chemicals, pharmaceuticals, medical devices, personal care and household products. Given the wide range of potential new application areas the UK should be able to develop other world-class clusters of companies based around the application of microfluidics to one or more of these sectors.

At the other end of the technology pipeline a number of UK universities are engaged in research into the fundamental aspects of microfluidics and the development of novel devices suitable for a range of applications. Some of the universities involved in the development of microfluidics are Leeds, Cardiff, Bristol, Edinburgh, Imperial, Southampton, Cambridge, Cranfield and Hull. Two of these universities, Leeds and Cardiff, were represented on the mission team. In addition to the universities involved in the development of microfluidics technology a number of research organisations are involved in the development of microfluidics technology and devices. Some examples include the Centre for Microfluidics and Microsystems Modelling at Daresbury, Council for the Central Laboratory of the Research Councils (CCLRC) and QinetiQ.

There are a number of organisations capable of fabricating microfluidic devices including two that are participating in the DTI-funded programme to establish centres of excellence in MNT. The two centres are Fluence, which is hosted by Epigem, focusing on polymer microfluidic devices, and Dolomite focusing on glass microfluidic devices. A number of other organisations have the capability to prototype and/or manufacture microfluidic devices including Innos (silicon) and Centre for Integrated Photonics (glass). There are also companies that are developing microfluidic devices and integrated systems that use microfluidics as a component. Many of the companies in the Cambridge ink-jet cluster fall into this category. Outside of the ink-jet cluster there are a number of small or medium sized biotechnology companies such as Genapta, Q-Chip, Randox and Syrris.

The area where the UK is relatively weak compared to the target countries, and Germany in particular, is in pull for microfluidic technology from existing industries. It is the objective of this mission to stimulate interest from a number of industrial sectors where it is believed that prospective competitors are already engaging with this technology and are likely to reap the benefits in terms of more competitive products in the near future. Many UK companies engaged in biotechnology have already started to take microfluidics seriously and a few, such as GlaxoSmithKline, are making significant progress in leveraging this technology. However, there are many more sectors where the level of interest is considerably lower, for example fine chemicals, personal care and household goods.

2.4 Broad objectives of the mission

- To increase awareness in UK manufacturing industries such as FMCG, chemical and pharmaceutical about commercial benefits of the application of microfluidic technologies

- To promote exploration of application of microfluidics to consumer products and their packaging, in particular in relation to food, household, personal care and pharmaceuticals

2.5 The Netherlands and Germany

The mission visited the Netherlands and Germany due to their world-leading position in these technologies at both academic and industrial level, with a surge of commercial activity and several high-profile start-up companies being formed or company acquisitions taking place, as evidenced via recent conferences and workshops covering these technologies.

Many of the world's leading microfluidic component suppliers are based in Germany (D) and the Netherlands (NL). These include Burkert (D), Boehringer Microparts (D), Bartels Mikrotechnik (D), Erhfeld Technologies (D), ThinXXS (D), LTF (D), LioniX (NL), C2V (NL), Micronit (NL), Mikroglas (D) and many more.

Dutch and German research institutes are world class in microfluidic technologies, eg the Universities of Delft, Eindhoven and Twente (which hosts the MESA+ Institute) and TNO (NL); IMM, HSG-IMIT, the Universities of Freiburg and Munich, and FZK (D). HSG-IMIT and the University of Freiburg have implemented a technology transfer network over the last few years aimed at commercialisation of microfluidic technologies, funded by the European Union's (EU) Europractice programme.

German and Dutch end-user industries and systems integrators are actively working with microfluidic technologies, eg Shell, Akzo-Nobel and DSM (NL); Degussa, Bayer, BASF, Clariant, Merck and Siemens Axiva (D).

2.6 Mission team

The team represents all areas of interest in microfluidics in the UK including academics, component manufacturers, system integrators, large end users and technology strategy. Profiles for the team members are included in Appendix B.

2.7 Background research

A number of pieces of background information and research have been used in designing this mission. One of the main pieces of research has been carried out by TFI in conjunction with the global MNT commercialisation organisation MANCEF. In this work, TFI has been developing roadmaps for the development of microfluidics in a number of application sectors. Other background research has been carried out at MANCEF's global commercialisation conference COMS2005.

3 INTRODUCTION TO MICROFLUIDICS

Microfluidics is a platform technology that can be manufactured using a wide range of substrate materials which can be structured to create a number of different types of functions (channels, mixers, valves etc) on a single chip. The technology has potential to realise disruptive changes in many application areas.

3.1 Substrate materials

Polymer is likely to be the most widely used substrate material in the long term because of its low cost which makes it very suitable for applications where a microfluidic device is either used once and disposed of or where cost is very critical. The disadvantages of polymer are that it is not a robust material and it will not withstand high temperatures or harsh chemical environments, and there is a likelihood of materials leaching from the substrate and contaminating sensitive chemical processes being carried out on the chip.

Glass is a more robust material with better chemical and temperature resistance; however, the evidence to date indicates that glass microfluidic devices will have a higher cost per function when manufactured in volume than their polymer equivalents. Glass is often favoured where sensitive chemical reactions are involved as its properties and effect on reactions are well characterised.

Silicon has been used widely in the past because of the recent developments in high-precision processing of this material and is still used to provide low-volume prototypes and products and where direct integration of electronics adds value. However, the cost of silicon is likely to be uncompetitive in the long run and a more likely approach that is already finding favour in some products is that silicon sensors will be hybridised, eg with polymer microfluidic devices, to create advanced sensors.

Metals are also finding favour in some microfluidic devices, particularly in the volume processing of chemicals where the excellent temperature, pressure and chemical resistance and thermal conductivity are essential. Metal microfluidic devices are likely to be more expensive than polymer devices and are therefore likely to be used in applications where a permanent device is used to carry out manufacturing of high volumes of materials.

3.2 Functions that can be implemented

Microfluidic devices can be manufactured in a number of different ways including bonding of silicon and glass wafers, plastic injection moulding or lamination and metal machining and bonding. This diverse range of techniques can be used to make devices that have just one function (eg a mixer) or chips where several functions are integrated into one substrate.

The range of functions that can be implemented includes:

- Channels which can be used for moving fluids around 'on chip'
- Functionalised channels where there has been either surface modification to interact with the fluids flowing past or separating media to assist separation processes
- Mixers – basically long channels where

diffusive mixing of different fluids can take place
- Heating and cooling
- Valves to control flow down channels
- Pumps to move fluids around on chip – several methods are available including capillary mechanisms, mechanical pumps and electrical pumping
- Sensors such as electrodes or optical sensors which can be either printed in the channel or introduced by combining sensors
- Optical windows and other components
- Nozzles for delivering fluid droplets
- Microfilters

With this wide range of capabilities it is possible to build single fluidic chips that can carry out a diverse range of functions such as chemical synthesis, chemical analysis, DNA amplification, nanoparticle production, nanodispersion production and many more possibilities.

One of the challenges in designing complete systems on a chip is controlling the cost and time of design to achieve a given function. Design and simulation tools are available for microfluidics; however, they are still relatively new and it may require a number of physical iterations to converge on a working design for a device.

3.3 Market sectors

Microfluidics has the potential to penetrate a large number of market sectors. There are a number of technology drivers such as small sample volumes, improved process control and the ability to make disposable devices that make it an attractive solution to a number of challenges.

Microfluidics has already been successful in information and communication technology (ICT) where ink-jet printers are widely used for domestic and commercial applications. The total market for ink-jet print heads is estimated at \$2.5 billion (~£1.4 billion) for 2009. Exhibit 3.1 is a roadmap for the application of microreaction technology into a number of the sectors that are covered in this report. It indicates that microfluidics should be used in the short term in lab-based tests such as analysis of DNA or proteins. In the medium term it will move into pharmaceuticals, fine chemicals and personal/home care. Longer term applications include the food sector and bulk chemicals.

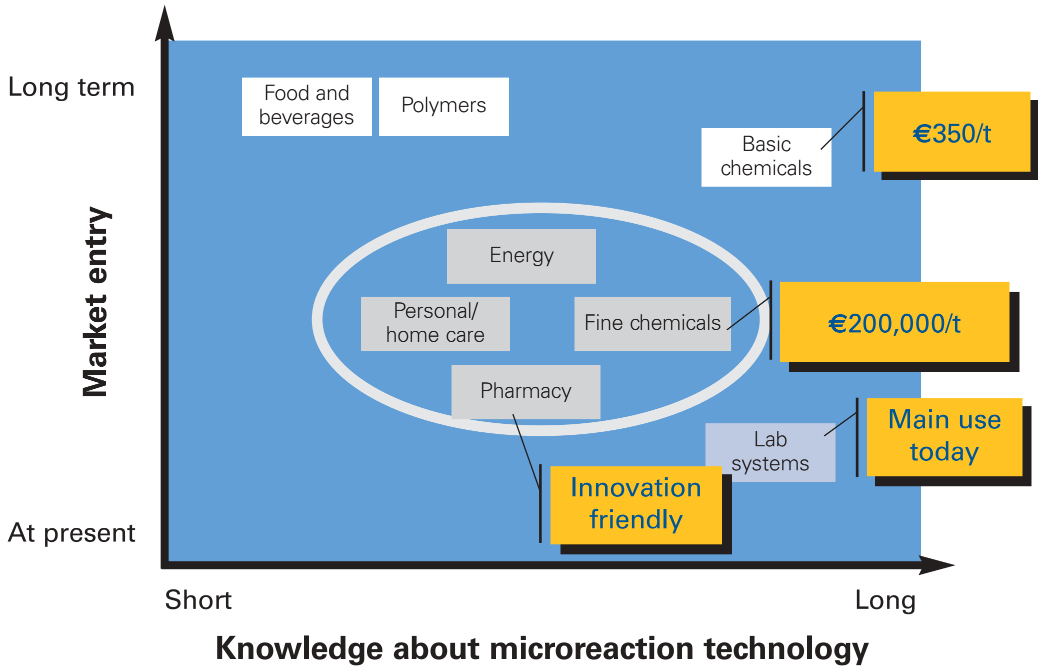

Exhibit 3.1 Applications of microreaction (source: PAMIR study, IMM, 2002)

4 OVERVIEW OF THE MICROFLUIDICS SUPPLY CHAIN

Exhibit 4.1 is a schematic supply chain for microfluidics technology. It can be seen that many different types of organisations need to be involved in bringing a new microfluidic device or technology to the market. In order to have a vibrant microfluidics industry within a country, it is important that a complete supply chain should exist in that country. It is possible for gaps in the supply chain to be filled by external sources; however, in emerging technologies such as microfluidics, close proximity of suppliers and users can accelerate the commercialisation of new technology.

At present, a lot of new microfluidic devices and technology concepts are being developed in universities and other research laboratories, either as part of 'blue skies' projects or increasingly in more application-focused projects. Device foundries manufacture microfluidic devices and can be either an

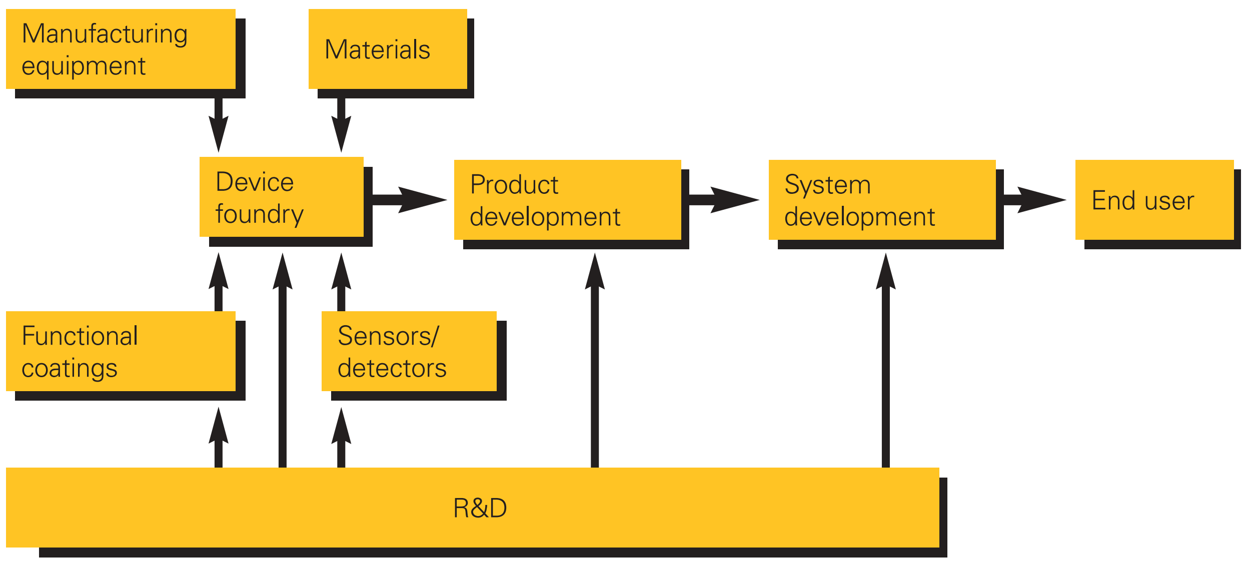

Exhibit 4.1 *Schematic supply chain for microfluidics technology*

internal captive facility or one of the increasing number of independent foundries that are becoming available around the world. It is often necessary for the device manufacturers to add additional components into the microfluidic system, for example sensors or some form of functionalisation to optimise selected regions of the device for specific processes.

Product development for microfluidics is still an area where there are a number of challenges:

- Modelling and simulation tools are still quite immature, and product development can have a significant trial and error component
- The cost of design iterations can be quite high
- Many of the technologies employed to manufacture microfluidic devices are not very cost effective for low-volume production
- Microfluidic product design is still relatively new and there are few experienced designers in this area

The issue of product development can be further complicated by the fact that a microfluidic device is often just one component of a larger system that is needed to deliver the desired function to the end user. The larger system may involve additional hardware (eg pumps, flow controllers), software, and measurement systems (eg optical probes).

Many product and system development groups are part of an end user of microfluidics. However, many end users do not wish to engage with the technology at this level; rather they require a turnkey solution that delivers the desired result with no need on their part to understand the underlying technologies. One encouraging feature of the last few years has been the emergence of product and system development houses to serve potential user communities.

Of the two countries studied in this visit, Germany has the most developed supply chain for microfluidics, with many organisations at all points in the chain from fundamental research and development (R&D) through to end users engaging with the technology and product groups within Germany. To some extent this is to be expected as the German economy is much larger than the Dutch economy (for example the GDP is estimated to be five times larger). Due to a combination of this scale and the commitment of German regional and national governments to industry and manufacturing using advanced technologies, the overall microfluidics industry appears to be very strong in Germany and in the process of generating a number of commercial success stories.

In comparison, microfluidics in the UK (with a GDP around 80% that of Germany and a little less than four times that of the Netherlands) is underperforming relative to either of the countries studied. As is often the case in many areas of technology, the UK is well endowed with R&D groups that are actively researching the technology; however, the rest of the supply chain is relatively poorly populated, and end-user communities are lagging behind those encountered, especially in Germany. In general, the UK user communities appear to have a lower level of awareness of microfluidics and its potential impact on their sector; where there is some awareness, they appear to be more reluctant to engage with this disruptive new technology.

4.1 The microfluidics supply chain in the Netherlands

The supply chain in the Netherlands is somewhat better developed than that in the UK. There are organisations throughout the chain that can engage with end customers and, based on activity levels observed amongst the product designers, there are some end customers starting to engage with the technology. Although there are end users in the Netherlands, many of the supply companies nonetheless adopt an international outlook, some even supplying into the UK market already.

4.1.1 Technology R&D

Three technology R&D centres were visited in the Netherlands:

- TU Delft
- University of Twente
- TNO

There are a number of other active R&D centres including the Universities of Groeningen and Wageningen and Philips MiPlaza. Exhibit 4.2 shows a map of the academic groups involved in the Netherlands MinacNed – a nationwide network of groups active in MNT, including microfluidics.

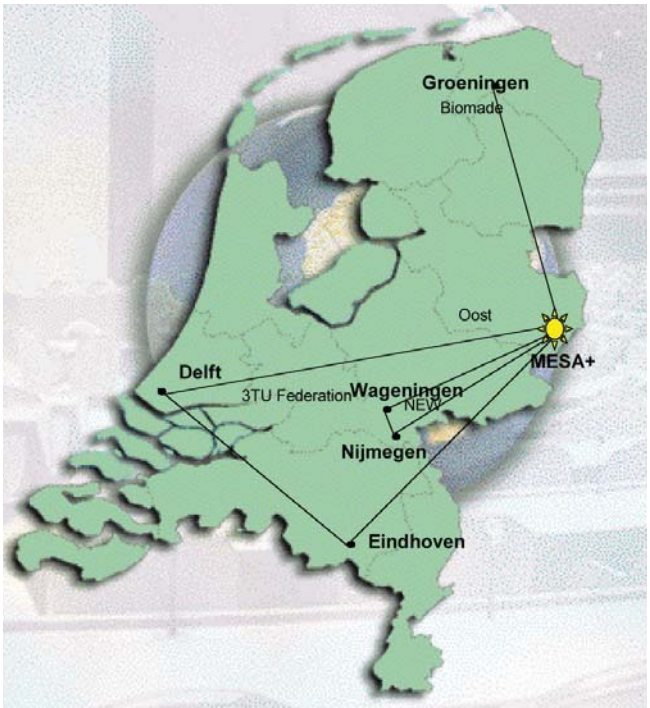

Exhibit 4.2 Map of microfluidics R&D centres in the Netherlands (courtesy Richard Schaafoort, MinacNed)

Of the centres visited, Delft was biased towards more fundamental research while Twente had a very comprehensive programme integrated into the MESA+ Institute which covered everything from fundamental physics through to applied device research. MESA+ has also spawned a number of spin-outs which are commercialising microfluidics. Interaction with the MESA+ Institute is possible at a number of different levels.

4.1.2 Foundries

The main foundries available in the Netherlands are all based around Twente, one being Micronit, a spin-out from MESA+ that focuses on the production of glass microfluidic devices for a wide range of applications and is competing with companies worldwide such as Micralyne in Canada. The other foundry is the MESA+ Institute itself which offers some potential for the fabrication of microfluidic devices via an open access university environment.

4.1.3 Product and system design

The mission saw a few organisations engaged in product and system design in the Netherlands. The majority were small or medium sized enterprises (SMEs) although TNO, the Netherlands Organisation for Applied Scientific Research, was also involved with some industrial product developments.

Many of the SMEs were spin-outs from the MESA+ Institute and had been through the MESA+ incubation process. Examples include LioniX (general MNT design and product development), ChemtriX (microfluidics for chemical applications) and C2V (developing microfluidics based gas chromatographs). Other companies had also taken advantage of the MESA+ incubator such as Aquamarijn, which itself was a business accelerator for a number of focused product companies (eg Nanomi BV, Medspray BV) developing micro- and nanofiltration for a range of applications. Overall, the impression was of a number of small companies actively developing products and succeeding in engaging with larger end users.

4.2 The microfluidics supply chain in Germany

The supply chain in Germany is more mature than in the Netherlands with organisations throughout the supply chain and supply companies successfully engaging with end-user companies. There has been some merger and acquisition (M&A) activity in Germany wherein SME companies with promising products have been acquired by large corporate players that want to use the technology in core product ranges. As in the Netherlands, companies in Germany are addressing international markets.

However, in contrast to the Netherlands, complete supply chains exist within Germany, sometimes clustered within one region. For example the mission uncovered a very strong supply chain for microfluidic devices in the chemical industry based in the state of Hessen where technology suppliers, product developers and end users all work together to develop microfluidic-based manufacturing plants for commercial use. The mission visited the Frankfurt region and was able to sample some of the overall activity in Germany.

