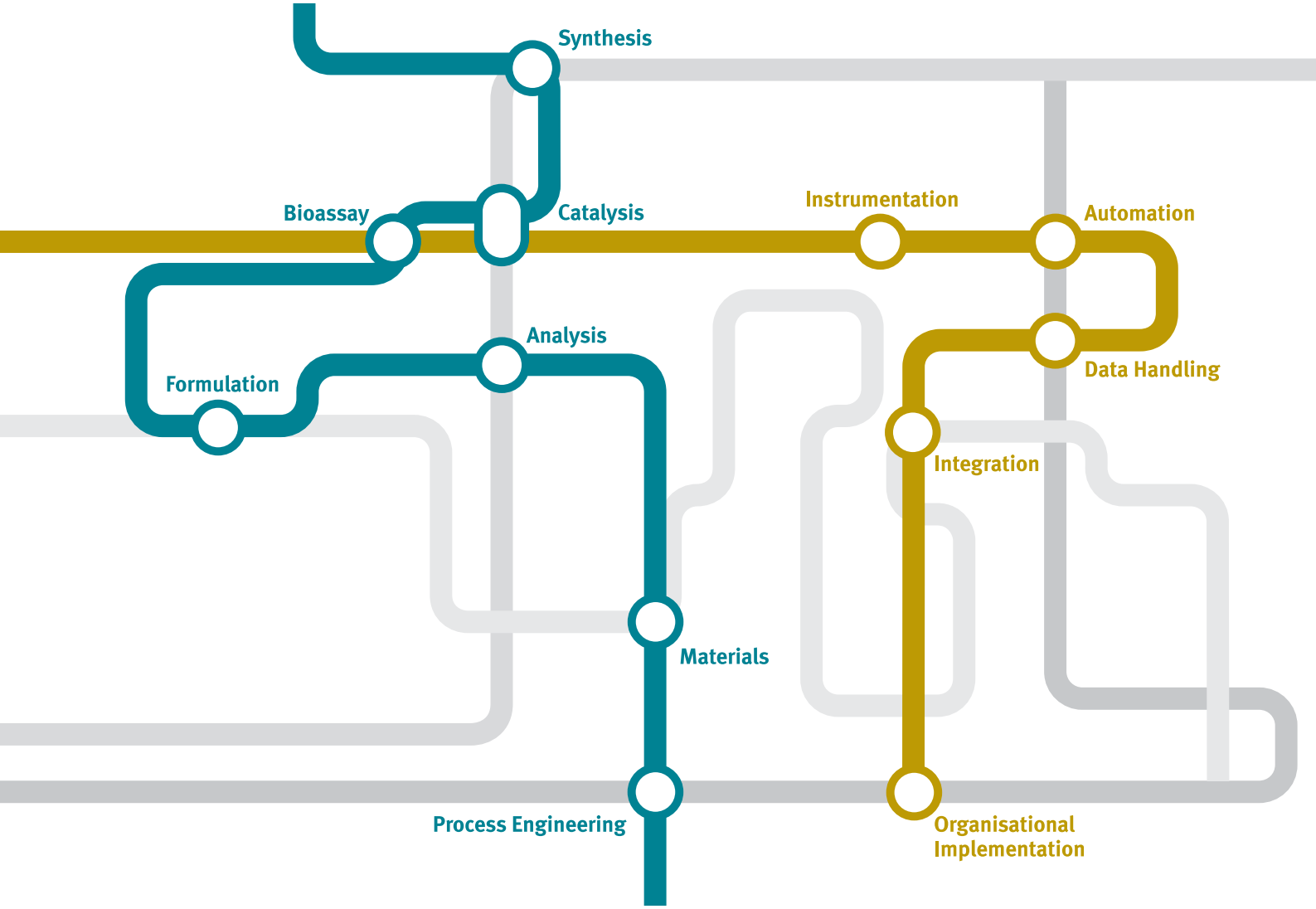
Insight
High throughput technologies

A Roadmap for High Throughput Technologies



- economic benefit
- industry sectors
- skills and capabilities
- access to facilities
- action plan

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An executive summary of this technology roadmap is available from InsightFaraday.
www.insightfaraday.org

Introduction

The Technology Roadmap and its purpose

The InsightFaraday Partnership's role is to stimulate knowledge transfer between industry and the knowledge base to increase the rate of innovation in the UK by focusing on the exploitation of High Throughput Technology (HTT) applied to new product and process development.