4.2.1 Technology R&D

There are a number of microfluidics technology R&D centres in Germany. The mission visited the Institute for Microtechnology Mainz (Institut für Mikrotechnik Mainz GmbH – IMM), one of the leading institutes for applied research into microfluidics technology, which has produced a number of spin-out companies (see below). Other institutes that are working on microfluidics include FZK (Forschungszentrum Kahrlsruhe) and HSG-IMIT (Institut für Mikro- und Informationstechnik der Hahn-Schickard-Gesellschaft eV).

4.2.2 Foundries

Although no foundries were visited on the official agenda, a number were contacted at the Hannover Messe and at other previous events. These include private companies such as Microtec (polymer microfluidics), Chemnitz, Microfluidics Chip Shop (polymer microfluidics) and Micreon (laser micromachining). With the exception of Microfluidics Chip Shop, the foundries were not specialised in microfluidics but offered the ability to build microfluidic devices. Discussions with Microtec during the Hannover Messe indicated that it expected to see significant growth in its microfluidics business, mainly from Germany but also from outside the country.

In addition to the private companies, there are a number of university-based open-access centres such as the Microsystems Centrum Bremen (MCB), MST Factory Dortmund, Bayerisches Laserzentrum and Institut für Mikrosystemtechnik (IMTEK, Freiburg) which offer access to facilities and technologies and support a number of spin-outs. All of these institutes are working in several different areas of microsystems but they have some level of activity in microfluidics.

4.2.3 Product and system design

There are a number of product and system design companies in Germany. Overall activity levels appeared to be significantly higher than in the Netherlands and the companies are better linked in to local end users.

There are a number of organisations such as IMM, HSG-IMIT (Villingen-Schwenningen) and FZK which are federal and/or state backed but engage with industry on commercial projects. These organisations typically work with a local university-based foundry to develop prototypes for industry. They are also involved in technology transfer of manufacturable devices to industry.

In addition there are a number of private companies that are developing microfluidic devices. Many of these are spin-outs from institutes such as IMM. For example, ThinXXS, Ehrfeld (recently acquired by Bayer and being integrated into its chemical business), Cellular Process Chemistry Systems GmbH (CPC), Mikroglas and Azurchem have all spun out of IMM and are engaged in microfluidics.

Many companies are associated with a university-based technology centre which acts as its prototyping and low-volume manufacturing foundry – Protron Mikrotechnik/MCB and ThinXXS/IMM are examples of this. One result of the relationship with a local foundry is that the company tends to specialise in a starting material such as silicon, polymer, glass or metal.

A wide range of different markets are being addressed by German companies, including the chemical industry, medical devices, proteomics and genomics, security and defence.

4.3 Summary of key microfluidics activities elsewhere in Germany

4.3.1 Baden-Wuerttemberg

FZK is arguably the most important research institution in Germany in the field of microsystems technology, with a strong focus on microfluidics. Other important organisations in Baden-Wuerttemberg include the Fraunhofer Institute for Chemical Technology (ICT) in Karlsruhe, IMTEK at the University of Freiburg (medical/life sciences), Fraunhofer IPM, IAF and ISE (also in Freiburg), Fraunhofer IPA and IGB (Stuttgart), and HSG-IMIT in Villingen-Schwenningen.

HSG-IMIT coordinated the European network of excellence on microfluidics, the Liquid Handling Competence Centre (LICOM) from 2000 to 2005 whose focus was to support the industrial take-up of microfluidics.

The focus was initially across all sectors but later narrowed to life sciences due to limited success in other sectors where development costs often proved prohibitive. Key barriers to the utilisation of microfluidic technologies were identified as:

- Lack of suppliers of components and systems, and limited commercial infrastructure
- Lack of standards
- High component costs

Typical applications included implantable drug delivery systems, capillary chips, flow sensors, and biosensor systems for chemical biological agent detection (defence). The importance of mixed technology prototyping and manufacturing, including polymer, silicon, glass and metal technologies as well as add-on process such as surface functionalisation were highlighted, and therefore the need for strongly interdisciplinary consortia.

HSG-IMIT has now refocused on the development of self-generating energy systems, smart textiles and micro-medical technologies (dosing instruments, intelligent plasters, smart pills).

Fraunhofer ICT heads the Fraunhofer Alliance for Modular Microreaction Systems (FAMOS) which comprises six Fraunhofer Institutes covering chemical, ceramic, laser, production, microintegration and environmental technologies. FAMOS has developed a modular microreaction system (Exhibit 4.3).

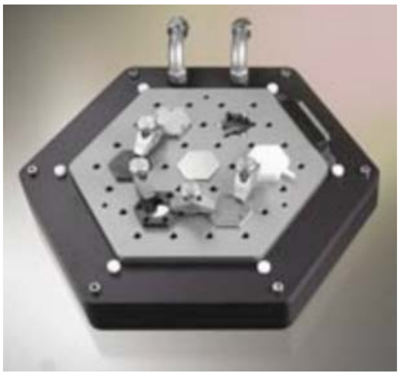

Exhibit 4.3 FAMOS microreaction platform

The Baden-Wuerttemberg region is also home to a number of important companies such as Bosch and BASF, Siemens Axiva, and a range of SMEs with biochip and laboratory automation technologies.

4.3.2 North Rhine-Westphalia (NRW)

In 1999 the city of Dortmund decided to invest in microsystems technology (MST) as part of its regeneration strategy, and attracted a number of start-up companies to locate in a new MST incubator with the first open-access facility in Germany (mst.factory). Dortmund now has 28 MST-related companies employing 8% of all European employees in MST/MEMS (micro-electro-mechanical systems). It has the only business competition for microtechnology in Germany (www.start2grow.de).

IVAM, Germany's trade association for MST, is based in Dortmund and manages a national MST technology transfer network funded by the Federal Ministry of Economics and Technology (BMWi).

Other important organisations in NRW are the Forschungszentrum Jülich, one of Germany's large-scale research facilities having a strong life science focus, the Fraunhofer Institute for Microelectronic Switching and Systems (IMS, Duisburg), and a number of companies around Düsseldorf.

4.3.3 Berlin-Brandenburg

Berlin's activities in MST focus on medical and biotechnologies, automotive and transport technologies and ICT.
Noteworthy organisations:

- The technology transfer network Microsystems Technology (www.mst-berlin.de)
- Centre for Microsystems Technology (ZEMI) – ZEMI has started a collaboration (named EMiL) with the Leibniz Institute for Agricultural Engineering Potsdam-Bornim (ATB) aiming to develop MST for innovative food production; projects will include a mobile system for the measurement of meat freshness and other sensor systems for the monitoring of the supply chain from manufacturer to point of sale
- Fraunhofer Institute for Reliability and Microintegration (IZM)
- Technical University Berlin, Institute for Engineering Design, Micro and Medical Technology
- Fraunhofer Institute for Production Systems and Design Technology (IPK)
- BESSY (Berlin Synchrotron Radiation Facility) Application Centre for Microengineering (AZM) – AZM has developed a microfluidic system for the amperometric analysis of cosmetics and foods; a micromixer has been developed that can overcome mixing problems with viscous fluids; made of polymethyl-methacrylate (PMMA), it is cheap and transparent, reusable and chemically resistant

4.3.4 Thueringia (Erfurt-Jena-Ilmenau triangle)

This region has substantial activity in microfluidics with a strong emphasis on life science applications, built on its historical strengths in optics and laser technologies, with organisations such as the Friedrich-Schiller University, Technical University of Ilmenau and the Applikationszentrum Mikrotechnik Jena (AMT), competence networks BioInstruments and Optonet, and companies such as Carl Zeiss Jena, Jenoptik and Jenapharm, with a large number of SMEs including Analytik Jena AG, Clondiag, Cybio and Mildendo.

TU Ilmenau established a Centre for Micro- and Nanotechnologies (ZMN) adjacent to its existing MNT Institute in 2002. This 2000 m^2 facility has 680 m^2 of clean rooms (classes 10,000, 1,000 and 100) and is set up to work with various materials – silicon, polymer, ceramic and hybrid. The focus is on chemosensors and fluidic platforms for single cell and single molecule manipulation, with applications in diagnostics, in particular in pharmaceutical and environmental applications. The €32 million (~£22 million) investment cost was financed by the Freistaat Thüringen and the Federal Ministry of Education and Research (BMBF), and up to €10 million (~£6.9 million) is available over 10 years to attract leading researchers to Ilmenau.

4.3.5 Bavaria

The Munich region (Martinsried) is Germany's leading biotechnology location, with a focus on therapeutics, and there are a number of companies such as Advalytix utilising microfluidics in such applications, as well as the Technical University, Ludwig-Maximilians University, and the Fraunhofer IMS.

Siemens is developing a multi-analyte continuous online water sensor to detect chemical contamination – a cost-effective, online fluorescence immunoassay biosensor system utilising microfluidic sampling and flowcell, and 32 signal detection array monitoring.

4.3.6 Saxony

There is a strong focus in this region (centred around Dresden/Chemnitz) on automotive applications, with significant microfluidics activities in the universities and technology parks in both cities.

5 MICROFLUIDICS IN THE CHEMICAL SECTOR

Chemistry in microfluidic systems has been widely performed across Europe, the USA and Asia at the laboratory scale for both screening compounds and developing reaction mechanisms either as part of high-throughput automated systems or as part of manual reaction pathway development programmes. The laboratory use of microfluidics to carry out chemistry has been most widely adopted by the biochemical sciences for diagnostic and screening applications. Due to its relative maturity and widespread global commercial adoption, this area was not covered by this mission, which focused on emerging technologies and applications.

The popular chemistry and chemical engineering magazines have carried a number of articles over the last few years which have announced the arrival of microchemical manufacturing.[1] All of these articles have highlighted the strength of microchemistry in Germany.

The transfer of microfluidics from chemistry to chemical engineering occurred first in Germany, largely driven by IMM and DECHEMA, the German Association of Chemical Engineers, and building on Germany's strong chemical and chemical engineering industries, particularly along the Rhine and Main rivers. To a lesser extent this transfer is also taking place in other countries, either directly or indirectly under the auspices of programmes such as process intensification. In Germany, the focus has changed from purely providing evidence that a reaction can be carried out to focusing on the technology needed to underpin the engineering and design philosophy needed for the production of larger quantities of chemicals using micro process engineering by 'microreactors'. The progress has been well documented in a series of international conferences.[2] A number of textbooks have been produced which document how to use microfluidics for chemical processing.[3]

1 www.rsc.org/chemistryworld/Issues/2004/January/bountiful.asp – C O'Driscoll, *Small is bountiful*, Chemistry World, January 2004; http://pubs.acs.org/cen/coverstory/83/8322finechemicals.html – A M Theyer, *Harnessing microreactions*, Chemical & Engineering News, 30 May 2005, 83(22): 43-52

2 IMRET 1-8 – International Conference on Microreaction Technology – odd proceedings published by Springer, even proceedings published by AIChE, eg IMRET 8 in Proceedings of AIChE Spring Meeting 2005

3 V Hessel, S Hardt, H Lowe, *Chemical Micro Process Engineering – Fundamentals, Modelling and Reactions*, Wiley-VCH, 2004; V Hessel, H Lowe, A Muller, G Kolb, *Chemical Micro Process Engineering – Processing and Plants*, Wiley-VCH, 2005; N Kockmann, *Micro Process Engineering – Fundamentals, Devices, Fabrication and Applications*, Wiley-VCH 2006

5.1 'Microreaction'

Microreaction is the carrying out of chemical processing operations in microfluidic systems or, more generally, in systems with microstructured components. It is possible to carry out many of the classical unit operations of chemical engineering in microfluidic systems – mixing, heat exchange, chemical reaction etc. However, microreaction research has generally concentrated on the reaction part of chemical processing and less on the pre- and post-reaction steps of purifying reagents and products, removing waste products and introducing catalysts.

Microreaction is most likely to be suitable for reactions where:

- Reaction times are short
- Reactions are highly exothermic or highly endothermic
- Reactants, intermediates or products are explosive or unsafe in large quantities
- Scale-up issues are to be avoided
- Optimisation of selectivity and/or yield is required

Microreaction is not suitable for all chemical reactions, particularly those involving highly viscous reactants or products and truly long reaction times. In addition, the presence of solids or gases will complicate the design of an appropriate microchannel system, where large particles or large gas bubbles have the potential to stop the system from functioning. However, one of the most often quoted examples of microreaction production is that of azo pigments by Clariant (80 t/y), where a system has been built which uses microstructured components to produce a particulate product.[4]

One of the most significant differences between microreaction and standard laboratory chemical development (and many chemical production processes) is that microreactions are inherently continuous processes. Whilst continuous processes are well understood by chemical engineers and process chemists, they are not the development methods traditionally taught to organic chemists, and hence a degree of retraining will be necessary to have such systems adopted at the discovery stage within chemical companies. Equally, while continuous processes are common within commodity chemical manufacture, much of pharmaceutical, fine and speciality manufacture occurs in batch reactors. The value of the chemicals manufactured and the rate of change of these batch chemicals would normally mean that these companies would be the early adopters of a novel advantageous technology; however, the inexperience of the development chemist and the current reliance on batch technology for manufacture have certainly been factors which have prevented wide-scale uptake. Needless to say, the examples that do exist are in the fine chemicals area – such as Clariant's pigment processing, Merck's two tonne production with 10 different two-stage reactions[5] and Sigma-Aldrich advertising its use of microreaction for the manufacture of small quantities of materials using traditionally difficult chemistries.[6]

5.2 Microreactor component construction

Microreactors have been constructed from all the standard materials used to make microfluidic components but, depending on the approach to microreactions, some materials may be favoured over others.

4 www.clariant.com/C12568C5004FDBD7/vwWebDownloadsWT/development_clariant_factbook_1_E.pdf – description by Clariant of its use of a microreactor to make an azo pigment

5 www.abctechnologies.ch/2004/download/Grund-Web.pdf – presentation at abc Technologies 2004 (Accelerated Bio and Chem Technologies), Basel, Switzerland, 22-23 January 2004

6 www.sigmaaldrich.com/aldrich/bulletin/al_chemfile_v5_n7.pdf – Sigma Aldrich ChemFiles, Vol 5(7), July 2005

A number of academic groups and companies have concentrated on construction materials and methods – embossing/moulding of polymers (Epigem[7], ThinXXS[8]), etching of silicon (Protron Mikrotechnik[9]), etching of glass (LioniX[10], Mikroglas[11], Micronit[12]), metal systems based on build-up of machined foil layers to give complex internal fluid paths (CPC[13]), microengineered metal systems bearing a closer relationship to precision engineering (Ehrfeld Mikrotechnik BTS[14]), and IMM[15] has used all these fabrication methods.

5.3 Approaches to microreaction engineering

There have been two different approaches developed to microreactor design:

- **Design an individual microreactor for each reaction**. This has typically involved the use of glass to make reactors with optimised reaction volumes and/or reaction times and the incorporation of necessary elements such as mixing or heat exchange. This approach has also been put into production using metal systems. The ultimate version of this approach has been suggested for complete reaction processing including the incorporation on the glass microreactor of pre- and post- reaction process operations such as filtration (Delft/Twente, LioniX/ChemTrix, IMM).

- **Develop a set of classical chemical engineering unit operations (modules) at the microscale** which can be bolted together in the correct form for a particular reaction and then reassembled in a different form when a different reaction is required (IMM, Ehrfeld, Mikroglas).

The first approach includes many of the essential advantages espoused for microreaction – optimum reaction times, heat exchange conditions, optimum mixing – but requires the development of a complete new microreactor system for each reaction (or at least each class or type of reaction) to be performed. The second approach is more pragmatic, allowing a toolkit to be produced which can be reused, albeit at the cost of potentially imperfect reaction conditions.

The German Chemical Engineering Society's (DECHEMA) Reaction Engineering Division has set up an industrial panel on Micro Process Engineering which ran a strategic research project Modular Micro Chemical Engineering (MicroChemTec/µChemTec) from 2001 to 2005.[16] This project produced the design of a construction kit from which modular microsystems can be built for microprocess engineering. This was effectively a standard which manufacturers of microsystem components could use to offer components to an end user who could then combine them with those from other manufacturers to construct a complete reactor system. Hence the project defined standard electrical, fluidic, optical and mechanical interfaces as well as geometric, thermal and technological housing interfaces. While it is possible to buy a number of components which do adhere to this standard, it would not

7 www.epigem.co.uk/products-fluidics.htm – polymer microfluidic kit

8 www.thinxxs.com/development/index_development.html – modular polymer microfluidic kit

9 www.protron-mikrotechnik.de – microfluidic systems from silicon, using MEMs techniques of construction

10 www.lionixbv.nl/microfluidics/mf.html – glass microfluidic and microreactor systems

11 www.mikroglas.com/index_e.html – glass microfluidic systems made using Foturan as photosensitive glass

12 www.micronit.nl/en/about_microfluidics.php – glass microfluidic systems, focused on lab-on-chip applications

13 www.cpc-net.com – metal microreaction systems

14 www.ehrfeld-shop.biz/shop/catalog/index.php – metal microengineering reaction systems

15 www.imm-mainz.de/seiten/en/u_050527115229_2085.php – range of IMM's manufacturing technologies

16 www.microchemtec.de/content.php?pageId=2435&lang=en – description of MicroChemTec approach, list of members and components catalogue

appear to have been widely adopted as a number of companies prefer to offer their own proprietary modular architectures (Ehrfeld/ Mikroglas/FAMOS[17]). One reason for this may be that the requirements for standardisation led to a system with a relatively high dead volume which can be detrimental to overall system performance.

A hybrid approach also exists where systems are constructed which are optimised for a class of reactions rather than a single reaction (IMM, CPC).

IMM's presence in all areas really underlines the key role it has played in the development of microreaction technology.

5.4 Scale-up (numbering up/ scaling out)

Normal chemical process development involves scale-up where chemistry developed in round bottom flasks in a laboratory is taken via pilot plant operation to full production processing. This scale-up is complex due to the big difference in scale resulting in fluid flow and heat transfer process changes which can not be fully predicted. Hence scale-up is an expensive and time-consuming process, with the potential risk of failure due to unforeseen problems.

Pure microreaction offers a new paradigm called either 'numbering up' or 'scaling out', where multiple copies of the laboratory microreactor are taken to the production plant, and simply by running multiple systems in parallel the necessary quantities are produced (ChemTrix). It has been argued that this introduces new complexity due to the number of individual reactors that potentially need independent control and monitoring systems.

A more pragmatic approach has been taken by a number of companies where production devices are produced which are larger in size with a higher throughput, but the internal microstructure is essentially identical to that of the original laboratory microreactor (CPC, Ehrfeld, IMM). It has been argued that despite the change in microreactor this method of scale-up avoids the normal lengthy scale-up process. Currently these larger devices have all been made in metal, either stainless steel or Hastelloy.

5.5 Process chemistry expertise

A number of companies have developed microchemical systems for laboratory-scale use that produce small quantities of chemicals for development. Syrris, a UK-based company, is a leader in this area.

The initial work in microprocess chemical engineering was driven by the ability of the groups involved to construct microchannel systems using the technology with which they were familiar. These groups then interacted with other groups who were able to specify the key features needed to run a particular chemistry in a microreactor. A number of companies were established that were able to make the necessary components but did not offer the application expertise. These companies fell into two categories: companies that were effectively microfluidic foundries who had found another market for their products (LioniX, Mikroglas, Micronit) and companies specifically set up to produce microreaction systems (CPC, Ehrfeld).

This has now changed, with the major players in the microprocess engineering market offering to develop a complete reaction pathway, design a microchemical plant, optimise the process, deliver the complete chemical plant and operations manual for a user-defined chemical requirement.

17 www.microreaction-technology.info – Fraunhofer Alliance's (FAMOS) modular microfluidics system

Ehrfeld has become part of Bayer Technical Services[18], CPC has spun out a new company, Synthacon[19], and LioniX has invested in a joint venture (JV), ChemTrix, with the University of Hull. All these companies now offer a complete 'turnkey' service, but at this time it is not known how extensive the work carried out by these companies has been due to the proprietary nature of their work.

Mikroglas has produced a number of laboratory systems which are self contained with microfluidics, pumps and controls all integrated.

5.6 Advantages of microreaction

5.6.1 Quality of chemical reaction

Processes within microfluidic systems can be designed in such a way that transport processes can be made highly reproducible, resulting in better selectivity, higher yields of the correct products with the correct stereochemistry and better control of reactions.

These benefits are gained by the scale of the microfluidic channels resulting in both shorter and more reproducible times for transport processes. Heat can be introduced and extracted from within a few micrometres of where the reaction is happening. Mixing can be effected by a number of mechanisms to give very precise conditions and hence highly homogeneous conditions over time.

5.6.2 Exothermic reactions

The small scale of the reacting volume means that even if a reaction is highly exothermic, resulting in 'runaway' in normal chemical production systems, at the microreaction scale no such problems exist. The heat can be removed from the system rapidly due to the inherently large surface-to-volume ratio and short distances.

5.6.3 High-pressure reactions

The small scale of operation also facilitates reactions being easily carried out at high pressures with minimal extra engineering due to the low stored energy within the system.

5.6.4 Novel chemistry

The combination of the improved quality of reactions, ability to carry out exothermic reactions and operate routinely at high pressures offers the facility to change the chemistry toolkit being used.

The potential to carry out novel chemistry within microreactors has yet to be fully exploited; however, there are strong indications of the potential. The work of Paul Watts at the University of Hull has pointed towards some of the potential, and Han Gardeniers in the BioChip group at Twente has produced 'open bench' high-pressure laboratory microreactor systems that would normally have required special facilities to operate under these reaction conditions.

5.6.5 Scaling

In the development of any new chemical manufacturing process using classical chemical engineering technology, scale-up is a time consuming and often difficult process, where the laboratory flask chemistry is transferred to steel reactors or continuous large-scale processing. This is due to major differences in mixing, residence times and heat transfer brought about by the difference in physical scale of operation. One of the key benefits of using microreactors is that scale-up issues can be avoided, as scale-up is not necessary.

18 www.research.bayer.com/medien/pages/3985/microreaction.pdf – chemical plant in a briefcase

19 www.synthacon.biz/index.php?menuSel=1 – 'from milligram to ton quantities within the same production environment'

Ideally, the microreaction is developed and optimised in a specific microreactor in the laboratory, experimental quantities of chemicals are produced, tested and qualified, and then pilot plant scale production is carried out by scaling out or numbering up the system. Scaling out or numbering up involves the operation of multiple microreactors in parallel with no difference in the microreactor geometry, flow conditions, residence times or heat transfer conditions from the laboratory microreactor, as a large number of identical microreactors are being used to get the increased output instead of one large one. Production operation is then similar, but with even more microreactors run in parallel.

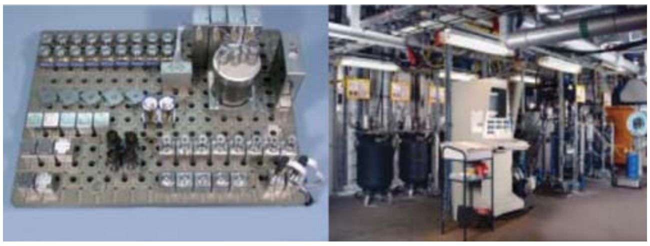

Exhibit 5.1 Ehrfeld modular microreaction toolbox and pilot/production plant system

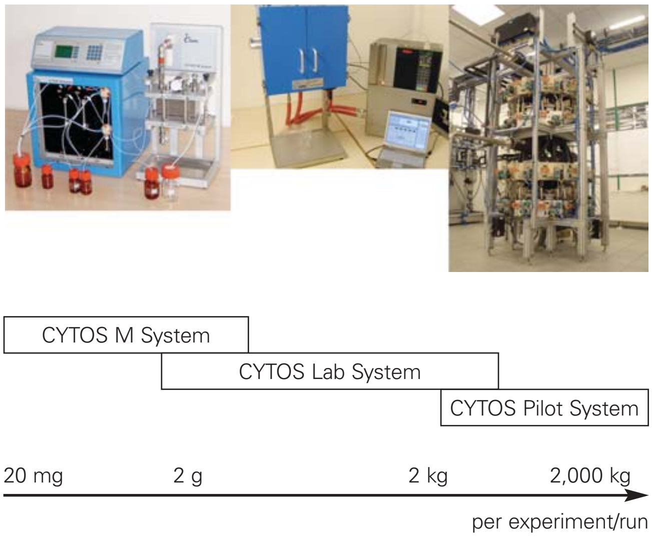

Exhibit 5.2 CPC's CYTOS M (micro), L (lab) and P (pilot) systems

Scaling has also been achieved by construction of new microreactors of a larger scale but with the same internal microchannel dimensions – nominally once again overcoming scale-up issues but with far higher throughput than achieved with the original laboratory-scale devices.

CPC offers a range of different system configurations to deal with scale-up (Exhibit 5.2).

5.6.6 Safety

Microfluidic processes are inherently safer than macrofluidic processes, purely due to the smaller quantities of materials present within the system at any one time. In addition, as small quantities of explosive materials do less damage than larger quantities, toxic materials are less hazardous in smaller quantities and the energy stored in pressurised systems scales with the size of the pressure vessel meaning failure of a small system results in a minuscule energy release when that vessel is only micrometres in cross section.

IMM has developed a parallel microreactor plant for the manufacture of nitroglycerine for pharmaceutical application, which is operating in China.[20] Each tablet only requires a small amount of nitroglycerine, so the continuous small-scale operation of a microreactor was ideal for this application and entirely removed the need to handle large quantities of explosive nitroglycerine.

However, it should be borne in mind that this does not overcome issues with storage of potentially large quantities of reactants or products due to economies of scale in supply or shipping.

The nitroglycerine production story was also reported as a dangerous trend in the proliferation of high technology that could be used by terrorists.[21]

20 www.imm-mainz.de/upload/dateien/PR%202005-11-09e.pdf – nitroglycerine production in China

21 http://news.nationalgeographic.com/news/2005/08/0811_050811_terrorism.html – *Pocket-size reactors may raise chemical terrorism risk*, National Geographic News, 11 August 2005

5.7 Summary

Microstructured or near microstructured flows have long been key to chemical process engineering and will continue to be so, in heterogeneous catalysis, filtration, heat exchangers etc. A number of companies around the world, but particularly in the Netherlands and Germany, are now offering a different vision where a large range of processes can be most effectively carried out in micro flows.

The companies offering microprocess engineering have now reached a size where they are able to offer integrated services to the chemical industry. There is now a competitive supplier situation, with supplier organisation and some attempts at standardisation. However, it is not obvious that the customers are as well developed as the suppliers.

The next five years will be a critical proving time for microchemical manufacture. Either microprocess engineering will have become almost invisible as a standard tool within the chemical engineer's toolkit, brought into use for certain processes at certain scales, or microreaction will have been reconfined to the laboratory with the current production examples having been seen as unique opportunities.

5.8 Future prospects

Currently, microreaction technology is still in technology push mode, whilst collaborative projects such as those detailed below aim to produce more market pull. All these projects combine technology producers with chemical producers and as such aim to bridge the technology gap between them.

NEDO in Japan carried out a three-year strategic project during 2002-2005 aimed at producing practical application of microchemical process technologies in 2005.[22] The project built and demonstrated a microreactor system to carry out organometallic chemistries.

The IMPULSE (Integrated Multiscale Process Units with Locally Structured Elements) project is a four-year, 20 company, EU collaborative project which started in 2005.[23] IMM is one of the partners. The background to the IMPULSE project is that the adoption of microstructured components in chemical applications has been almost entirely at the laboratory scale; however, the benefits for the EU are far greater if the technologies are adopted widely in production. IMPULSE is aimed at addressing the factors which are stopping technology push being turned into market pull and hence mass uptake. IMPULSE states that these factors are that 'no reliable design methodologies, techno-economic evaluation tools or decision criteria for this purpose exist today'. The goals of the IMPULSE project are the following:

- Proof of principle for IMPULSE approaches in several supply-chain sectors
- Validated business cases for selected applications
- 'Teachable' generic design methodology and optimisation techniques
- Evaluation of the benefits of multiscale design to eco-efficiency, safety and sustainability in chemicals production and use

To do this the IMPULSE consortium has a set of process-technology objectives which will determine the choice of the chemical processes for investigation:

22 www.nedo.go.jp/english/activities/1_sangyo/3/p02016e.html – Production, Analysis and Measurement System for Microchemical Technology Project of the New Energy and Industrial Technology Development Organisation (NEDO), Japan

23 www.impulse-project.net – Integrated Multiscale Process Units with Locally Structured Elements.

- Replacement of batch processes by steady-state continuous flow systems
- Modular processes for variable throughput and mass customisation
- Integration/connection of innovative equipment for retrofit into existing plant
- Miniaturisation of process systems for distributed/delocalised production

A more focused EU project aimed at proving the benefits of microreaction technology, specifically nitration reactions, is NEPUMUC (New Eco-efficient Industrial Process Using Microstructured Unit Components).[24] This is an eight-partner pan-European project which will integrate sensors, actuators and reactors to produce a complete nitration system.

The educational gap has also been noted, where microsystems courses teach how to construct systems that could be used as microreactors, but traditional chemistry/ chemical engineering courses do not teach the use of such systems. Both the Netherlands and Germany are funding increases in the use of microsystems throughout technical education, some of which is directed at the use of microreaction technologies.

24 www.nepumuc.info/index.htm – New Eco-efficient Industrial Process Using Microstructured Unit Components – 'Safe and environmental friendly production of sensitive compounds ensured by process intensification' – EU funded project, started 2005

6 MICROFLUIDICS IN THE PHARMACEUTICAL SECTOR

To put the opportunities available into perspective it is perhaps best to look at the various stages in the life cycle of a commercial drug. For this discussion they can be divided as follows:

- **Discovery** – compound generation and screening
- **Scale-up** – increasing amounts of material available
- **Quality control** – during manufacture
- **Delivery and clinical testing** – for introducing the drug to the body and for measuring the sensitivity and effectiveness of a particular compound

In all stages of the life cycle of a commercial drug, microfluidic technology could have a significant impact on the time to market, quality of outcomes and cost. Each stage is now considered in turn.

6.1 Discovery

Using the inherent properties of microfluidic systems, it is possible to synthesise compounds dynamically using flow chemistry systems. In particular, small organic molecules can be generated using an automatic multistep reaction system. The potential is that the method will begin to obviate the need for compound libararies, which are by nature complicated and expensive. In order for this to happen, large pharmaceutical companies will need to substantially change their approach to valuing their discovery systems from counting the number of compounds in libraries to understanding the flexibility of their automated chemistry systems and how inventive their medicinal chemists are.

The systems of Ehrfeld and CPC/Synthacon went some way to satisfying the requirements of being able to synthesise very simple compounds 'on the fly' but lacked a sophisticated mechanism for performing multistage synthesis, needed for small-molecule generation. In most cases a continuous microreactor based system needs to be flexible and perform dozens of sequential steps. From the evidence presented, this surpasses the capability of the current product offerings.

Another issue that needs to be addressed is that of quality assurance (QA). In particular, if the chemistry is done in stainless steel channels then characterising the reaction is difficult. In contrast, Mikroglas and Micronit make transparent and electrically insulating glass chips allowing electrical and optical probing of the reactions taking place. This ability would provide an extra level of assurance to the chemist that the reactions are proceeding as expected. In the UK, Syrris Ltd has developed systems dedicated to compound formulation based on glass chips, which from the above appears to be the best strategy.

A central issue which is intrinsic to microfluidic-based systems is the limited production capacity of a single channel. Presently this is probably too small for all but the most frugal of plate-based assay systems. To some extent, until this deadlock is broken it could well be the limiting factor in the rollout of such technology as a replacement for conventional sample-in-a-bottle compound libraries.

6.2 Scale-up

Once an interesting compound is discovered, increasing amounts are needed during the various phases of clinical trials, maturing to a capability to produce the quantity of product required by the market. It will continue to be the case that most compounds fail to become drugs released onto the market. If this happens, any investment in plant to make a failed compound further heightens the ultimate cost. Unfortunately, with current batch processing techniques a perfect synchronisation of investment in new plant and successful passage through clinical trials is difficult. With the flexibility and inherently modular nature of microfluidic-based systems it is possible to grow the production system from a single continuous line to multiple lines as the demand for compounds increases. Using the fine-grained nature of microfluidic production systems it is possible to match the output capacity to the compound requirements in almost real time.

As scale-up can be achieved by forming parallel arrays of smaller pretested production units then there is hope that the US Food and Drug Administration (FDA) approval process can ultimately be simplified. However, it is open to question whether using an array of small production units does not raise other questions in terms of monitoring and control of the process. In particular, each channel contributing to the end product would have to be monitored. If a significant number of channels were to be used, ie many hundreds, then this could result in an unacceptable measurement and control overhead being introduced. Inevitably this would reduce the overall advantage of such an approach.

From the companies and organisations profiled, there were a number of examples of how this type of scale-up can occur given the caveats expressed above. One of the most pertinent examples was from IMM that is developing a pharmaceutical nitroglycerine production plant, now operating in China.[25] Here the parallel microreactor concept has been developed into a monolithic unit where many parallel reaction channels are fabricated into the volume of a plate device (Exhibit 6.1).

Exhibit 6.1 *Nitroglycerine production plant (>100 l/h solution) using microstructured reactors set in operation in Xi´an, China (courtesy IMM, Germany)*

The advantages of microfluidics in this example are safety and yield. Because the microreactor has a high surface-to-volume

25 www.imm-mainz.de/upload/dateien/PR%202005-11-09e.pdf

ratio, heat can be pumped into an endothermic reaction or, conversely, easily taken out if it is exothermic. This allows the reaction temperature to be optimally controlled within strict predetermined limits. Such control has other added benefits in this case as the product is highly explosive. The ability to exact fine control of the temperature means that a microfluidic-based plant is always kept within strict operational limits, increasing safety.

When this ability is coupled with the fast diffusion-mediated mixing and the almost intrinsic ability to pressurise the channel to many bars, many reactions could be speeded up significantly. If all these factors are taken together, the time to reach the reaction equilibrium can be shortened, sometimes significantly, which has the effect of increasing the purity of the end product compared to standard flask-type reactors. Overall this leads to a significant saving in time, materials and energy. This should be looked at in the context of the performance of the current production methods. In particular, there have been studies which show that presently, in the average pharmaceutical production process, for every kilo of finished product, up to fifty kilos of waste are formed, which are often hazardous and as a result expensive to dispose of.[26, 27]

There are other, more specialised areas of the pharmaceutical industry that could benefit disproportionately from this technology. Orphan drugs are loosely defined as those that fight rare diseases and as a consequence are only needed in small quantities. An orphan drug might only require 100 kg/y, in which case the microfluidic system used to develop the compound could also, if run continuously, produce enough finished chemical for the end market. This has the possibility of revolutionising the field, where at present compounds with a significant potential benefit often languish in the laboratory as the cost of the scale-up is not compensated for by the size of the end market.

Overall the use of microfluidic-based production systems offers the virtuous combination of cost reduction, increased yield and improved safety.

6.3 Quality control

Despite the high capital cost and the high gross margin on drugs, batch production is still dominant in the pharmaceutical industry. This leads to a relatively slow and expensive ramp-up process and high cost of failure if there is a quality control (QC) problem with a particular batch as very often the whole batch is proved worthless.

Microfluidics could contribute significantly to alleviating these shortcomings. In particular, microfluidic-based measurement systems could monitor batch quality throughout the manufacturing process. To obtain a valid reading only minute samples are needed, and being able to perform a wide range of chemical reactions quickly will help to stem any problems that might end up spoiling the whole batch, particularly in the more complex, multistage reactions. In the longer term, if continuous production microfluidic reactors replace batch systems, diagnostic elements could be included in situ as part of the reactor.

6.4 Delivery and clinical testing

When a drug compound enters the body it can undergo a number of chemical reactions, either in the process of its therapeutic action, or ones which cause unwanted side effects.

The clinical effectiveness of a compound and any potential side effects need to be

26 http://nano.cancer.gov/news_center/monthly_feature_2005_jun.pdf

27 www.rsc.org/chemistryworld/Issues/2004/January/bountiful.asp

thoroughly characterised in the clinical trials before release. After a drug is launched into the market, testing certain characteristics of the recipient can augment its effectiveness. This could also help to detect whether a drug is likely to cause side effects in a particular candidate. Furthermore, although at first sight it seems elementary, dose monitoring of blood serum levels usually ensures that the course of treatment works at optimal effectiveness.

In all these aspects, microfluidics could, and probably will, make significant contributions. Even before clinical trials begin, techniques such as single-cell patch clamping will help in ascertaining a detailed understanding of the mechanism of action and any associated toxicity of a compound. In this respect the ability of ThinXXS to produce small featured silicon microfluidic structures is being utilised by Sophion Bioscience A/S in Denmark to make a state-of-the-art single-cell patch clamping device (Exhibit 6.2).

Exhibit 6.2 *An integrated microfluidic device for the ion channel screening of living cells co-developed and manufactured by ThinXXS Microtechnology for Sophion Bioscience A/S (courtesy Sophion Bioscience A/S)*

In first-stage clinical trials, the ability to rapidly test potential adverse side effects before the patient has been injected will alleviate a number of risk factors that could result in patient harm. These could be simple chemical tests or more sophisticated genomic-based tests that look for genetic markers in the patient indicating positive or adverse activity of the compound. As the compound progresses to commercial release the same tests could be used in frontline care to optimise who gets the drug and who doesn't.

Another issue faced in frontline care is that of patients not taking the drugs in the prescribed manner, normally termed as noncompliance. In this case either the blood serum levels of the compound do not remain high enough or they vary widely as patients try to 'catch up' if they have missed a dose. It has recently been shown that 25% of patients do not take a sufficient amount of the drugs they have been prescribed to gain any medical benefit. The benefit of using microfluidics in solving this is exemplified by the work of the Bios Lab-on-a-Chip Group at the University of Twente. Here the group has developed a rapid test for measuring blood levels of lithium in patients diagnosed with bipolar disorder. Lithium helps to stabilise the condition, but if the levels drop too low through noncompliance or other issues, a relapse of the condition can occur.

6.5 Summary and conclusions

Due to the nature of its product, the pharmaceutical industry must be extremely safety conscious and conservative in its approach to all phases of development and manufacture. At the moment the industry and its investors strongly perceive there is a lack of new drugs being discovered. Accordingly, despite microfluidics offering significant benefits at all stages of the process, it will be adopted initially in the primary stages of development, in the so-called discovery phase. Initially it will concentrate on areas such as real time generation of compounds for screening systems and as a diagnostic tool in early stage drug trials to screen out various genetic factors that may influence the outcome of human trials.

Looking at the evidence, it appears that microfluidics is not being used for the manufacture of mainstream medicines at the moment, although it is being used for certain specialised compounds (nitroglycerine) and precursors. The mission encountered a number of groups who had or were developing technology with the goal of creating mainstream manufacturing systems, but the hurdles to be overcome are many and varied and will demand an interdisciplinary approach. Crucially it needs the buy-in of the pharmaceutical companies themselves and although the mission saw evidence that this is beginning to happen in Germany, with Bayer's acquisition of Ehrfeld, it did not see a wholesale embrace of the technology by the sector as a technology for manufacturing. Despite this, the potential contribution of microfluidics to the manufacturing process is significant and as the pharmaceutical industry is often fairly coy about its means of production, many aspects will probably be shrouded in confidentiality at this time.