This technology roadmap is a unique framework for quantifying the value of HTT to the UK and for developing a strategy to optimise its exploitation by industry, academe and indeed society as a whole. Although the starting point for this roadmap is the current status of HTT in the UK the aim is to create a dynamic document which will be reviewed and updated regularly by InsightFaraday.

The contents of the roadmap are based on information gained from three major consultation events, in addition to multiple company visits. In particular our consultation event held in London on 3rd March 2004, attended by representatives from 50 companies in diverse industry sectors, provided the bulk of the data. Whilst there were a number of very important and significant inputs from academics, the majority of the information has come directly from industry – hence it is very much an industry driven roadmap.

In general terms, a technology roadmap provides a framework to develop and share a "big-picture" view of the economic impact of a technology and to define strategic actions to optimise its exploitation. There are some key recommendations for industry, academe and government on what needs to be done in order to stimulate the uptake of HTT.

For InsightFaraday, the roadmap will help focus our effort and resources on how HTT can deliver significant improvements in industrial and academic R&D, both through defining the potential opportunities and also identifying the major constraints and barriers to achieving these goals. It identifies:

- what will a successful future look like?
- what are the constraints to achieving this?
    - knowledge and skills
    - science and technology
    - economic
    - cultural

It will also guide the allocation of resources, for example:

- which investments and initiatives can remove the constraints & so accelerate implementation?
    - research themes
    - knowledge transfer activities:
        - education and training
        - technology transfer
        - technology and partnership brokering

What are High Throughput Technologies?

High Throughput Technology (HTT) is the generic name associated with an expanding range of advanced experimental and computational tools and techniques that enable very rapid, intelligently applied parallel experimentation to significantly increase the productivity of R&D over traditional approaches. The real value of these tools lies in their ability to enable:

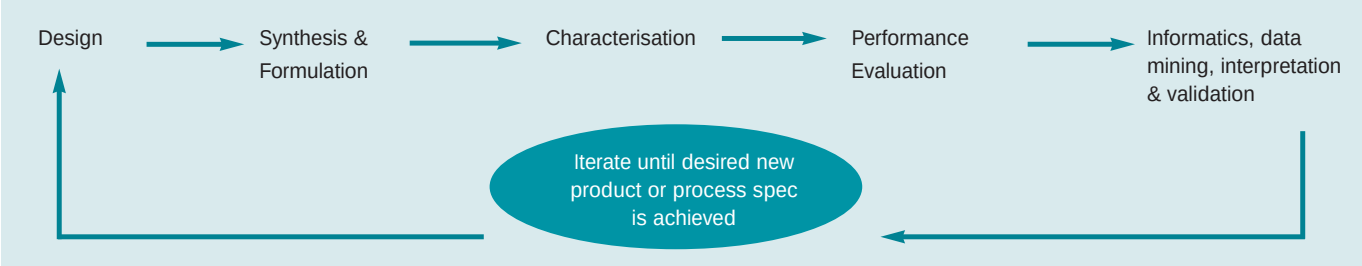
- faster discovery and optimisation of new compounds and materials with specific properties and effects
- better understanding of the parameters relating to synthesis, process development and manufacturing
- new science which would be difficult or impossible with conventional equipment and processes.

Although the origins of HTT lie in the pharmaceutical sector's automation of new drug discovery, its potential range of application is revealed by this roadmap.

Tools and techniques normally associated with HTT include laboratory automation, miniaturisation and parallelisation, combinatorial chemistry and parallel synthesis, high throughput screening, rapid continuous processing, effective design of experiments (DoE), complex data visualisation and interpretation, modelling and in-silico screening. HTT also encompasses new platforms capable of increasing throughput even further, such as microfluidic systems and microarrays, and novel approaches to intelligent experimentation. The application of HTT requires a true multi-disciplinary approach.

It is worth emphasising that, contrary to the widely held perception in the early days of high throughput chemistry, HTT does not imply an approach whereby chemists carry out large numbers of random experiments until a new compound or material with the desired properties is found. The numbers of experiments required to obtain successful results from an entirely random experimental design are often unachievable with current technologies, and thanks to scientific rationale it is not necessary or useful to use this purely combinatorial approach. The use of intelligent experimental design and modelling now means that it is possible to rapidly identify likely fruitful areas of experimentation and use HTT to obtain more information in a number of well-focused areas – thus not only identifying new products but also increasing the fundamental understanding of the science and technology.

The real value and benefit of HTT is derived when appropriate tools and techniques are combined into an integrated, iterative cycle:



The Benefits of Exploiting High Throughput Technologies

Sustainable Benefits

InsightFaraday focuses on how new product and process developments are undertaken in manufacturing sectors. In an increasingly competitive global economy the challenge is sustaining growth through innovation. In large part this will be driven through creating and bringing to market exciting new products and novel processes, although other forms of business innovation are just as valid and equally important, for example in the marketing and finance functions. These new products and processes will often be based on technological advances which enable new capabilities to give customers and consumers greater benefits or novel solutions. High Throughput Technology (HTT) aims to impact product and process development practices to significantly increase R&D output and productivity and hence strengthen a businesses intellectual property position and market share. HTT is as much about stimulating new thinking on step changes in ways of working, as it is about particular technologies and their integration into systems for specific applications.

It is important to recognise that HTT impacts not just manufacturing sectors but also the way academic research is undertaken. It impacts on all three dimensions of sustainable development, namely economic, environmental and social, as highlighted below:

Sustainable Benefits from HTT

Economic	Environmental	Social
▸ Value Added ▸ New Products ▸ IP (patents)	▸ Reduce ▸ Reuse ▸ Recycle	▸ Quality of life
In these Key sectors:		
• Energy (oil & gas) • Food & Beverages • Pharmaceuticals • Biotech • Chemicals • Health • Personal care & household • Materials & Metals • Academe	• Sustainable raw materials • Green products & processes • Catalysis • Reformulation • Waste recycling processes • Real time monitoring & analysis	• Healthcare • Security • Crime

HTT can be viewed both as enabling and disruptive, as it can open up new development opportunities across many existing sectors and also fundamentally change the status quo thereby stimulating the emergence of new sectors.

By allowing relatively low-cost exploration of a much wider composition, reaction or parameter space, it is more likely that unpredictable properties or materials will be discovered. Coupled to the data capture, visualisation and process control of HTT, it is

also likely that conditions giving rise to such unpredictable results can be detected and reproduced.

A related source of potential innovation is that automating experimental methods frees up much more "thinking" time for industrial research scientists: long a criticism of the increasing pressure for improved R&D efficiency in the chemical industries.

Equally, patent protection can be strengthened by being able to define the range of chemical composition or performance properties protectable by the invention. This may be critical in the decision on how much risk of disclosure may result from the patent publication process, allowing patent protection for areas which previously have been held as "know-how".

HTT has the ability to find more rapidly sustainable solutions for many of today's and future problems and challenges, by enabling a much larger range of options and opportunities to be explored faster. These will range from finding new chemistry and processing routes for producing a diverse mix of materials from sustainable and renewable raw materials resulting from advances in so-called "precision chemistry", through to enabling customised and personalised products to be developed more rapidly by finding more specific and active compounds and tailored formulations. Precision chemistry will enable exquisite control of transformations at the molecular scale yielding greater efficiency and reducing environmental impact. Some 80% of manufacturing process industries (including pharmaceuticals) that exploit chemistry rely on catalysis, often under extreme conditions in organic media. However, nature can manufacture a huge variety of materials in the more favourable aqueous media and under near ambient conditions. HTT is already making a big contribution to catalyst and catalytic process development, including biocatalysis. It is also important to note that increased R&D productivity should also lead to expanding a business's knowledge base and deepening the understanding of its products and processes which must be of growing importance in a so-called "knowledge-driven economy".