In the USA the FDA has begun a long-term programme for increasing the effectiveness of medicines whilst reducing their often very high costs.[28] FDA has identified that microfluidics could play a key role in this programme.

Due to the dominance of the pharmaceutical industry in the UK, creating such a coordinated approach could reap rich dividends for the UK high-tech economy as a whole. In part this could be done by leveraging off the products and services available worldwide.

28 www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

7 MICROFLUIDICS IN THE HOUSEHOLD, PERSONAL CARE AND FOOD SECTORS

Various advances in microfluidics technology were observed during this mission. The advances that could benefit the food and home and personal care (HPC) businesses are summarised as the following.

7.1 Increased availability of compact, low-cost and low power consumption microfluidic components

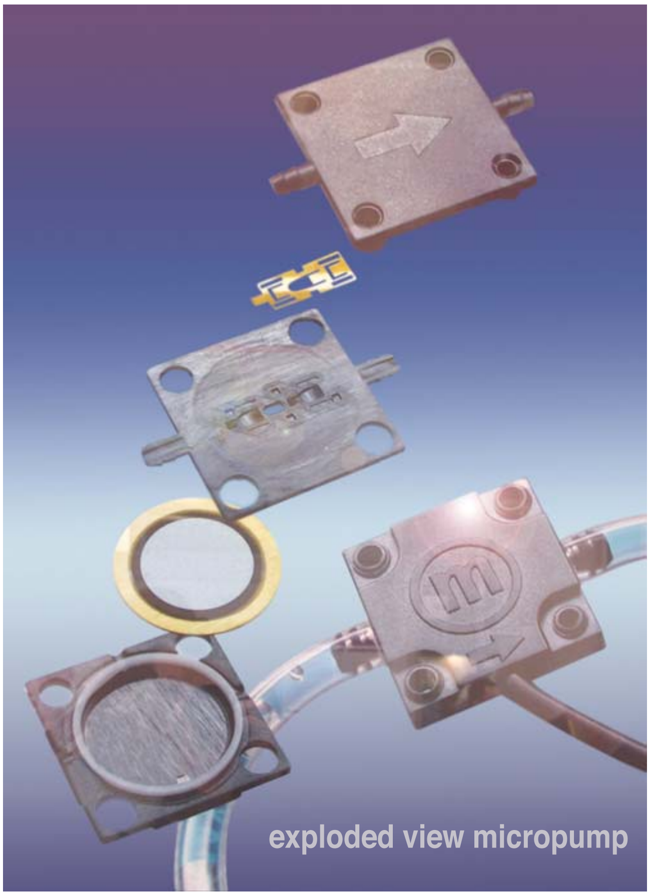

Exhibit 7.1 Micropump manufactured by Bartels Mikrotechnik GmbH

One example is the micropump developed by Bartels Mikrotechnik GmbH, overall size 14 x 14 x 3.5 mm and weight 0.8 g, which can be operated for up to 72 hours on an AA battery and can deliver 500 mbar pressure. According to Bartels, the cost of this pump could be reduced to <€1/unit (<£0.70/unit) for large-volume production. This pump has been developed in collaboration with a consumer goods company for pumping fluids in a commercial perfume delivery device.

Such components are applicable for the novel packaging of foods and HPC products. In fact, packaging of this kind can already be found on the market. For example, in the SK-II air touch foundation, launched by Procter & Gamble (P&G), a nozzle-based ionisation technique has been integrated into the packaging. According to P&G, a perfect veil of luxurious monolayer coverage of foundation droplet can be delivered through such a packaging, and SK-II is sold as a premium product in Japan. Such embedded microfluidic devices, even invisible to the consumers, can greatly improve usage experiences of the products.

Innovative packaging of this kind could be further stimulated by the availability of an even wider range of functional and reliable microfluidic components.

Exhibit 7.2 P&G's SK-II air touch foundation

7.2 Self-diagnosing and self-monitoring devices

According to the companies visited in this mission, such as ThinXXS, the range of microfluidic-based self-diagnosing and self-monitoring devices is expanding. Currently, most of these devices are developed for people with health problems, particularly chronic problems such as stress and diabetes, which demand long-term self-management.

However, as the concept of preventive health becomes more widespread, such devices could be accepted by the majority of the population as the tools to help them remain healthy, include consuming healthier foods and HPC products. As the cost of these devices decreases, thanks to innovation and economies of scale, the barrier of introducing such applications is becoming progressively smaller.

7.3 Highly integrated microanalytical systems for kinetic studies, process control and product development

Such systems have been widely used by the pharmaceutical and chemical industries, as well as life science research, for over a decade. Still, novel systems are being developed by research institutes and SMEs which aim to provide further improved functionalities and serve a wider range of applications. Examples include integrated systems containing multiple microfluidic and optic components developed by LioniX, and the micro NMR being developed in the MESA+ Institute.

These systems, along with the methodologies developed upon them, are highly applicable to the food and HPC industries, for developing, screening, and modifying novel ingredients, such as ingredients used for functional foods and appealing cosmetics.

7.4 Advance of module-based microfluidic systems

Module-based microfluidic systems are comprised of various blocks; each one performs a basic process operation, such as mixing, dispersing or heat transferring. These modules can be freely combined by means of clamping devices on top of a base plate to form completed systems, therefore can be tailored towards particular applications by the end users. Such systems have been developed in Germany since 2000 and the technical advance in this area is highly evident.

A few SMEs that are pushing this field have been visited during this trip; they are Ehrfeld Mikrotechnik, CPC, Synthacon and Mikroglas. According to these SMEs, the number of pharmaceutical and chemical companies in Germany that are testing and adopting such systems has increased rapidly in the last couple of years.

These are encouraging developments. However, the applicability of such systems to foods and HPC products is still limited for at least three reasons:

- **The main application** of such systems is continuous chemical synthesis. There are considerable differences between chemical synthesis processes and material structuring processes such as encapsulation and emulsification, which are the more commonly used processes for food and HPC products. Furthermore, the fluidic materials involved in food and HPC products are often of high viscosity. This presents further challenges to the microfluidic systems, in the sense of controlling pressure and flow distribution, as well as managing clogging and surface contamination-related fouling.

- **The economic return** of such systems is a debatable issue. For example, CPC recommends that its system is most suitable for making products with a market value >€5,000/kg (>£3,400/kg) due to the considerable installation and maintenance cost. However, Ehrfeld claims that its system could be economical for making products with a value as low as a few €/kg. Such a difference is not obviously explainable; therefore further investigation and verification would be valuable.

- **The experience** of running such systems for extended time periods is still very limited; therefore information on longer term reliability and maintenance costs is sparse. This will be perceived as a high risk factor by the relatively low cost-based food and HPC industries.

Nonetheless, there is great value in the capability of manipulating system designs to meet the reaction requirements, and the knowledge on manifold design and flow distribution management which can be learned from modular microfluidic systems.

7.5 Novel membrane-based material processing techniques

Using membrane-based techniques for material processing is not new. However, a couple of SMEs, such as Aquamarijn and Nanomi, and the Membrane Technology Group in the MESA+ Institute, consider that their membranes have more to offer than the conventional ones. The common features of these membranes are massively parallel pores with reduced pore size and improved pore distribution, all enabled by microfabrication techniques. Applications that are relevant to foods and HPC products are:

- Aerosol generation, as proved by its adaptation into drug inhalers
- Filtration, as demonstrated by its usage for large-volume filtration of beers
- Emulsification, which is still mainly in the R&D stage

7.6 Summary

The potential applications of microfluidic devices for foods and HPC products could be broad. This field is currently lagging behind fine chemicals and pharmaceuticals. The realisation of such potential depends on the balance of cost, reliability, life span and the throughput of microfluidic devices.

8 MECHANISMS FOR STIMULATING THE UPTAKE OF MICROFLUIDICS BY INDUSTRY IN THE NETHERLANDS AND GERMANY

8.1 Introduction

The objective of stimulating investment in new industries, company formation, products, and the restructuring of large companies to meet the challenges and opportunities of globalisation, is an issue on all national and regional agendas. Microfluidics is an enabling technology that has for a while created new industry (eg ink-jet printing), is now enabling the creation of new mainstream products (eg point-of-use diagnostics) and is expected to create many more (eg precision synthesis of chemicals). Processes aimed at the effective utilisation of the science and educational base, in creating new technologies, their understanding and uptake were presented to the mission team. This also extended to the range of processes, and current initiatives to extend and improve them, that have been implemented over the last 10-15 years, particularly in the Netherlands. The team were exposed to the measures being taking within the educational system in the Netherlands and the associated roles of the universities and technology institutes (TNO in the Netherlands and, until recently privatised, IMM in Germany), together with case histories of several beneficiary companies.

8.2 Overview of the Netherlands

In the last 10-15 years the Netherlands has maintained a steady investment in microelectronics, ICT, microsystems, speciality chemicals and polymers. Resources have been focused in areas where the country has competitive advantage and strategic need. Investment in the integration and expansion of these technologies is being progressed, in part, under the promotion of nanotechnology. The technical universities (TUs) have held a distinguished role in the innovation process which is 'managed' and is being reinforced by government and industry led actions. In the university sector, five centres of excellence, with 30 new professorial positions, are to be created in nanotechnology, ICT, sustainable energy, fluid and soil mechanics with €50 million (~£34 million) of government investment. Applications where microfluidic R&D is relevant to the Dutch economy include consumer electronics, healthcare products, process intensification in food manufacture, and sensors for quality control in greenhouse agriculture.

The Netherlands has a well integrated national infrastructure for innovation with engagement of the universities, technology transfer and industry support institutions (eg TNO, MESA+) and industry (eg Philips, Unilever). Government support and stimulation measures in the field of MNT were apparent at all levels with emphasis on ensuring the science and technology (S&T) base was at the high level required to sustain both (1) the global competitiveness of key large companies, such as Philips and Unilever, and (2) the generation and support of an entrepreneurial environment in which start-up and spin-out companies are created from both universities and large companies. Managed networking, reconfiguration and support initiatives are well-funded, mature and operational at all levels as evidenced by the examples below.

8.2.1 Networking

The University of Delft is a partner in a global bionanotechnology R&D programme with leading academic groups in the USA (Harvard, MIT) and Japan (Tokyo) and where microfluidics is employed as an enabling tool.

In 2007 the three TUs (Twente, Delft, Eindhoven) are to be formed as a federation. This will (a) build, and further focus activity, on business through new company and product creation, and (b) further support the existing good success rate in spin-out company creation and incubation through facilities access and research programmes. Within these universities are (1) the MESA+ Institute for Nanotechnology at Twente; (2) the Kavli Institute of Nanoscience at Delft University *(coordinating the MicroNed programme – see below)*; and (3) specialist micro- and nanoengineering groups at Eindhoven University.

Additional to the government subsidised programmes already referred to there is an established National Microfluidics Network led by Richard Schasfoort at Twente University. This is an inclusive supply chain network which acts to enable a coherent visibility of technology providers to end users. Some companies interviewed found this network useful whilst other more established microfluidics supplier companies were less enthusiastic.

8.2.2 Reconfiguration

The Holst Centre represents an innovative and international collaboration on ‘foil’ or ‘panel’ based microsystems between the Netherlands (TNO) and Belgium (IMEC) bringing together technology platforms *(including microfluidics)* in both silicon and polymer electronics.

The restructuring of Philips has (1) created spin-out companies with expertise in both electrowetting (surface microfluidics) and polymer ‘microfluidic displays’, (2) provided open-access MNT facilities at the Eindhoven High Technology Campus, and (3) invested in new R&D towards applications in healthcare. Unilever may also restructure to stimulate more innovation.

8.2.3 Support

Regional initiatives continue to be taken including the use of European Regional Development Funds (ERDF) – East Netherlands.

A jointly funded €30 million (~£21 million) micronanostructuring and characterisation facility is under construction at TU Delft as a collaboration with TNO. This will provide a state-of-the-art facility in which microfluidic (and other) devices, components and systems may be developed by both academe and industry.

TNO has a presence on the management boards at the technical universities of Delft and Eindhoven to guide, facilitate and support the wider industrial use of the science base. TNO has facilities and objectives of its own including inward investment.

Young and old entrepreneurs are motivated and provided with the training and facilities needed to start up new companies, and their achievements are recognised and openly celebrated by government ministers (eg Micronit Microfluidics BV).

The University of Twente which hosts the MESA+ Institute has a uniquely supportive environment for the creation of new enterprises from academic research. An entrepreneurial attitude is instilled in both academic staff and PhD graduates alike by two distinctive factors:

- PhD graduates receive a salary (not a stipend as is usual in the UK), undertake more teaching and supervisory responsibilities, and also must consider the commercial implications of their research and opportunities for a spin-out or start-up within their four-year work-study period

- Academic staff hold devolved responsibility to raise the main part of their own research funds which includes all infrastructure and facilities provision; despite this, business angel and venture capital (VC) investment appears to be in short supply and some of the Dutch microfluidics companies visited were backed by British financiers

Long-term commitment and continuity of regional support spanning over 20 years in the field of lab-on-chip technology is evident, particularly at Twente University which hosted the first international conference on micro Total Analysis Systems (µTAS) in 1994.

A summary of recent stimulation measures by the Netherlands Government was presented to the mission team by Leo Zonneveld, Science Attaché at the British Embassy in Den Haag. In The Netherlands a convergence approach to nanotechnology is taken, integrating the molecular and nanoscale within microelectronics, microsystems and macro-scale systems to enable new business opportunities. Microfluidics (and indeed millimetre-scale fluidics) is therefore treated as an integral part of the nanotechnology programme and thus an accurate figure on support for microfluidics cannot be easily determined.
Nanotechnology, genomics and ICT are the three national priorities which together received €800 million (~£550 million) in grant aid under ICES/KIS following a 1999 review of competitiveness in key technologies.
€147 million (~£101 million) grant aid specifically for nanotechnology (€130 million (~£90 million) in 2004 and €17 million (~£12 million) in 2006) comprises three delivery platforms:

- **NanoNed** – €95 million (~£66 million) – nanotechnology R&D and infrastructure largely at MESA+ and Kavli
- **BioMaDe** – €7 million (~£5 million) – biomaterials and biosensor R&D at TU Enschede
- **MicroNed** – €23 million (~£16 million) – microsystems awareness and R&D activities directed from TU Delft

NanoNed, the largest platform, is executed by a consortium of seven universities with TNO and Philips with an industrially enhanced value totalling €235 million (~£162 million) during 2005-9. NanoNed comprises 11 large independent programmes of which 'nanofluidics' (incorporating microfluidics) is one. In addition, the programme also incorporates an €85 million (~£59 million) laboratory infrastructure enhancement programme.

8.2.4 Company-university relations

The British Embassy assisted meetings between the mission team and leaders of the initiatives referred to above as reported in sections elsewhere in this report.
Testimonials from the management of three start-up microfluidics companies clustered around the Twente University MESA+ Institute in Enschede were taken. These example companies included C2V, LioniX and

Micronit, all of which have made good use of the measures made available by government to assist the creation and growth of their companies.

Significantly, the survival rate of this company cluster is ~75% (unusually high for start-ups) and is attributed, in part, to the close working relationship with the MESA+ micronano-fabrication clean-room facility which the companies have direct, hands on, open access to. This key enabling action allows engineers from the companies to use the clean-room facility on a swipe card, account charging basis. Extremely close proximity of the companies' offices adjacent to, and contiguous with, the offices of MESA+ academic staff enables intimate cooperation and intermixing between staff.

The MESA+ Institute has enabled 33 spin-out enterprises (several in microfluidics) during the last 15 years. This success rate is attributed also in part to the devolved duty to scout and convert to a business two of the most promising opportunities per year, two years earlier than would otherwise occur. Significantly, a centralised technology transfer office for the university was long recognised as essentially ineffectual.

8.3 Overview of Germany

The mission visited IMM and some of its associated spin-out and start-up companies. IMM is one the oldest experiments in technology transfer in the development of European MNT and the use of government stimulation measures to create new technology and markets. Over a 15-year period IMM has evolved its mission from leading edge, fast-track research to applied research and dissemination through spin-outs. IMM and its associated spin-out companies arguably represent the leading cluster of microfluidics companies in Germany to date and were the focus for the mission activities in Germany.

8.3.1 Support for IMM

IMM was founded as a non-profit making research institute (company) using public money from the region and other public sources. This involved the transfer of its founder, Professor Wolfgang Ehrfeld, and associated technology from FZK to lead the Institute in Mainz. At around this time Microparts, a polymer component micromoulding company, was also established as a spin-out company from FZK. Microparts was later acquired by one of its customers, Boehringer Ingelheim, to produce drug delivery nebulisers. Over a 15-year period IMM has evolved from being a wholly public funded non-profit making company to being a limited company or GmbH and has progressively reduced its dependence on public funds to ~60% in 2006.

With significant foresight the original purpose of IMM was to encourage the adoption of MST in the chemicals, polymers, manufacturing and processing industries whilst simultaneously minimising risk. The implementation of this plan involved machinery suppliers of strategic importance to the German economy in order to maintain the industrial competitiveness. IMM evolved from a period of R&D leadership to technology transfer and exploitation by industry. Of particular note is the role of the Ehrfeld family in leading the first two phases. Innovation (success in the marketplace) is being achieved by application development by IMM and its spin-out companies and market exploitation by companies adopting the technology.

8.3.2 IMM reconfiguration

The positioning of IMM continues to change as a result of personnel and equipment transfer to spin-out companies. The migrations of most significance were the creation of the companies CPC, Ehrfeld and ThinXXS which were all visited by the mission. Whilst IMM is a company it still receives a certain level of state subsidy through research and training grants. IMM continues to operate in similar markets as its spin-out companies with activities in metal microreactor development and polymer micromoulding. This is considered by some to distort the marketplace against the favour of its spin-outs. In the case of metal microreactors, CPC and Ehrfeld relocated. Polymer micromoulding capital assets were transferred to a new IMM-enabled technical facility at Zweibrücken. The principal motivation for creating this new facility was to regenerate the economy of the Zweibrücken region after military operations had diminished there. ThinXXS is essentially a polymer microfluidics spin-out that currently rents office and microfabrication facility space but also has direct open access to the new Zweibrücken microfabrication facilities.

Mikroglas, also a spin-out of IMM, visited the mission team in London. This helped formulate a more substantive picture of the process by which a microfluidics industry has been created in Germany. Each company occupies its distinctive niche space in the market whilst there is some inevitable business overlap. Nevertheless, this has created a supply chain to larger companies in both the medical products and chemicals industries and where inter-company trading and acquisitions were evident. Although each IMM spin-out has a distinct business model there is an internal competitive market between the parent and offspring, particularly now the former has become a GmbH.

8.3.3 A wider view of microfluidics in Germany

The Federal Ministry of Education and Research (BMBF) is the main funding vehicle for microsystems technology in Germany and has allocated over €600 million (~£410 million) to microsystems engineering since 1990.

According to the Association of German Engineers (VDI) study *Schlüsseltechnologien 2010*, the annual turnover (2003) of German industry in selling MEMS components was €4.2 billion (~£2.9 billion), whilst systems sales accounted for €277 billion (~£191 billion). An estimated 680,000 jobs depend on MEMS, with 49,000 directly in the production of MEMS components. The value creation landscape is dominated by SMEs but Germany's large companies, particularly in the chemical, pharmaceutical, electronics and automotive sectors, provide a route to market – Merck, Aventis, Siemens, Bosch, Degussa, BASF, Bayer, Boehringer Ingelheim to name just a few.