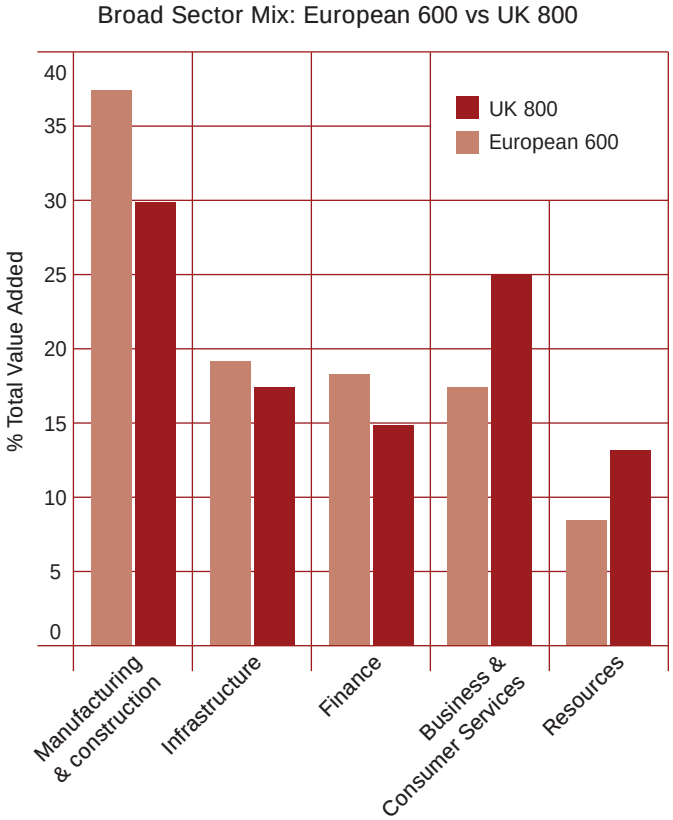
Another sustainability issue that HTT could address is the growing need for environmental risk and impact assessment of new products and processes. More rigorous testing regimes and validation are demanded for a growing range of sectors and applications. One of the biggest challenges is reducing or eliminating animal testing where HTT approaches might generate alternative and superior solutions.

HTT approaches might help the development of systems that "learn" in real-time by monitoring and analysing (including data handling and decision making algorithms) experimentation and testing routines to yield "intelligent dynamic" product and process development against both performance and sustainability criteria.

Finally, quality of life issues such as healthcare, security and crime are already benefiting from HTT approaches to dramatically improve the speed with which diagnostic and forensic data are generated and analysed in laboratories. The next leap will be to there being an increasing array of tests and "intelligent" analyses at or in the person or environment where there is a potential threat or risk.

Benefits to the UK Economy

This section draws on a number of high level UK reports and scoreboards. Sustaining innovation was the focus for the 2003 Innovation Report from the Department of Trade & Industry (see http://www.dti.gov.uk/innovationreport/index.htm). Underpinning this report was an Economic Paper No 7 "Competing in the Global Economy – The Innovation Challenge" which for the first time drew together a comprehensive set of data on the UK's innovation performance (see http://www.dti.gov.uk/economics/). In previous years the DTI had produced a variety of industrial scoreboards (see http://www.innovation.gov.uk/), ranging from the oldest on R&D investment through Capex investment to the most recent on Value Added. All these publications paint a picture of the relative commercial performance of the UK versus other European and international businesses. They also reference international R&D scoreboards such as those from the OECD and the US1000.



There are three key measures identified in the Innovation Report which we will focus on as these can be applied at the national, regional, sector and individual company level, namely:

- Value Added (VA)
- % sales from new products
- Patents

VA is essentially the wealth created by business. VA is defined as sales less the cost of bought-in materials, components and services and can be calculated from data published in company accounts. The DTI's 2004 VA Scoreboard contains details on the top 800 UK and 600 European companies by VA. Even for these larger companies, the range of VA is huge, spanning DaimlerChrysler with £24.2bn to Carclo at £53.8m. It is important to note the sector mix which is very different between the UK and Europe:

Even within these broad sectors there are significant differences between the UK and Europe:

Sectoral Spread of Value Added in UK and Europe

	European 600 Sectors			UK 800 Sectors		
European Top 10 Sectors	**% European 600 VA Sector (% change in sector VA in brackets)**		**Concentration**	**% UK 800 VA in sector (% change in sector VA in brackets)**		**Concentration**
1. Banks	14.0%	(-6%)	13%	1. 10.4%	(-2%)	48%
2. Automotive	7.7%	(+5%)	41%	*2.0%*	*(+10%)*	*35%*
3. Telecomms	6.9%	(-8%)	39%	4. 7.0%	(+20%)	82%
4. Oil & Gas	6.3%	(0%)	41%	2. 10.4%	(0%)	74%
5. Support Services	5.0%	(+1%)	24%	3. 10.4%	(+3%)	31%
6. Transport	4.6%	(+23%)	26%	6. 4.6%	(+3%)	22%
7. Construction	4.6%	(+5%)	20%	10. 4.0%	(+8%)	17%
8. Electricity	3.9%	(+8%)	39%	*1.9%*	*(+20%)*	*39%*
9. Engineering	3.8%	(-1%)	23%	*2.3%*	*(-2%)*	*19%*
10. Utilities	3.8%	(+4%)	45%	*3.4%*	*(+37%)**	*45%*
Food Processors	*3.0%*	*(+4%)*	*56%*	5. 4.7%	(+1%)	57%
General Retailers	*3.2%*	*(+5%)*	*23%*	8. 4.6%	(+9%)	23%
Pharmaceuticals	*3.4%*	*(+0%)*	*43%*	7. 4.6%	(+12%)	81%
Media	*3.4%*	*(-8%)*	*36%*	9. 4.3%	(+3%)	28%

*These were significant changes in the definition and content of this sector between the two years.
Concentration = The proportion of VA added by the top two companies.

This shows that in the UK food processors and pharmaceuticals are key manufacturing sectors. Interestingly, HTT was pioneered within the pharmaceutical sector but is only recently being considered and applied in food processing.

The key inputs for creating VA are skills and investment intensity. The latter consists of R&D and Capex. The data show that there is a correlation between Value Adding efficiency (VA/[employee costs + depreciation]) and investment ie the higher the investment then the higher is the VA efficiency. Examples given include pharmaceuticals with high R&D and oil & gas with high Capex; whereas in services sectors, such as financial services, high skills intensity is required. Companies can therefore simply seek to increase their VA by investing more. However, it is important to consider how effectively that investment is used, ie the productivity of R&D; which is the focus for InsightFaraday. The key argument is that simply increasing investment in R&D is not in itself sufficient to create competitive advantage. One key way of improving R&D productivity is through exploiting HTT to increase the work flow through the experimentation stage. This early approach was adopted in the drugs discovery arena for screening vast numbers of potential compounds. It is debatable how well this has delivered the promised end results. The realisation today is that HTT has to encompass the complete R&D system from design through experimentation to data capture and analysis linked to modelling and simulation, and be integrated with other business functions, particularly business development and marketing.

The desired deliverable is increased output from R&D which should enable it to become better placed to capture new business opportunities. The extent of that increase is not easily quantified and will vary from sector to sector, from application to application and from company to company. However since HTT systems have the potential to increase outputs by several times, if not orders of magnitude, the impact should manifest itself in increased VA. We can take the pharmaceutical sector as a

leading indicator of investment in HTT and their case for it based on increasing their pipeline for new drugs. It has been conservatively estimated that VA could be boosted by up to 5% (Frost & Sullivan Report. 1998, "Opportunities in genomics and associated high throughput screening markets", http://www.mindbranch.com/listing/product/R1-781.html, Datamonitor 2001 "R&D productivity: Getting more bangs for your R&D buck!", http://www.mindbranch.com/listing/product/R313-0050.html).