The current Microsystems Framework Programme 'Mikrosystemtechnik 2004-2009', with a budget of some €260 million (~£180 million), is the fourth consecutive five-year funding programme. The first three programmes involved 349 collaborative projects with total funding (including industrial contribution) of over €1 million (£690,000), and involving 800 organisations of which 80% were SMEs. It is not known what proportion of this funding has gone into microfluidics and microreaction technologies; however, it is substantial – for example, BMBF contributed €15 million (~£10 million) over three years to 2004 for the development of a microreaction technology supply chain. Exhibit 8.1 is a short history of microfluidics technology indicating some of the progress that has been made in Germany.

The current funding programme is set within the framework of four themes:

- **Life science** – healthcare and diagnosis, personalised therapy, microsurgery, intelligent implants, food/nutrition
- **Mobility** – self-generating energy systems, eg via radio frequency identification (RFID); miniaturised energy systems, eg via micro fuel cells

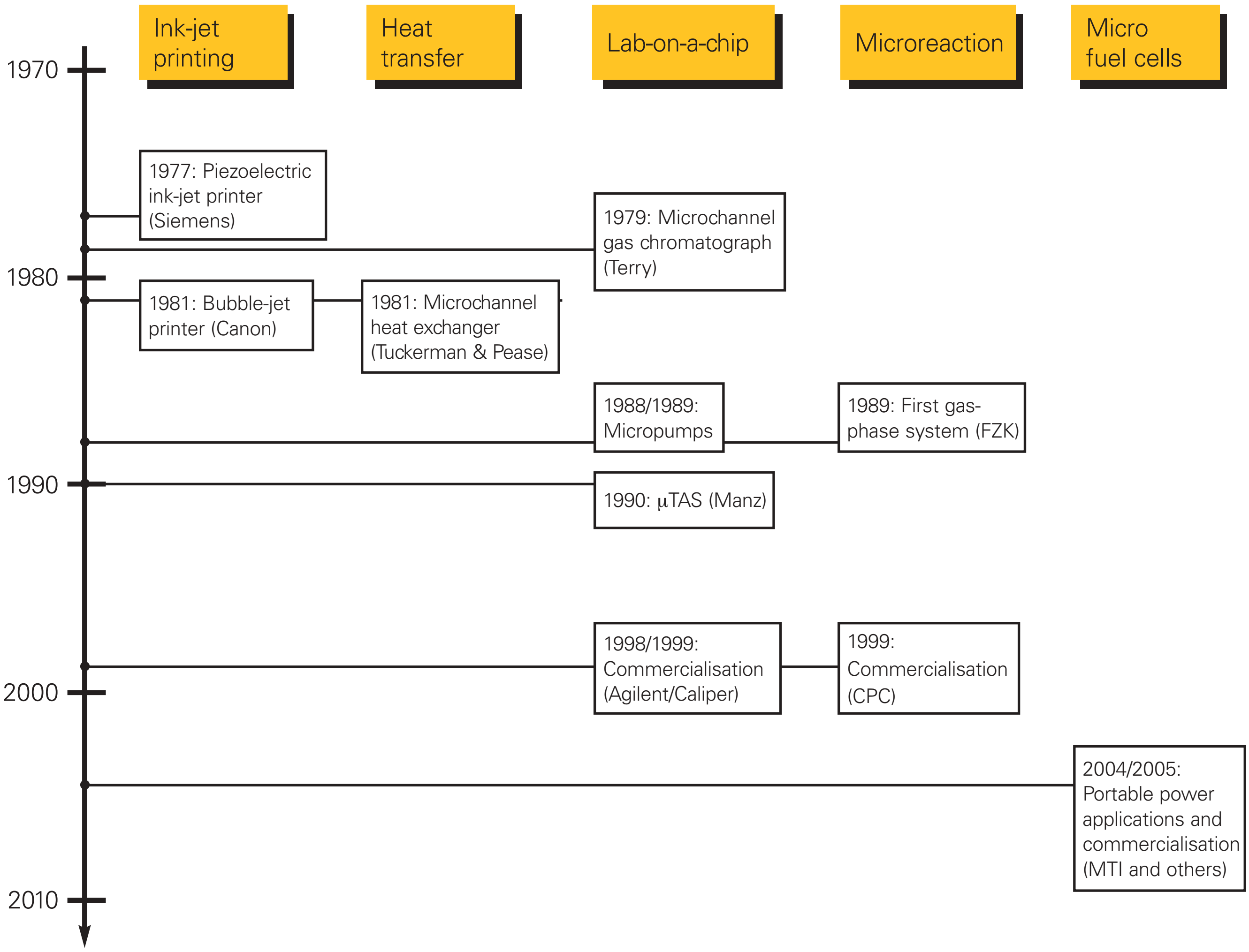

Exhibit 8.1 Microfluidics development

- **Industrial processes** – 'new chemistry', automation, robotics
- **Systems integration** – intelligent systems involving macro-, micro- and nano-scale integration

The programme covers collaborative R&D, infrastructure, information/communication activities, with a strong focus on microprocess engineering, particularly safe synthesis in turnkey microchemical and biochemical processes, microfluidic analysis and the integration of sensing in microprocess technologies. The emphasis is close to market, ie on the development of industrial manufacturing processes, and specifically on the removal of identified barriers such as:

- Shortage of peripheral components, particularly for process control
- Standardisation and modularisation of complex systems
- Improving knowledge on stability and reliability
- Establishing complete processes that can allow economic impacts to be properly assessed
- Training and educational needs

An introduction to the aims of the current programme can be found at www.bmbf.de/pub/microsystems.pdf

Funding has included some major activities such as Projekt Mikrosystemtechnik at FZK, with a current annual budget of €34 million

(~£23 million), focused on industrial applications of microprocess engineering, microsensor systems, microfluidics and micro-optics, with healthcare applications being dominant. Longer-term work on microstructuring techniques, new materials development and characterisation (polymers, metals and ceramics) and packaging methodologies is also undertaken, in cooperation with 50 other research facilities.

Funding for microfluidics technologies is also contained within other BMBF funding programmes such as Framework Concept Nanotechnology (€50-200 million/y ≈ £34-140 million/y), New Materials, Research for Tomorrow's Production, Intelligent Systems, production-integrated environmental technology, healthcare and biotechnology programmes. Further funding may come from research foundations such as the German Environment Foundation (DBU), as well as from the German Research Foundation (DFG) which funds university and technical college research programmes. The current six-year DFG funding programme which started in 2004 includes 14 priority themes which collectively have €38 million (~£26 million) funding for collaborative projects. These include:

- Nano- and microfluidics: from molecular motion to continuous flow – coordinated by the University of Saarland
- New strategies for measurement and testing in the production of microsystems and nanostructures – coordinated by the University of Erlangen

8.3.4 uVT network and standarisation

An innovative industry-driven consortium project on modular microprocess engineering (uVT) was funded by the BMBF. uVT sought to develop standard interfaces for functional microfluidics modules that, when integrated, would constitute a miniaturised chemical processing plant, or retrofit to existing plant. The interfacing of modules each performing different discrete functions has long been considered a hindrance to the commercialisation of microfluidics technology (particularly microreactors for long-duration usage).

The project output a very impressive solution to this requirement with several companies initially adopting the standard for its modular products. This potentially allows users and systems integrators to construct multifunctional systems based on devices sourced from several different manufacturers. However, despite this seemingly excellent development, the standardisation approach is being increasingly abandoned by the consortium partners, each preferring to promote their own specific standard in order to corner the market.

8.3.5 Training and education

There are many initiatives to assist the development of MST skills. 'Microsystems Engineer' has been a formal profession since 1998 and some hundreds of apprenticeships have been completed since then. There are also MST retraining courses offered by a number of public institutions that are offered on a local basis. Teaching is generally done by company experts. 'Pro-mst' is a dedicated training foundry in Zweibrücken – a comprehensive clean-room facility and infrastructure for MST training and education, based in the Fachhochschule Kaiserslautern. The 'model project' Corporate-Learning-Network MST in Dortmund is a network of educating institutions in the MST/MEMS sector. Other regions have similar initiatives.

8.3.6 Important intermediary organisations

- IVAM – Association of Companies and Institutes in Microsystem Technology: www.ivam.de
- DECHEMA – Society for Chemical Engineering and Biotechnology: www.dechema.de

- AMA – Association for Sensor technology: www.ama-sensorik.de
- VDMA – German Engineering Federation: www.vdma.org/microtechnology
- ZVEI – Electrical and Electronic Manufacturers' Association: www.zvei.org

8.4 Conclusions and recommendations

A new focus on systems integration is now enabling the acceleration of microfluidics commercialisation which has hitherto been hindered in the Netherlands and Germany. The UK would do well to recognise that many end-user corporations, particularly in bulk materials manufacture, require complete turnkey solutions (not curiosity chips) if the potential of microfluidics is to be realised.

The example of Twente University demonstrates that risk-averse centralised technology transfer offices in UK universities, which once may have served a useful purpose, are now possibly a hindrance to the accelerated establishment of spin-outs, and a scheme to decentralise target-based responsibility to departments and research groups could be piloted, benchmarking the Twente example. Twente University also held a sensible attitude regarding the value of its intellectual property (IP).

The evidence from the microfluidics companies clustered around or associated with Twente University and IMM suggest that affordable, direct, hands-on access to microfabrication tools is a key (if not *the* key) requirement for encouraging a dynamic industrial microfluidics cluster where start-ups and spin-outs are the principal commercial entities.

9 EMERGING AREAS OF MICROFLUIDIC TECHNOLOGY

9.1 Introduction

Microfluidics represents one of the most important and exciting technological areas in microtechnology over the past two decades. It was driven principally by the needs of microflow sensors, micropumps and microvalves in the early stages of development. This has undergone substantial changes over the years and microfluidics developments have been dominated by life science and chemistry related applications. Today's emerging application areas include DNA separation and analysis, drug screening, microfiltration/emulsification, detection of Legionella and of a range of biological and chemical contaminants in potable and waste water.

Germany and the Netherlands are seen as two major players in microfluidics R&D in Europe. The mission enabled the team to see, to meet and to discuss with both academic and industrial representatives of the two countries. Although the overall impression is that there are numerous microfluidic products that await industrial take-up, there are new R&D programmes aiming at new technologies related to microfluidics. Examples are given in Section 9.2 below.

Much of the innovation in the microfluidics area is being driven by the needs of new products. The use of microfluidics in manufacturing is clearly an immature yet emerging area. As reported elsewhere, there are applications of microfluidics to be found in the process industries – production of nanoparticles, refining, filtration etc – and in commercial use, many in the medical field.

Product innovation companies demand complete systems rather than individual components to meet the functionality required to fulfil a specific application. Because microfluidics is still at an immature stage of commercialisation in many applications, there is still considerable innovation in the application of the technology and the design of devices for each new application. This is leading to a highly diverse set of underlying materials and microfluidic technologies and this situation will persist for many years into the future.

9.2 Examples of new technologies and applications

9.2.1 Micro boiling heat transfer

Thermal management of small-scale devices, particularly electronics, is regarded as the bottleneck of further device miniaturisation. Researchers at Delft University looked at small-scale boiling heat transfer with a 4.5 mm boiling container.[29] They found that

29 www.ahd.tudelft.nl

the wall-water heat flux could be 10 times higher than large pool experiments at a superheat of ~10 K. This is significant and may bring in innovations to thermal management.

9.2.2 Liquid-wall interactions

The behaviour of liquid flow and heat transfer in microchannels depends on the properties of both the liquid and wall materials and their interactions. The presence of a second component, particularly gas, greatly affects the flow and heat transfer. This is not new and microfluidics device/product manufacturers and operators know this very well. For example, degassing the liquid is absolutely necessary in many cases to ensure a successful operation. However, how the gas component distributes over the cross section of the microchannels and how they would affect the flow and heat transfer behaviour are unknown.

This has recently been addressed by scientists of the University of Twente using the molecular dynamics simulation approach.[30] They found that liquid-gas mixtures in contact with walls exhibit gas enrichment at the wall, and the enrichment increases with increasing wall hydrophobicity. For hydrophobic walls, the gas concentration at the wall can be over two orders of magnitudes higher than that in the bulk liquid. The presence of the gas enrichment at the wall can modify the liquid structure considerably and enhances the wall slip. The enrichment of gas at the wall region was also shown to reduce the surface tension.

The findings above bear significance in the design and operation of microfluidic devices and could lead to innovations.

9.2.3 Fluorescence enhancement technology

Assay sensitivity can be an important issue faced by scientists and engineers working in the pharmaceutical and biotechnology areas. Attophotonics Biosciences GmbH[31] has developed a fluorescence boosting technology termed Attophotonics REF chips. The technology is able to give 10-100 times enhancement of the fluorescent signals thus allowing increased sensitivity, improved data output and optimised utilisation of the valuable sample materials.

The Attophotonics technology utilises thin-film physics and Maxwell equations as the theoretical basis. The technology is realised by a stable setup together with well established surface chemistries for biomolecule immobilisation. The incident field of an electromagnetic wave excites the fluorophores on top of the setup. Additional excitation derives from the reflected wave, and the enhancement in fluorescence signal is gained by a focusing effect. More photons per fluorophore are directed towards the objective of the analyser. The technology can be used with the established protocols and buffer solutions. Array scanners, fluorescence microscopes and standard lab equipment can be used.

9.2.4 Micro inhaler for drug delivery

Inhalation is regarded as one of the most promising technologies for drug delivery. There are lots of R&D activities in this area within both academic and industrial communities. Under the brand of Respimat Soft Mist, Boehringer Ingelheim Microparts[32] has developed a propellant-free inhalation device for the therapy of respiratory diseases. The device makes use of microfabricated high-precision nozzle structures which enable

30 See, for example, Dammer S M and Lohse D (2006): *Gas-enrichment at the liquid-wall interfaces*, submitted to Condensed Matter, 0510687

31 www.attophotonics.com

32 www.boehringer-ingelheim.de/microparts

uniform nebulisation of a small dose of medicine in the respirable droplet size.

9.2.5 Micro electrolyte analysers for point of care

Monitoring of the lithium level in the blood on a regular basis is important for people on medication for manic depressive illness. Medimate[33] has been developing lab-on-a-chip technology based on the microchip capillary electrophoresis for lithium level monitoring. The technology uses an electric field across a microchannel, which enables the charged species to be separated and detected in only a few seconds.

The technology only needs one droplet of blood for the analysis and patients can use it at home so providing point-of-care diagnostics. Medimate is expected to launch the prototype by the end of 2007.

9.2.6 Micro fuel cell technology

Micro fuel cells are small-sized power sources that convert chemical energy into electrical energy. Fuel cells operate by oxidising combustible fuel, such as hydrogen or alcohol. These energy sources, on a large scale, have been deployed in motor vehicles. Most of these devices use hydrogen. Recently, scaled-down fuel cells have been developed for use with devices such as digital cameras, portable radios and notebook computers. These devices use fuels other than hydrogen, most notably methanol. Microfluidics plays a major role in such technology.

Despite not playing the leading role in the development of micro fuel cells, there are some activities in European countries, particularly in Germany, where a BMBF-funded programme ‘Micro Fuel Cell’ has operated since 2004 with technical goals clearly defined:

- Electrical capacity <100 W
- Gravimetric power density >200 W/kg
- Volumetric power density >150 W/l
- Energy density >1,000 Wh/l
- Cost <€4/W (£3/W)
- Operating lifetime >2,000 h

A number of German institutes and a few companies such as Smart Fuel Cell GmbH (Munich) and 3P Energy GmbH (Schwerin) are developing microfluidic fuel cell components and systems. Examples include:

- Fraunhofer IZM in Berlin has adapted wafer-level and foil processes, used in the production of high-density interconnect electronic modules, for the fabrication of low-cost polymer electrolyte membrane (PEM) micro fuel cells; a demonstrator of 4 cm^3 volume (complete system) is claimed to yield 2.1 Wh at a current of 10 mA

- A research partnership between the University of Freiburg and Micronas AG is developing a 4 mm^2 PEM fuel cell on a low-power chip for use in powering autonomous sensors

- Fraunhofer ISE in Freiburg has developed a miniature electrolyser that enables metal hydride hydrogen storage units to be filled with hydrogen quickly and at point of use; in just 12 minutes it generates enough hydrogen from water to power a camcorder for 2 hours

- FZK’s Institute for Microprocess Engineering and IMM are both working on microstructured reformers and gas cleaning for a range of fuels

- Biofuel cells are being developed at IMTEK (University of Freiburg) within an EU Framework VI project ‘Healthy Aims’; the work is evaluating a direct glucose fuel cell

33 www.medimate.nl

(DGFC) and a mammalian bio fuel cell for low-power medical implants (~100 μW) and integration into medical devices

- Other prototype products[34]

The worldwide market for micro fuel cells is expected to increase in the coming years as technologies improve and costs reduce.

9.2.7 Nanowires

The use of nanowires was demonstrated at TU Delft. Silicon nanowires (20-50 nm) have the same thickness as DNA, certain enzymes, viruses etc. This could lead to detection of single viruses, antigens, proteins, toxins and be of use in the design of smart drugs, biocides/herbicides etc. Earlier diagnosis and online monitoring of health are short-term applications. The ultimate goal could be 'proteomics on a chip' to aid the study of diseases and development of appropriate vaccines, diagnostics, drugs and treatment regimens.

9.2.8 Lab-on-a-chip

TNO in Delft described the development of a 'lab-on-a-chip' which could reduce the time taken to detect agents such as anthrax from 12 days via agar plates to a few hours and below. This is one of the major current interests in microfluidics, enabling DNA and protein analysis, chemical reactions, high-throughput screening, ion/particle characterisation and all manner of mixing/heating/control/separation of liquids.

9.2.9 Microporous structures

Outside the space of channel-based devices, the mission team observed that there are a number of related applications for pores and very small surface features. The use of microporosity was discussed by a number of the host organisations. Potential uses include microsieves for filtration and separation, scaffolds for tissue engineering, and self-cleaning surfaces.

A related area is in fuel cells where microstructured polymer surfaces can be used to improve the efficiency of these devices.

9.2.10 Polymer-based microfluidics

One of the key trends in microfluidics is the increasing use of polymer-based devices. Polymers are expected to offer the lowest price per unit for individual devices, and using currently available high-volume production technologies such as microinjection moulding or hot embossing are able to manufacture devices at costs that are suitable for disposable applications.

According to ThinXXS in Zweibrücken, future applications for polymer-based microfluidics devices based on lab-on-a-chip technology include point-of-care diagnostics, drug discovery and development, and environmental analysis (water/food/agrochemical). The main volume driver currently is human diagnostics, eg the blood-glucose testing market.

Where test is administered	Value of market
Laboratory	\$36 million (~£20 million)
Physician's office	\$500 million (~£275 million)
Self administered, home based	\$1,700 million (~£935 million)

Exhibit 9.1 *Value of the blood-glucose monitoring market as a function of where the test is administered*

34 www.fuelcells.org/microTechnical.pdf

Appendix A

VISIT REPORTS

A.1 British Embassy, Den Haag

A.1.1 Lyn Parker – British Ambassador

The Ambassador gave a brief introduction and an overview of the mission.

A.1.2 Leo Zonnefeld – Science Attaché

A.1.2.1 Government policy

Nanotechnology is one of three Netherlands government technology platforms, alongside genomics and ICT. The three platforms received €800 million (~£550 million) in grant aid under ICES/KIS in 1999. Nanotechnology was awarded a further €130 million (~£90 million) (2004 extended programme) and €17 million (~£12 million) in 2006. Under this national platform there are three specific programmes:

- **NanoNed** – activities at MESA+ and Kavli) – €95 million (~£66 million)
- **BioMaDe** – largely in biosensors, Enschede – €7 million (~£5 million)
- **MicroNed** – activities directed from Delft University – €23 million (~£16 million)

The mission would meet most of the key people involved in these programmes.

The Ministry of Education and Sciences believes current regulatory structures are sufficient for nanotechnology development; however, it has been stated that supplementary regulations will be introduced for nanoparticles once new toxicity models have been developed. Overall the government believes there is no real ground for unrest or unease. Obviously any Netherlands action has to be seen in the context of the EU Action Plan for 2005-2009 demanding a coherent European strategy and implementation which takes society with it.

A cross-departmental Netherlands group has been set up to create conditions for favourable and safe development of nanotechnology; this will present a paper to parliament in July 2006 and from this a Government Vision for nanotechnology will emerge. It is planned to start a programme of public engagement when the Government Vision is in place. Michael Rose of UK Defra visited two weeks earlier to compare notes with his Dutch counterparts. It would appear that the Dutch public is about 12 months behind the UK public in its awareness of nanotechnology.

A.1.2.2 Universities

The Government has announced it will be investing €50 million (~£34 million) in the creation of centres of excellence, with 30 extra professorial posts being created. The first step of the process is the creation of five centres of excellence in nanotechnology, ICT, sustainable energy, fluid and soil mechanics. The second step will be the federation of the three TUs (3TU – Twente, Delft and Eindhoven) to take effect next year.

The leading universities for nanotechnology within the Netherlands are:

- **Twente** with the MESA+ Institute for Nanotechnology
- **Delft** with the Kavli Institute and input in MicroNed
- **Eindhoven** with specialist engineering experience

A.1.2.3 Commercial organisations

The largest companies in the Netherlands – Shell, Akzo, Unilever and Philips – are all involved in nanotechnology activities. Philips with organic electronics and self-assembly of displays being key new technology platforms which have been publicly announced. The activities of the other companies are only seen through a number of university collaborations and funding.

A number of small companies are active in the area – the mission would meet CV2 (Vincent

Spiering in Twente) involved in manufacture of microsystems, optics design software and recently OEM products for analytical instruments based on microtechnology; and LioniX (Rene Heideman in Twente) involved in integrated optics and microfluidics. They recently developed a capillary electrophoresis chip. They work with Pirelli, Siemens, Unilever and ESTEC Noordwijk. Micronit (Ronnie van't Oever in Twente) is well known for lab-on-a-chip developments and a kit for fluid interconnections – it has been awarded the van Kroonenburg prize.

A.2 Ralph Lindken – Laboratory for Aero- and Hydrodynamics, Delft University of Technology

The Delft work on microfluidics grew out of macrofluidics work. The department started doing microfluidics work fairly recently and has been looking at a range of different applications. Another activity of the department is to study better process control where use of scaling effects is key.

In the transfer of computational expertise from macrofluidics to microfluidics, the scaling effects mean that in microfluidics different forces, surface tension and viscosity, dominate compared to macroscopic systems where gravitational effects are key; this has meant that novel computational codes have been developed to include these forces.

The group has deep expertise in particle image velocimetry (PIV) and has developed a µPIV technique that is able to carry out single-pixel correlation which gives very high spatial resolution. The group also make extensive use of stereo µPIV to give a full picture of three-dimensional (3D) particle flow. Epifluorescent imaging combined with µPIV is used to reduce reflections which enable good images to be obtained from microfluidic systems. Image preprocessing is used to eliminate noise and get particle centres; these are then correlated to get a full 2D velocity map – then enhance this further by looking for movement over single pixel area.

A number of studies have been undertaken with the enhanced µPIV technique:

- An extensive work programme is being carried out to characterise flow profiles at the walls of microfluidic channels. This will allow the characterisation of the exact magnitude of wall slip which is a key factor in the behaviour of fluid in microfluidic channels.

- The study of avian embryo hearts has been made possible by the use of µPIV combined with ultrasound Doppler measurements to get the heartbeat. The velocity measurement can then be fitted to the heartbeat rhythm. Stealth liposomes are used as tracer particles. The analysis produces a 3D distribution of shear stress within the heart. The objective of the work is then to link the behaviour of the heart to the expression of different genes, which are manipulated to understand the link between genetics and heart performance.

- Studies have been carried out on thermophoresis and thermodiffusion – basically particles move more when hot so some of the particles move into the cold area, where they don't move as much, so particles that move to the cold region don't get out. This effect is the basis of thermal field fractionation.

The group is setting up collaboration with TNO to investigate microevaporation which it sees as a highly promising method of producing high-efficiency cooling systems.

The group has been working with Philips on on-site analysis.

Work has been carried out on precipitation in a microreactor, with a tortuous mixing/nucleation region followed by a long growth region and then a quench region where a cold channel is used to kill the reaction. An antisolvent is introduced to bring the salt fully out of solution and allow separation. This is achieved on a single glass chip.

A.3 Delft University of Technology

The team first visited the Delft Centre for Mechatronics and Microsystems located at Delft University of Technology. Professor van Keulen gave a brief introduction to the University, the Centre and his own research, followed by a presentation by Professor Van Rijin and discussion.

The University was founded in 1842. It now employs 4,700 staff members and has ~14,000 students. The university has faculties and takes ~180 PhD students a year. The Delft Centre for Mechatronics and Microsystems involves ~100 full-time equivalents (FTEs). It has four cluster areas, including precision motion (nano-scale precision), precision bio-nano, and microfabrication. Facilities are shared across the centre. It is a virtual centre with PhDs and postdoctoral research associates (PDRAs) shared by different groups. Equipment can only be purchased if several groups express common interest.

Professor Keulen also briefly described MicroNed, a network comprising ~30 research centres and industrial partners, with funding of €56 million (~£39 million) for 2010 with 50% met by industrial companies. MicroNed has four clusters: SMACT (wet microsystem), MUFAC (micofactory), FUNNMOD (modelling) and MISAT (microsatellite).

Professor Keulen briefly described his own research on modelling and optimisation using multilevel optimsation.

Professor Cees Van Rijn presented his activities, particularly the spin-offs he helped to set up, eg Microfiltration BV, Medspray Drug Delivery BV, Nanosens BV, Lotus Polymer Moulding BV. He highlighted ultrafast filtration using nano and micron membrane (Microsieve), and demonstrated the application areas of the filter, eg milk and beer. The use of microsieve could process a liquid flux of ~8,000 l/m^2 h and reduce the cost of filtration from ~€0.75 (£0.52) to ~€0.25 (£0.17) per hectolitre (hl) of beer.

Professor Cees Van Rijn also briefly introduced technologies of emulsion, porous capillary breakup, nanowire biosensors and biochips.

A.4 TNO

The team then visited the Industrial Modelling and Control department of TNO Science and Industry located in Delft, where three presentations were given by TNO personnel:

Dr Heri Werij
Manager
Industrial Modelling and Control

TNO is a national research organisation. It is a company but receives funding from the Government. It has five core areas:

- Quality of Life
- Defence, Security and Safety
- Science and Industry
- Built Environment and Geosciences
- ICT

The area of Science and Industry consists of nine departments:

- Materials Technology
- Design and Manufacturing
- Micro Devices Technology
- Opto-mechanical Instrumentation
- Industrial Modelling and Control
- Imaging Systems
- Automotive
- Testing and Consultancy
- Holst Centre

TNO employs about 5,000 people and has an annual turnover of ~€550 million (£380 million) of which one third is from Government funding and two thirds from sales.

TNO Science and Industry employs ~1,000 people (excluding hired staff) and has an annual turnover of €112 million (~£77 million).

TNO Science and Industry has been working in areas such as:

- High-end equipment for ultraprecise production and measurements – TNO is the preferred R&D supplier of ASML (microchips), supplying equipment and technologies for micro and nano lithography, optics, precision mechanics etc
- Optimising production for the process industry – flow and structural dynamics, process modelling and control, separation technology and acoustics
- Innovations in materials – material performance, multilayer devices, surfaces and coatings
- Smart manufacturing
- Mobility and transport safety

TNO and Delft are investing €17 million (~£12 million) in building a joint centre for MNT. New facilities are shared by the two organisations and are for open access.

Cor Rops
Process Systems and Processes Division
Industrial Modelling and Control

Mr Rops – who is a TNO employee but is doing a PhD at Delft – gave several examples of projects that TNO is or has been working on:

- Micro heat spreader – aiming at developing a technology that has a cooling capacity exceeding 1 MW/m^2, low mass, high reliability and can be space-proven; getting space-proven is difficult
- Micro evaporator – a project with QinetiQ aiming to increase the heat transfer capacity and to enhance operational stability
- SAMPRED – sample preparation techniques for detecting warfare agents and bioagents

Christophe Hoegaerts
Project manager
Industrial Modelling and Control

TNO is not a technology push but rather an industrial pull.

There is a JV between TNO and iMac.

A.5 MESA+ Institute at Twente University

A.5.1 Twente University

Professor Henk Zijm, Rector Magnificus of Twente University, explained how the rapid loss of 125,000 textile worker jobs around Enschede in two decades was a primary impetus to establish the university. He outlined how the board was industrially dominated and extolled the entrepreneurial ethos that pervades the university where budgets for research groups (staff and infrastructure) are output based, responding rapidly to changing scientific and technical opportunities and priorities.

A.5.2 MESA+ Institute of Nanotechnology

Professor Kees Eijkel is Technical Commercial Director of the MESA+ Institute of Nanotechnology which is now an internationally recognised centre. MESA+ was originally founded on sensor-actuator technologies and a very strong focus on microfluidics. This stems in part from the pioneering research of Professor Piet Bergveld who invented the ion-sensitive field-effect transistor (ISFET) whilst at the Institute. MESA+ accommodates 450 people (60%

temporary), has 20 chairs and is one of the leading European players in the field of microfluidics. It is funded by an annual budget of ~€31 million (£21 million), 50% of which is derived from industry.

Developing the theme of Twente as the entrepreneurial university, Professor Eijkel explained how MESA+ has taken a leading position in the development of MNT in the Netherlands, for example as founder of MINAC[35] which is the Dutch microsystems and nanotechnology supply chain cluster that undertakes coordination and promotion of research and education.

Additionally, Professor Eijkel outlined the theme of how MESA+ had developed a strategy for rapid business formation through its accelerator MESA+ International Ventures Ltd *(see Chapter 8)*. Significantly, he highlighted the lack of a centrally orchestrated technology transfer office for the university as a key success factor contributing to the 33 businesses that have spun out of MESA+ over the last 15 years. Thirteen of these companies are active along the microfluidics value chain, including (directly) IBIS, Aquamrign, C2V, LioniX, Micronit, Medspray, Immunicon, Nanomi, CapiliX, Medimate and (indirectly) Sentron, Nanosense, EMI, Optisense.

Extensive facility sharing *(the local MNT ecosystem)* between research groups and with industry was shown to be a very important success parameter. The current 1,250 m^2 comprehensive clean-room micronanofabrication facility, which is shared by academics and industry on a swipe-card fee-paying basis, is now being supplemented by a completely new clean-room facility that will be built adjacent to the existing one.

The success story of MESA+ has been due in part to the long-duration commitment of support received from the regional development agency. Albert Hoogeveen, senior project manager for foreign investments, explained how there was an intimate day-to-day liaison between MESA+ operations and his regional office in Enschede, ensuring that the Institute is efficiently and effectively promoted and supported. Additionally, he detailed how pre-seed financial support could rapidly be made available to develop fledgling business ideas into viable business propositions.

With a wider overview, Mr Hoogeveen showed how the Netherlands had identified *food, health and technology* as its 'triangle' of industrial priorities, with Twente University acting as a focus for its 'Techno Valley' (highlighting biomedical engineering, nanotechnology, ICT, tissue engineering, rehabilitation and minimally invasive diagnostics). He identified interdisciplinary 'collaboration' and effective industrial-academic relations as the cornerstone to future success.

A.5.3 Microfluidics Network

Dr Richard Schasfoort provided an overview of the Dutch Microfluidics Network led by Twente University. This is a priority networking platform within the umbrella project MinacNed[36] which has a wider role in MNT.

The Microfluidics Network is an inclusive supply chain network of ~50 organisations which acts to enable a coherent visibility of technology providers to end users. Approximately 60% of the partners are industrial, ranging from micro enterprises such as Aquamarijn BV and LioniX BV to large corporates such as Philips and Texas Instruments.

35 www.minac.nl

36 www.minacned.nl

The principal activities are to provide a portal to Dutch activities in microfluidics, promote facility sharing, entrepreneurial ventures and facilitate new R&D and technology transfer.

A.5.4 Technical highlights

Several key presentations provide a snapshot of the extensive research activities undertaken at the MESA+ Institute:

A.5.4.1 Fluid physics

The fluid physics research group led by Professor Detlef Lohse undertakes theoretical, modelling and experimental research on fluid motion, surface interactions, particle movement and, in particular, bubble phenomena.

A custom, high-speed framing camera employing a helium-driven turbine rotating at speeds of up to 20,000 Hz provides a unique tool for experimental investigations. The instrument is equipped with 128 charge-coupled devices (CCDs) allowing image capture at rates up to 25 million frames per second.

The group specialises in sonic-induced phenomena, especially the role of bubble behaviour at boundaries such as cell membranes and fluidic duct walls. Research teams range from interest in macroscopic (Navier Stokes) to mesoscopic (Lattice Boltzmann) and microscopic (molecular dynamics) effects. The research investigates some of the fundamental questions (eg liquid-surface interactions at the nano-scale) which will underpin future more applied developments of microfluidics.

A.5.4.2 Lab-on-a-chip

The Lab-on-a-Chip Group (BIOS) is led by Professor Albert van den Berg, who holds a distinguished international reputation in the field. His colleague Dr Han Gardeniers *(see also Section A.5.4.5)* provided some 'snapshot samples' of research themes with a highly selective overview of microfluidics for chemical processing. These developments included:

- Integrated microsensors (pH, CO_2, biomass) for process control of bioreactors
- Chip-based microcoil NMR detector for on-line analysis of chemicals synthesis
- PDMS (polydimethyl siloxane) split-and-mix microfluidic reactor arrays
- Micromachined chip-based monolithic (packed) HPLC (high-performance liquid chromatography) columns
- High-pressure chips for use with supercritical fluid-based chemistry

A.5.4.3 Membrane technologies

The Membrane Technology Group takes an interdisciplinary approach to molecular separations (filtration and emulsification) by combining the disciplines of colloid interface science, materials science and processing, mass transport modelling, systems and device integration. The Chair in Membrane and Interface Science is held by Professor Mathias Wessling, who outlined the several research themes orientated on applications to pharmaceuticals, gas, water, chemicals, petrochemicals and food.

In particular, the technique of phase separation micromoulding was considered in some detail. This is a new versatile replication method to produce thin polymeric microfluidic devices with tunable porosity. The method is based on phase separation of a polymer solution on a microstructured mould. Compared to existing microfabrication techniques, such as etching and hot embossing, the technique offers four advantages:

- A simple and cheap process that can be performed at room temperature outside clean-room facilities
- Very broad range of applicable materials (including materials that could not be processed before)

- Ability to make thin flexible chips
- Ability to introduce and tune porosity in the chip

By introducing porosity, the channel walls can be used for selective transport of gases, liquids and solutes. This leads to the on-chip integration of multiple unit operations, such as reaction, separation, gas-liquid contacting and membrane emulsification. Using a hollow-fibre variant, the production of monodisperse emulsions with droplets ~1.4 times capillary diameter were shown. This appeared to hold considerable near-term application potential in many fast-moving consumer products.

A.5.4.4 Future industrial developments

Discussions resulting from the presentations focused on how microenterprises developing microfluidics could identify the most appropriate application and target end-user companies for their technologies. Whilst applications in point-of-use diagnostics had been prominent in the past it was considered that future mass-market applications may be less immediately obvious. The examples of electrowetting lenses for mobile phone cameras and microfluidic large-area ‘diagnostics displays’ using flat-panel technology were cited.

A.5.4.5 Han Gardeniers – BioChip

The BioChip group at Twente has been developing a range of microfluidics for chemical processing, based on glass microreactor technology. In order to manufacture the microfluidic devices they use the MESA+ facilities.

A novel high-pressure microreactor has been developed which needs no containment as a pressure reactor, allowing a full high-pressure laboratory to be run on an open laboratory bench. The microfluidic system is able to achieve 700 bar and is able to carry out reactions in supercritical CO_2.

Dr Han Gardeniers is a member of BIOS – the Lab-on-a-Chip Group directed by Professor Albert van den Berg, one of the key developers of the original lab-on-a-chip concept 20 years ago.

A variety of other projects within BIOS are aimed at developing chemical solutions:

- ChipChemStation – on-line kinetic studies of organic reaction in a chip by mass spectrometry
- Fed batch on a chip – the development of a new technological platform to perform controlled fed-batch fermentations in a very small volume (50-300 μl) arranged on plates (eg 96 or 384 wells)
- PicoASPECT – on-chip cleavage of peptides with analysis of the resulting fragments by mass spectrometry
- Versatile micro NMR

The BIOS group also uses a range of different technologies to produce ‘chips’; silicon technology, via use of the MESA+ facilities, allows the production of chips with integrated sensors as reactor which allow the measurement of pH, dissolved oxygen, biomass etc to be carried out in situ; PDMS, simple in laboratory fabrication, is used for rapid microfabrication of passive chips; more sophisticated fabrication technologies are being used to produce chips with nanopillars which allow micromachined HPLC columns to be fabricated.

A.6 Concept to Volume (C2V)

PO Box 318
7500 AH Enschede
NETHERLANDS

T +31 534 889 889
F +31 534 889 890
www.c2v.nl

Employees: N/A
Annual growth: N/A

Profile

C2V supplies high-added-value OEM products for analytical instruments and detectors, for security, life sciences and process control applications, using MEMS technologies and its microDELTA integration platform. These comprise:

- Microanalytical components
- Microchromatograph components and systems – HPLC, micro gas chromatography (GC)
- Microfluidic components and integrated systems
- Microvalves and microvalve arrays
- Micro flow sensors, nanomixers, nanofilters
- Micro nozzles, sprayers, actuators/ positioners

Customers

C2V often works on a customer-specified basis. Its customers operate in security, life sciences, industrial process control, telecom, and space markets and are located worldwide. The customer profile varies between large multinationals and SMEs. It also works for research institutes enabling universities to perform leading-edge research by providing customised tools such as innovative hardware as well as its software tools. The projects are divided into milestones connected with deliverables, in order to minimise risks and costs.

Business model

C2V is an OEM product supplier of high-added-value custom MEMS and integrated optics products and services, offering:

- Design to manufacturability
- Supply of products in variable volumes
- Industrialisation of specific processes and packaging
- Software toolkit supporting design and manufacturing

Clean room

C2V process engineers and operators work in a 1,030 m^2, four inch clean-room facility, where the wafers are handled in a class 100 environment. The clean room is fully equipped with all necessary apparatus and process facilities. The largest part of the clean room is dedicated to MST to make MEMS devices.

Assembly and test facilities

C2V has a qualified precision engineering team with focused experience on micro and miniature packaging and assembly services. These activities fit into a systems integration approach or design for manufacturing approach, where they assist in the whole development cycle from early concept to (high) volume production.

C2V's precision engineering capabilities are offered to achieve solutions which satisfy customer design problems and production needs. The precision engineering capabilities enable integration on the system level, often leading to higher yields and lower manufacturing costs. Its precision engineering services are part of MEMS development programmes, or are stand-alone projects.

A.7 Micronit Microfluidics BV

Hengelosestraat 705
7521 PA Enschede
NETHERLANDS

T +31 53 483 65 84
info@micronit.com
www.micronit.com

Employees: 25
Annual growth: 50-80%

Profile

Micronit focuses on lab-on-chip development, design and production. It is capable of rapid prototyping of microfluidic chips. These chips are available in various dimensions, created with several techniques and different materials.

The company serves customers worldwide, mainly in Europe and North America. Markets served are pharmacy, biotech and fine chemicals, and are large multinationals, start-up companies, institutes and universities.