We can therefore take the data from the VA scoreboard for the most relevant manufacturing sectors where HTT is starting to be or could be applied to estimate the impact of a 5% increase in VA as follows:

Potential gain in VA from HTT

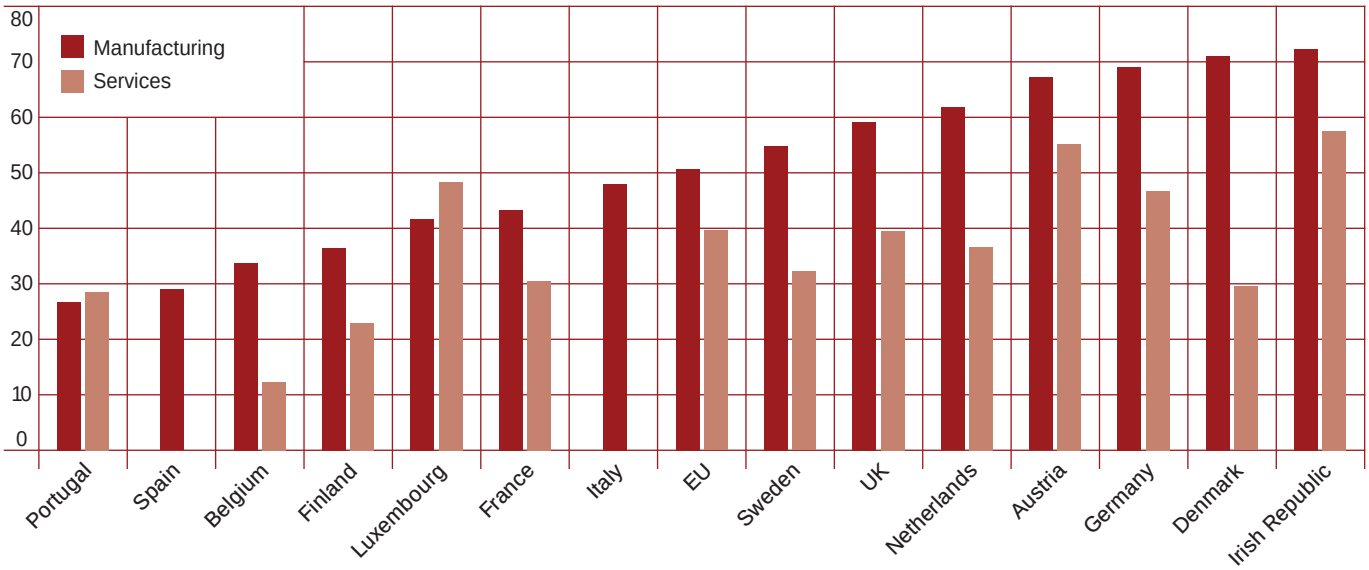
Sector	Total VA £m)	5% increase in VA (£m)	Investment in R&D + Depreciation (£m)
Beverages	8832	442	878
Chemicals	7960	398	1774
Food producers & processors	20914	1045	3283
Health	2791	140	510
Oil & Gas	46404	2320	14089
Personal care & household	2022	101	275
Pharmaceuticals and biotech	20540	1027	7498
Steel & other metals	1864	93	542
Totals for UK	**111327**	**5566**	**28849**

Clearly, growing VA by up to 5% is ambitious but it does highlight the potential gains from investing in HTT as a key element of R&D. Decisions on the scope and benefits from HTT could influence investment to the order of several hundred millions in such sectors as pharmaceuticals & biotech, oil & gas, food processing, beverages, chemicals, health and personal care. In a number of these sectors formulated products are the norm and, as described in later sections of this report, HTT can offer a number of significant advantages.

In other sectors, such as defence or automotive and aerospace, component materials, including ceramics; polymers; textiles; composites etc, are key constituents in their products and processes. Here again HTT can bring gains in invention, design and performance optimisation.

If HTT has the potential to increase productivity in R&D then it should also be highlighted as a key element in the EU Lisbon target of increasing gross expenditure on R&D by 2.4-3% by 2010.