With a combination of its standard products, technical capabilities and knowledge, Micronit develops microfluidic devices for a variety of applications.

Facilities

For the majority of production, Micronit has its own clean-room infrastructure. There is an in-house powderblasting line and a class 1,000 clean room capable of producing up to 500,000 glass chips per year. Micronit also hires clean-room space at the MESA+ Institute. In this space Micronit manages its own pilot line for rapid prototyping and medium-volume production. Equipment includes a mask aligner, an aligned bonder, etching equipment, wet benches, programmable hot stages, annealing furnaces etc.

Other capabilities

Silicon processes supported are plasma-enhanced chemical vapour deposition (PECVD) and low-pressure chemical vapour deposition (LPCVD), deep reactive ion etching (DRIE), potassium hydroxide (KOH) etching of silicon, anodic and direct bonding, electroplating, dicing etc.

Micronit entered the Dutch Deloitte Technology Fast 50 in 2005 in thirteenth position, as the only MNT company in the ranking. The world market leader in developing and fabricating glass microchips was ranked that high thanks to its strong turnover growth. Over the period 2000-2004, turnover grew no less than 1,157%.

A.8 LioniX BV

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www.lionixbv.nl

Employees: 22
Annual growth: N/A

Profile

LioniX is a leading provider in development and small- to high-volume production of leveraging and innovative products based on MST and MEMS. Its *core technologies* are integrated optics and microfluidics.

Customers

Its customers operate in telecom, industrial process control, life sciences and space markets and include OEMs, multinationals and VC start-up companies as well as research institutions from around the world.

Strategy

LioniX offers *design for manufacturing* and *horizontal integration* by partnering with MEMS/MST foundries and suppliers of complementary technologies. Cooperations are based on subcontracting, licensing of intellectual property rights (IPR), or JVs.

IPR

LioniX has an IPR agreement on technology with the MESA+ Institute and is rapidly building up a firm IPR position in its core competences integrated optics and microfluidics.

Facilities

LioniX uses state-of-the-art facilities of the MESA+ Institute. In addition it has its private clean-room facilities with equipment for its proprietary technologies.

Additional notes

ChemtriX, a JV between LioniX and the University of Hull, was set up in December 2005 to manufacture glass chemical microreactor systems. Paul Watts, who is currently CEO from the University of Hull, provides the chemistry expertise and LioniX provides the manufacturing experience to produce the glass microreactor components. The company's initial aim is to produce products derived from the product line of another LioniX JV, Capilix, which manufactures capillary electrophoresis microfluidics.

The initial product will be based on a Capilix 'chip' holder which contains both fluid and electrical connections into which the desired microreactor chip is connected. This allows microreactor chips to be produced using standard microsystem techniques and then all the external connections are handled by docking with the chip handler. Scale-out will be achieved in the first instance by using a complete glass wafer which contains ten chips without dicing to produce a tenfold scale-out. Further scale-out will be achieved by stacking completed wafers into a matrix which could contain 100 microreactors in parallel.

The technology inheritance from LioniX to ChemtriX means that ChemtriX is able to incorporate electrodes and optic-fibre connections with ease. It is working on incorporating Peltier elements, so that the chip can be both locally heated and cooled.

A.9 CSEM SA

CSEM SA, the Swiss Centre for Electronics and Microtechnology, is a privately held, knowledge-based company, active in the field of MNT, microelectronics, systems engineering and ICT. It currently employs around 250 people and has research centres in Neuchâtel (headquarters), Zurich and Alpnach.

The company is subsidised by the Swiss Government, which provides about 25% of its finance. Other financial incomes are from EU and regional projects, as well as industrial projects. CSEM is not a profit-driven organisation – it reinvests heavily in order to stay ahead of the technologies. It releases the technology know-how to the market by generating spin-off companies – 22 spin-offs in the past five years.

CSEM has a microfluidics team with about 10 people, mainly working on separating and handling of cells, and smart chips for biochemistry analysis and environmental monitoring. According to Dr Krieger, CSEM's Marketing Manager, its technical strength is in system integration, ie putting optics, electronics and microfluidics devices into a single system to achieve specified functionalities.

Dr Krieger also emphasised that the company is interested in applying its knowledge in the mass production market, and intends to achieve that through collaborations – competing is not the way to survive in this still small market; small companies should find a way to work together instead of competing with each other.

Q: Is the Swiss microfluidic network useful in the sense of finding customers for SMEs?

A: Without the network, everyone acts individually, no-one knows what other people are doing and there are a lot of confusions. In this sense the network is useful. However, the cost of transferring functional prototypes to mass production has been tremendously underestimated by most people. This hinders the progress of SMEs, and the network is not that helpful in this aspect.

A.10 Protron Microtech

Starting from 1999 the company has expertise in microfluidics, micro-optics and RF-MEMS. Its current focus is on silicon-based devices, mainly for two reasons:

- Polymer-based microfludic devices are unsuitable for chemical reaction applications due to material instability
- Silicon can be processed into ultrafine structures which are unachievable in any other material

Its customers are from the USA and Europe, mainly Germany. Most customers use Protron's microfluidic devices for research purposes and for making DNA chips.

Q: How do you compete for the market and the killer application?

A: It is a growing market. Biotech companies were going downhill two years ago; however, they are now getting stabilised and the market is coming back. Protron has achieved more than 15% annual growth in the past couple of years. So far, the Internet has been the best marketing channel for the company.

A.11 Bartels Mikrotechnik GmbH

The company started about 10 years ago by using an excimer laser to structure plastic materials. Recently it has developed the piezoelectric-based micropump, which is entirely fabricated out of plastics except the piezo-diaphragm. It currently employs 25 people.

The specifications of the micropump are:

- Size: 14 x 14 x 3.5 mm
- Weight: 0.8 g
- Lifetime: >9,000 h
- Power consumption: 0.08 W, with battery life of 72 h for continuous operation
- Pumping pressure: 0.5 bar
- Flow viscosity: 120 mPa s
- Particle tolerance: < 50 mm
- Flow rate: 50 nl/min to 5 ml/min for liquid, 50 µl/min to 15 ml/min for gas

The cost of the micropump could potentially go down to €1 (~£0.69) for volume production (2 million units).

Other products from this company are microvalves, capillary electrophoresis (CE) chips and nanowell plates.

A.12 microTEC

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The microTEC stand at Hannover Fair was visited on 26 April 2006 at the invitation of the CEO/CFO Andrea Reinhardt, and discussions were held with joint CEO/CTO and founder Dipl-Ing Reiner Götzen and with Dr Helge Bohlmann.

The business of microTEC is in the use of its proprietary microsystems rapid-prototyping technology (RMPD) based on direct-write methods. In addition to its established services in micromechanics and microsystem packaging, microTEC is building a distinct offering in lab-on-a-chip device fabrication from computer-aided design (CAD) to series production. As with most of the companies visited employing polymer technology, microTEC is looking to benefit from the growth opportunities in diagnostics. It seeks to provide expertise in function integration and to deliver the product volumes required cost effectively.

The mission team is grateful to Andrea Reinhardt for her input to the study of start-up stimulation measures and her experience in funding microTEC through a combination of founder's contributions and, in the case of microTEC, the use of bank funds and equity. This again highlighted the relatively low use of VC funds in both the Netherlands and Germany. The importance of obtaining a mix of skills and genders to create an effective management team was noted. Also, studies on entrepreneurship highlighted that spin-outs resulting from large companies, including as a result of restructuring, had an important role to play as well as university start-ups.

A.13 IMM – Institut für Mikrotechnik Mainz GmbH

Personnel

Dr Klaus Stefan Drese
Head of Fluidics and Simulation Department

Company background

IMM is an application-oriented R&D enterprise whose aim is to bridge the gap between academic research and industry in the fields of:

- Chemical process engineering
- Bio-microfluidics
- 3D microstructuring techniques
- Fuel processing

An emerging fifth area of research is in polymer-hybrid technologies (especially conducting polymers).

IMM was established in 1991 by the local government under the leadership of Prof Ing Wolfgang Ehrfeld (coming from FZK).

Website

www.imm-mainz.de – this contains a lot of information, including the IMM catalogue of microreactors.

Vital statistics

- Turnover: ~€11 million (£7.6 million)
- Employees: 119
- Ownership: public (German federal state of Rhineland-Palatinate)
- Funding: 1/3 State, 1/3 industrial projects, 1/3 public projects
- Profit: non-profit organisation
- Spin-offs: ~11, creating more than 200 jobs in Rhineland-Palatinate
- Education: >1,000 people have done internship and research at IMM
- Projects: >800 high-tech projects completed
- Partnerships: extensive list of academic and industrial collaborations

The company is strongly market oriented and, apart from PhD students, the majority of the activities are industry driven, including publicly funded projects.

Given the legal structure the company cannot make more than 7% of turnover from direct sales.

Notable spin-offs are Microglas, CPC and Ehrfeld Mikrotechnik.

Up to 80% of personnel time is dedicated directly to projects (the rest being meetings, writing research papers, maintenance, and other non-project activities).

Chemical process engineering

IMM's major competence areas are:

- Chemical process development
- Component and process simulation
- Mixing technology
- Organic, fine and functional chemicals synthesis
- Catalyst preparation and testing
- Energy generation and heat management
- Fuel processing
- Customised and off-the-shelf components
- Customer-specific plant design and construction
- Unitised fluidic-bus for microstructured devices

IMM publishes a quite extensive *catalogue of microcomponents* that it sells on the open market *(available on the website)*. The aim of these sales is not profit but a service to the industry. To avoid competition with its spin-off Mikroglas, IMM does not offer glass.

Among the many products are the slit interdigital micro mixer (SIMM) which uses multilamination and geometric focusing and has been used by a large number of customers and is manufactured by advanced silicon etching (ASE); the high-pressure SIMM, resisting up to 600 bar; and the Caterpillar Split-Recombine Micro Mixer. A mixer more oriented to production is the Star Laminator, which is offered in flows ranging from 300 l/h to 30 m^3/h; also the micro falling film reactor and micro bubble column reactor; and microchannel heat exchangers are produced by diffusion bonding in collaboration with Heatric.

Some examples of applications are: cream manufacturing pilot plant to perform 8-15 component mixing with microstructured mixers; table-top plants for fine and speciality chemicals; lab-scale plant for catalyst testing for propane steam reforming; and pilot-scale plant for iso-octane reforming (5 kW).

Success stories from IMM include the September 2005 start-up of a plant in China for the production of nitroglycerine for medical applications (15 kg/h) for Hi-an Chemical Industrial Group (HAC).

Fuel processing

IMM's major competence areas are:

- Design, fabrication and testing of reformers for methanol, propane, octane
- Catalyst screening reactors
- Selective oxidation reactors
- Water-gas-shift reactors
- Heat exchangers
- Evaporators
- Preparation of catalyst coatings on microstructured devices
- Catalyst/reactor testing

Power range of the device is between 100 W and 10 kW.

Microstructuring technologies

IMM's major competence areas are:

- Deep lithography
- Photolithography
- Etching
- Micromoulding
- Diffusion
- Deposition
- Plasma treatment
- Micrometrology
- Laser micromachining
- Mechanical micromachining

IMM's facility includes several fabrication laboratories.

IMM is also active in the field of sensors, including optical sensors. An exemplar was given in the area of developing cost-effective sensor systems for ultraviolet-visible (UV-VIS) and near infrared (NIR) radiation.

One microfluidic development has been presented in detail, namely the chip-based-lab, whose code name is '1 week 2 chip', meaning that the development process is so optimised that with only an idea on Monday, the first tests on the actual chip can be performed on Friday, vs a typical development time of half a year.

The goal is to speed up to the maximum the development time for the microfluidic infrastructure in order to focus more on the biology and the actual fluidics.

The goal has been achieved by using standardised assembly process and standardised components.

General discussion

A very important and time-consuming aspect of microfluidic development is IP mapping.

Future for materials: for disposable this is plastic (as a cost of less than €1/pc (£0.69/pc) is needed); for microreaction technology it is stainless steel (can go up to 900°C, and plastics at the same characteristic cost €1,000/kg (~£690/kg)).

Successful start-ups in the field of microfluidics are often bought by bigger companies (example of Microparts, acquired by Boehringer).

VC in Germany is tight, while it is relatively easy to find partners, technology and infrastructure. Usually the VC comes from the UK or Switzerland.

The focus in the industry is moving from technology push to application pull.

The microreaction field is less developed than the microfluidic/bio field and is usually driven by chemical companies that want better quality and simpler processes. The most interested companies are into fine chemicals rather than bulk production.

Fuel processes are becoming more and more interesting because of the needs in the automotive industry.

A.14 CPC – Cellular Process Chemistry Systems GmbH and Synthacon GmbH

www.cpc-net.com
www.synthacon.biz

Personnel

Heinz J Benninghoff
Sales, CPC

Ansgar Kursawe
R&D, CPC

Martin J H Leitgeb
CEO Synthacon

Company background

CPC was established in 1999 as a spin-off from IMM. Synthacon was established in 2004, acquiring pilot capability from CPC. The two companies work together, and CPC owns 20% of Synthacon.

CPC owns the patents (17 families of patents filed) and manufactures the reactors, while Synthacon provides custom synthesis and custom manufacturing based on CPC technology.

Vision and mission

The vision for the foundation of CPC was: 'seamless small molecule synthesis from discovery through to manufacturing', and its stated mission is: 'accelerate drug development and eliminate synthesis transfer risk'.

Vital statistics

- Turnover: ~€2 million (£1.4 million) for CPC, ~€1 million (£0.7 million) for Synthacon

- Employees: 10 CPC, 20 Synthacon
- Ownership: private
- Funding: undisclosed
- Profit: undisclosed
- Projects: ~40 research units sold to chemical companies and universities globally; at least one customised manufacturing system sold to Clariant (for production of pigments of improved quality)

Technology

CPC is specialised in microreaction technology. The heart of CPC is the patented CYTOS microreaction technology. CYTOS is a standard and highly optimised integrated preheater, mixer, cooler, residence-time module, assembled by metal diffusion bonding. It comes in three sizes, each one targeted at a specific stage of the molecule development process (Exhibit A.1).

Module	Experiment size	Application
CYTOS M System	200 mg – 20 g	Route scouting, library synthesis, process development
CYTOS Lab System	2 g – 20 kg	Process development, kg synthesis, building blocks
CYTOS Pilot System	20 kg – 20 t	Fast 100 kg production
CYTOS Production	2,000 t/y	

Exhibit A.1 *CPC's CYTOS modules*

The technology uses massive parallel scale-up, ie there are more channels in the bigger versions but the fundamental transformations are the same, so the behaviour is identical. Within the ranges the scale-up concept is several times proven by CPC.

The M System is particularly indicated in those conditions where there is an extremely limited or expensive supply of reagents.

The reactor is integrated in a fully controllable module that can automate up to 50 different reaction conditions, with flows from 20 µl/min to 2 ml/min, temperature between -60 and 300ºC, including sequential synthesis.

The Lab System is more flexible and the flow rate is higher. Residence time modules up to 135 min can be added.

The Pilot System actually comprises 11 parallel Lab modules, each independently controlled.

Technically, the advantage of performing a reaction in a microreactor is stemming from:

- **Mixing:** very fast and uniform mixing by diffusion; typical reaction channel is 200 µm diameter, and one of the ingredients is added in a series of openings of ~60 µm at the beginning of the channel; this creates a series of striations with a dimension of 30 µm, where diffusion mixing is facilitated
- **Heat transfer:** greatly improved thanks to the high surface-to-volume ratio; the heat transfer coefficient is ~2,800 W/m^2 K (or 30,000 kW/m^3 K; for comparison a Mettler-Toledo reaction calorimeter RC1 has 7 kW/m^3/K)
- **Small volume:** flame-arresting effect of microchannels coupled with very small hold-up of reagents; the Pilot System is rated at up to 6 bar

The consequences on the production are better yields and selectivities, potentially resulting in lower costs, fast time to market and improved safety (including ability to handle unstable intermediates).

The CYTOS modules are not recommended in case of:

- Slow reactions
- Reactions starting or finishing with suspensions
- Reactions using or generating gases

- Incompatibility with stainless steel or hastelloy
- Highly viscous liquids (microtechnology allows operation at higher temperature, which lowers the viscosity)

A.15 ThinXXS Microtechnology AG

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On Friday 28 April 2006 the mission was hosted by the co-founders of the company, Dr Hans-Joachim Hartmann who presented the company and Dr Lutz Weber who led the tour of the facilities.

The Zweibrücken site was occupied by IMM at the request of the local region and linked to the local university, colleges and schools to assist with inward investment and job creation after the withdrawal of military personnel at the end of the Cold War. This model of locating microfluidics activity in old barracks has been followed elsewhere in Germany in the area of Freiburg, where HSG-IMIT is linked to the University of Freiburg.

IMM relocated its polymer micromoulding capability including precision mould tool fabrication and injection moulding machines. The founders and employees (12) of ThinXXS were previously employed by IMM; in the case of Dr Hartmann for 10 years where he was previously head of microfluidics.

The company's initial funding was supplied by the founders using the Government's unsecured loans programme to stimulate start-ups. Funding has also been obtained from 'Pricap', which is a group of 20-30 individuals. One of these individuals has become personally and proactively involved.

ThinXXS has access to the facilities of IMM on an open-accesss basis and has located ThinXXS machinery and employees in the IMM facility. ThinXXS was established to provide a route to manufacture using IP licensed from IMM.

The history of the company, since being established in 2001, has been to work with OEMs on a development contract basis and to provide a route to component and module manufacture to meet the needs of the customers it has worked with during the product development phase.

The company is focused on supporting emerging microfluidics applications where there is forecast to be a requirement for high volumes of components. These are markets driven by the expectation that healthcare diagnostics and environmental monitoring will become increasingly decentralised and portable, involving analysis of increasingly smaller sample quantities at the point of use and care. However, currently as elsewhere, its current customers are developing lab-on-a-chip devices mainly for in-lab use.

Appendix B

MISSION TEAM AND ITP CONTACT DETAILS

B.1 David Anthony Barrow
B.2 Martin James Day
B.3 Yulong Ding
B.4 Yiton Fu
B.5 Simon Robert Gibbon
B.6 Timothy George Ryan
B.7 Alberto Simoncelli
B.8 Nicola Smoker (ITP)
B.9 Julian Darryn White
B.10 Kevin John Yallup

B.1

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Founded in 1883, Cardiff is internationally recognised as being among the very top tier of Britain's research intensive universities and is a member of the prestigious Russell Group of leading universities. It has over 5,000 employees engaged in teaching and research.

DTI has established a network of open access facilities in MicroNanoTechnology (MNT). metaFAB is a new MNT network node and integrates the resources of diverse research centres and supply chain partners to offer innovative, high-level solutions based MNT convergence.

One strong component of metaFAB is its multidisciplinary activities in microfluidics and the new metaFAB Extreme Laser Facility which features a unique dual femtosecond/157 nm excimer laser machining station. This is ideal for rapid micromachining of fluidic structures in UV transmissive materials such as fused silica and fluoropolymers.

Platform technologies

- Multiphase microfluidics, encapsulation
- 157 nm laser micromachining

Areas for potential collaboration

- Emulsion formation
- Microseparations devices
- Laser micromachining of fluidic devices from fluoropolymers
- PEEK
- Fused silica
- Microreactor scale-out
- New company formation

B.2

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Carclo Technical Plastics specialises in injection moulding and assembly of high-volume diagnostic, optical, medical and pharma applications. It is a service company that manufactures for blue chip OEMs in Europe and the USA.

Turnover is £16 million with 250 employees. Facilities are based in Mitcham, South London and Slough. Group facilities are located elsewhere in the UK, USA, Czech Republic, China and India.

The business also focuses on technology development and has a large engineering staff to support this direction.

Platform technologies

- Injection moulding
- Assembly
- Plastics welding
- Plastics printing
- Optical design
- Mould tooling
- High-quality optical polishing
- Optical coating
- Plasma coating
- Ink-jet deposition

Areas for potential collaboration

- Fine feature tooling
- Optical design and readers
- Surface coating

B.3

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The University of Leeds is one of the UK's most popular universities, particularly in medicine, history, psychology, law, English, accounting and finance, management studies, theatre and performance, dentistry and geography. It is one of the top 10 universities in the UK in terms of research power, market share of research funding and number of applicants.

The university of employs 7,581 staff members. It currently has 32,241 students and an additional 32,062 on short courses. Its annual turnover is £345 million.

Platform technologies

- Nanoparticles
- Nanofluids
- Nanofluidics
- Scale-up
- Transport Phenomena

Areas for potential collaboration

- Multiphase flow, mixing and heat transfer in microfluidic channels
- Control of flow in microfluidic systems using noninvasive methods

B.4

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Unilever is one of the world's largest fast-moving consumer good companies. Its corporate purpose is to add vitality to life by meeting the everyday needs for nutrition, hygiene and personal care with brands that help people feel good, look good and get more out of life. The company employs 250,000 people worldwide and the annual turnover for 2005 is ~€40 billion (~£28 billion).

Platform technologies

- Microfluidics
- Miniaturised devices and systems

Areas for potential collaboration

- Point of sale/point of use manufacturing/delivery
- Function added packaging
- Microfluidic based portable devices for analytical and diagnostics applications
- R&D facilities for product formulation, material processibility etc
- Novel material processing/manufacturing techniques

B.5

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ICI creates, develops and markets products that make the world look brighter, taste fresher, smell sweeter and feel smoother: paint, food ingredients, fragrances, personal care, electronic adhesives, packaging adhesives, speciality polymers.

The ICI Group is an international business. It employs more than 33,000 people worldwide. Its product range is 50,000 strong and in 2004 its sales touched £5.6 billion.

The ICI Group comprises the international businesses of National Starch and Chemical Company, Quest International, Uniqema and ICI Paints – as well as the Regional & Industrial Group, made up of businesses which are more regional in their scope with principal locations in India, Pakistan and Argentina.

ICI Strategic Technology Group is ICI's corporate research centre based in the North-East of England, comprising 60 technologists.

Platform technologies

- Speciality chemical manufacture
- Formulation science

Areas for potential collaboration

- Chemical production using microfluidics
- Controlled delivery using microfluidics
- Formulation investigation using microfluidics

B.6

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Epigem's business is polymer microengineering for the optoelectronics and microsystems (MNT) industries. The company develops and manufactures components and modules for chemicals, electronics and instrumentation companies by integrating, for example, micro-optic, microelectronic and microfluidic technologies. Film wet coating and embossing/imprinting services are also offered.

Epigem is MNT Quality Mark and ISO 9001:2000 certified for all processes, and 'Investors in People' certified. Epigem was a finalist in the MX-2005 Manufacturing Excellence Awards in the Customer Focus and Best SME categories.

The company employs 12 people with a 2005 turnover of £920,000.

Platform technologies

Products supplied by Epigem are interconnect components providing micro-optical, microelectronic and microfluidic functionality. Epigem's facilities include a manufacturing line for microfluidic components and modules and a film coating/embossing pilot line for polymer waveguide manufacture that is also used for polymer display, auto ID and disposable sensors development. All Epigem's processes are scaleable by either batch or reel-to-reel manufacture. Energy/environment friendly additive processes are used. Technology owned by the company includes 3D interconnection of microfluidic channels; novel sealing of glass/silicon parts within a polymer package; integration of micro-optics (diffractive, microlenses, waveguides); fine line electrodes for analysis and process control and fluid handling using integral membrane diaphragm valves; micro- and nanoparticles; nanoporous film.

Areas for potential collaboration

- MNT product development services (polymer MNT specialists)
- Manufacture of microfluidic devices
- Tools to accelerate microfluidic product creation
- Device functions: microvalves, 3D channels and vias fluid interconnection, surface interaction options, micro-electrodes, micro-optics, antifouling
- Design of instrument modules and consumables in biotechnology
- Integration of analysis and process control functions

B.7

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Procter & Gamble (P&G) provides branded products and services of superior quality and value that improve the lives of the world's consumers. It manufactures a wide range of consumer goods for personal care, household and home, health and wellbeing, baby and family and pet nutrition and care. P&G employs over 139,000 people worldwide and has recently acquired Gillette. Group turnover for 2005 was $56.7 billion (~£31.2 billion).

P&G has a strong interest in fluidics processing and is interested in evaluating the potential for microfluidics.

Platform technologies

- Fluids processing

Areas for potential collaboration

- Microfluidics for formula development, novel fluid processing techniques and product quality improvements

B.8

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The DTI Global Watch Service assists UK industry in identifying and accessing new technologies from overseas and to identify collaboration partners for the development and implementation of new technologies.

This activity has three key elements:

- DTI International Technology Promoters (ITPs), who are technology transfer specialists providing UK (and overseas) companies with hands-on assistance with international technology transfer objectives and technology collaborations
- Technology missions, which allow groups of specialists to evaluate technologies that are under development outside the UK
- Information via www.globalwatchservice.com and a magazine – *Global Watch* – highlighting emerging technology developments from across the world

Areas for potential collaboration

- Providing assistance to UK companies seeking technologies and partnerships in mainland Europe, and to European companies seeking technology partnerships and licensees in UK

B.9

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Genapta is a specialist engineering company with core expertise in building optical equipment using narrow core optical fibres. The expertise has evolved into genapta developing full-up microfluidic assay platforms for GSK and academic groups. The device is used in order to test the activity of potential compounds in real time, using less than 0.1% of the material that a conventional test may consume, in fields such as drug discovery.

Single molecule DNA sequencing is also being addressed using genapta's technology. Here the device has the potential to directly read individual base pairs as unwound strands of DNA pass by the reading head.

In 2004/05 the company's turnover was £195,000 with five employees.

Platform technologies

- Optical fluorescence
- Resonant energy transfer
- Fluorescent polarisation
- Laser technology
- Motion control
- Confocal optical measurements
- Single molecule detection
- Reaction kinetics, time resolved

Areas for potential collaboration

- Optical microfluidic instrumentation, methods and new applications

B.10

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Technology for Industry (TFI) is a specialised consultancy that focuses on the commercialisation of micro- and nanotechnology (MNT). Over the last 14 years TFI has become the market leader in the MNT consultancy sector in the UK and has successfully carried out projects in Europe, Canada and the USA. TFI has extensive knowledge in the field of microfluidics which is one of the more promising MNT technologies in the short to medium term and has the potential to cause significant disruption across a wide range of market sectors.

TFI works with industry, regional and national governments and academics to help them address the challenges of turning new technology into profitable businesses. TFI has a good understanding of both the end-user markets for MNT and the technologies and is able to facilitate the process of finding new technologies for companies looking to strengthen their existing products, finding new markets for suppliers of technologies and identifying the best strategy for maximising return on investment for public and private investors in technology.

TFI has particular skills and experience in:

- Industrial sectors such as medical, pharmaceutical, advanced engineering, chemical
- Universities and research organisations
- Technology companies – working in areas such as microfluidics, biotechnology, microsystems technology, nano particles and coatings, microelectronics and photonics

TFI employs eight people and has a turnover of €530,000 (~£370,000).

Platform technologies

- Microfluidics
- Biotechnology
- Microsystems technology
- Nano particles and coatings
- Microelectronics and photonics

Areas for potential collaboration

- Commercialisation of technologies
- Benchmarking
- Development of roadmaps for technologies, products and applications
- Finding partners

Appendix C

LIST OF EXHIBITS

Appendix D

GLOSSARY

~	approximately
≈	approximately equal to
<	less than
>	greater than
%	per cent
€	euro (€1 ≈ £0.69 ≈ $1.26, Jun 06)
£	pound sterling (£1 ≈ €1.45 ≈ $1.82, Jun 06)
$	US dollar ($1 ≈ £0.55 ≈ €0.80, Jun 06)
µl	microlitre = 10^{-6} l = 10^{-9} m^3
µm	micrometre = 10^{-6} m
µPIV	microparticle image velocimetry
µW	microwatt = 10^{-6} W
2D	two-dimensional
3D	three-dimensional
A	unit of electric current = 1 C/s
AMA	AMA Association for Sensor Technology eV (Germany)
AMT	Applikationszentrum Mikrotechnik Jena – Application Centre for Microtechnology Jena (Germany)
ASE	advanced silicon etching
ATB	Leibniz-Institut für Agrartechnik Potsdam-Bornim eV – Leibniz Institute for Agricultural Engineering Potsdam-Bornim (Germany)
AZM	Anwendungszentrum für Mikrotechnik – Application Centre for Microengineering (BESSY, Germany)
bar	unit of pressure = 10^5 Pa
BESSY	Berliner Elektronenspeicherring-Gesellschaft für Synchrotronstrahlung mbH (Germany)
BIOS	Lab-on-a-Chip Group (University of Twente, Netherlands)
BMBF	Bundesministerium für Bildung und Forschung – Federal Ministry of Education and Research (Germany)
BMWi	Bundesministerium für Wirtschaft und Technologie – Federal Ministry of Economics and Technology (Germany)
^{o}C	degrees Celsius
C	coulomb – unit of electric charge
CAD	computer-aided design
CCD	charge-coupled device
CCLRC	Council for the Central Laboratory of the Research Councils (UK)
CE	capillary electrophoresis
CEO	Chief Executive Officer
CFO	Chief Financial Officer
cm	centimetre = 0.01 m
cm^3	cubic centimetre = 10^{-6} m^3
CO_2	carbon dioxide

CPC	Cellular Process Chemistry Systems GmbH (Germany)
CSEM	Centre Suisse d'Electronique et de Microtechnique – Swiss Centre for Electronics and Microtechnology
CTO	Chief Technology Officer
D	Germany
DBU	Deutsche Bundesstiftung Umwelt – German Environment Foundation
DECHEMA	Gesellschaft für Chemische Technik und Biotechnologie eV – Society for Chemical Engineering and Biotechnology (Germany)
DFG	Deutsche Forschungsgemeinschaft – German Research Foundation
DGFC	direct glucose fuel cell
DNA	deoxyribonucleic acid
DRIE	deep reactive ion etching
DTI	Department of Trade and Industry (UK)
EC	European Commission
ERDF	European Regional Development Fund (EC)
ESTEC	European Space Research and Technology Centre (Netherlands)
EU	European Union
F	fax
FAMOS	Fraunhofer Alliance for Modular Microreaction Systems (Germany)
FDA	Food and Drug Administration (USA)
FMCG	fast-moving consumer goods
FPP	Faraday Packaging Partnership (UK)
FTE	full-time equivalent
FZK	Forschungszentrum Karlsruhe (Germany)
g	gram = 0.001 kg
GC	gas chromatography
GSK	GlaxoSmithKline plc (UK)
h	hour = 3,600 s
hl	hectolitre = 100 l
HPC	home and personal care
HPLC	high-performance liquid chromatography
HSG-IMIT	Institut für Mikro- und Informationstechnik der Hahn-Schickard-Gesellschaft eV (Germany)
Hz	hertz – unit of frequency = 1 cycle/s
IAF	Fraunhofer-Institut für Angewandte Festkörperphysik – Fraunhofer Institute for Applied Solid-State Physics (Germany)
ICES/KIS	Interdepartementale Commissie voor Economische Structuurversterking/ Kennisinfrastructuur (working group, Netherlands)
ICI	Imperial Chemical Industries PLC (UK)
ICT	(1) information and communication technology (2) Fraunhofer-Institut für Chemische Technologie – Fraunhofer Institute for Chemical Technology (Germany)
ID	identification
IGB	Fraunhofer-Institut für Grenzflächen- und Bioverfahrenstechnik – Fraunhofer Institute for Interfacial Engineering and Biotechnology (Germany)
IMM	Institut für Mikrotechnik Mainz GmbH – Institute for Microtechnology Mainz (Germany)
IMPULSE	Integrated Multiscale Process Units with Locally Structured Elements (project, EC)

IMS	Fraunhofer-Institut für Mikroelektronische Schaltungen und Systeme – Fraunhofer Institute for Microelectronic Switching and Systems (Germany)
IMTEK	Institut für Mikrosystemtechnik – Institute of Microsystem Technology (University of Freiburg, Germany)
IP	intellectual property
IPA	Fraunhofer-Institut für Produktionstechnik und Automatisierung – Fraunhofer Institute for Manufacturing Engineering and Automation (Germany)
IPK	Fraunhofer-Institut für Produktionsanlagen und Konstruktionstechnik – Fraunhofer Institute for Production Systems and Design Technology (Germany)
IPM	Fraunhofer-Institut für Physikalische Messtechnik – Fraunhofer Institute for Physical Measurement Techniques (Germany)
IPR	intellectual property rights
ISE	Fraunhofer-Institut für Solare Energiesysteme – Fraunhofer Institute for Solar Energy Systems (Germany)
ISFET	ion-sensitive field-effect transistor
ISO	International Organization for Standardization
ITP	International Technology Promoter (network, DTI)
IVAM	Interessengemeinschaft von Unternehmen und Instituten aus der Mikrosystemtechnik – Association of Companies and Institutes in Microsystem Technology (Germany)
IZM	Fraunhofer-Institut für Zuverlässigkeit und Mikrointegration – Fraunhofer Institute for Reliability and Microintegration (Germany)
J	joule = 1 N m = 1 W s
JV	joint venture
K	kelvin – unit of temperature
kg	kilogram
KOH	potassium hydroxide
KTN	Knowledge Transfer Network (UK)
kW	kilowatt = 1,000 W
l	litre = 0.001 m^3
LICOM	Liquid Handling Competence Centre (Germany/international)
LPCVD	low-pressure chemical vapour deposition
m	metre
m^2	square metre
m^3	cubic metre
M&A	merger and acquisition
mA	milliampere = 0.001 A
MANCEF	Micro and Nano Commercialization Education Foundation (USA)
mbar	millibar = 0.001 bar = 100 Pa
MCB	Microsystems Centrum Bremen (Germany)
MEMS	micro-electro-mechanical systems
mg	milligram = 0.001 g = 10^{-6} kg
min	minute
MINAC	Microsystem and Nanotechnology Cluster (Netherlands)
MIT	Massachusetts Institute of Technology (USA)
ml	millilitre = 0.001 l = 10^{-6} m^3
mm	millimetre = 0.001 m
mm^2	square millimetre = 10^{-6} m^2

MNT	micro- and nanotechnology
mPa	millipascal – unit of pressure = 0.001 Pa
MST	microsystems technology
MW	megawatt = 10^6 W
N	newton – unit of force = 1 kg m/s^2
N/A	not available
NEDO	New Energy and Industrial Technology Development Organisation (Japan)
NEPUMUC	New Eco-efficient Industrial Process Using Microstructured Unit Components (project, EC)
NIR	near infrared (radiation)
nl	nanolitre = 10^{-9} l = 10^{-12} m^3
NL	Netherlands
nm	nanometre = 10^{-9} m
NMR	nuclear magnetic resonance
NRW	North Rhine-Westphalia (state, Germany)
OEM	original equipment manufacturer
P&G	Procter & Gamble
Pa	pascal – unit of pressure = 1 N/m^2
PDMS	polydimethyl siloxane
PDRA	postdoctoral research associate
PECVD	plasma-enhanced chemical vapour deposition
PEEK	polyetheretherketone
PEM	polymer electrolyte membrane
pH	potential of hydrogen (measure of acidity or alkalinity)
PhD	Doctor of Philosophy
PIV	particle image velocimetry
pl	picolitre = 10^{-12} l = 10^{-15} m^3
plc/PLC	public limited company
PMMA	polymethylmethacrylate
QA	quality assurance
QC	quality control
R&D	research and development
RF	radio requency
RFID	radio frequency identification
s	second
S&T	science and technology
SIMM	slit interdigital micro mixer
SME	small or medium sized enterprise
t	tonne (metric ton) = 1,000 kg
T	telephone
TFI	Technology for Industry Ltd (UK)
TNO	Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek – Netherlands Organisation for Applied Scientific Research
TU	Technische Universiteit – Technical University (University of Technology)
UK	United Kingdom
US(A)	United States (of America)
UV-VIS	ultraviolet-visible (radiation)
VC	venture capital

VDI	Verein Deutscher Ingenieure eV – Association of German Engineers
VDMA	Verband Deutscher Maschinen- und Anlagenbau – German Engineering Federation
vs	versus
W	watt – unit of power = 1 J/s
Wh	watt-hour = 3,600 J
y	year
ZEMI	Zentrum für Mikrosystemtechnik – Centre for Microsystems Technology (Germany)
ZMN	Zentrum für Mikro- und Nanotechnologien – Centre for Micro- and Nanotechnologies (Technical University of Ilmenau, Germany)
ZVEI	Zentralverband Elektrotechnik- und Elektronikindustrie eV – Electrical and Electronic Manufacturers' Association (Germany)

Other DTI products that help UK businesses acquire and exploit new technologies

Grant for Research and Development – is available through the nine English Regional Development Agencies. The Grant for Research and Development provides funds for individuals and SMEs to research and develop technologically innovative products and processes. The grant is only available in England (the Devolved Administrations have their own initiatives).
www.dti.gov.uk/r-d/

The Small Firms Loan Guarantee – is a UK-wide, Government-backed scheme that provides guarantees on loans for start-ups and young businesses with viable business propositions.
www.dti.gov.uk/sflg/pdfs/sflg_booklet.pdf

Knowledge Transfer Partnerships – enable private and public sector research organisations to apply their research knowledge to important business problems. Specific technology transfer projects are managed, over a period of one to three years, in partnership with a university, college or research organisation that has expertise relevant to your business.
www.ktponline.org.uk/

Knowledge Transfer Networks – aim to improve the UK's innovation performance through a single national over-arching network in a specific field of technology or business application. A KTN aims to encourage active participation of all networks currently operating in the field and to establish connections with networks in other fields that have common interest.
www.dti.gov.uk/ktn/

Collaborative Research and Development – helps industry and research communities work together on R&D projects in strategically important areas of science, engineering and technology, from which successful new products, processes and services can emerge.
www.dti.gov.uk/crd/

Access to Best Business Practice – is available through the Business Link network. This initiative aims to ensure UK business has access to best business practice information for improved performance.
www.dti.gov.uk/bestpractice/

Support to Implement Best Business Practice – offers practical, tailored support for small and medium-sized businesses to implement best practice business improvements.
www.dti.gov.uk/implementbestpractice/

Finance to Encourage Investment in Selected Areas of England – is designed to support businesses looking at the possibility of investing in a designated Assisted Area but needing financial help to realise their plans, normally in the form of a grant or occasionally a loan.
www.dti.gov.uk/regionalinvestment/

The DTI Global Watch Service provides support dedicated to helping UK businesses improve their competitiveness by identifying and accessing innovative technologies and practices from overseas.

Global Watch Information
Global Watch Online – a unique internet-enabled service delivering immediate and innovative support to UK companies in the form of fast-breaking worldwide business and technology information. The website provides unique coverage of UK, European and international research plus business initiatives, collaborative programmes and funding sources.
Visit: www.globalwatchservice.com

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Global Watch Missions – enabling teams of UK experts to investigate innovation and its implementation at first hand. The technology focused missions allow UK sectors and individual organisations to gain international insights to guide their own strategies for success.
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Global Watch Technology Partnering – providing free, flexible and direct assistance from international technology specialists to raise awareness of, and provide access to, technology and collaborative opportunities overseas. Delivered to UK companies by a network of 23 International Technology Promoters, with some 8,000 current contacts, providing support ranging from information and referrals to more in-depth assistance with licensing arrangements and technology transfer.
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