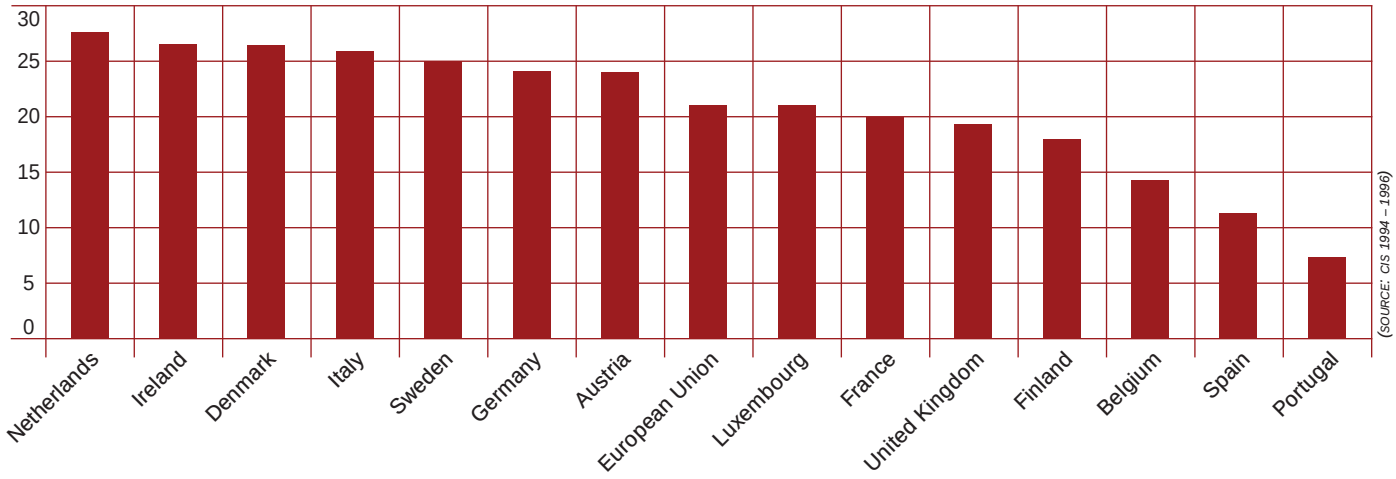
Proportion of enterprises that bring new products or services to market or develop new process technologies, EU comparison, 1994 - 1996



The Community Innovation Survey (CIS) data, included in the Economic Paper No 7 (see page 5), provides further insights into the other two measures of new products and patents.

The chart on page 7 shows that UK manufacturers routinely introduced incremental innovations above the European average.

Proportion of 'novel' innovators by country, manufacturing sector, 1994 – 1996



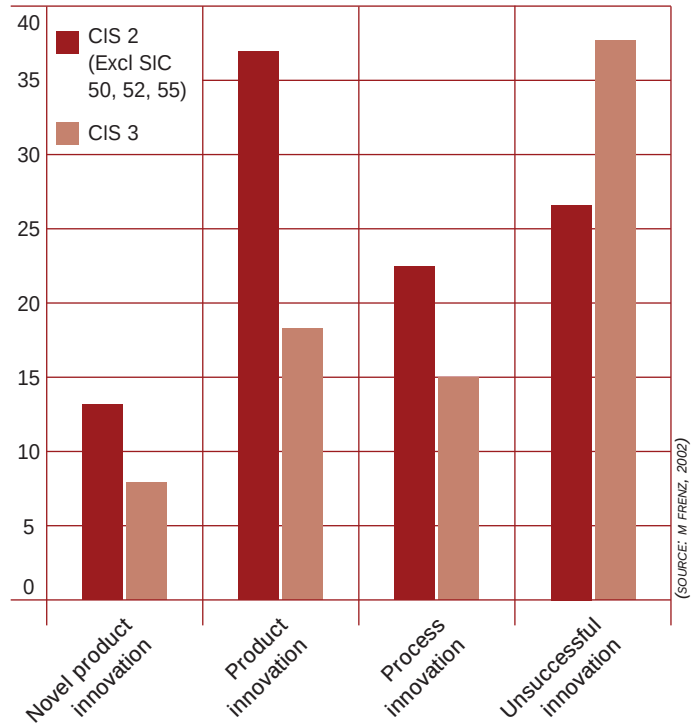
However, the above figure shows that the UK is below the European average for novel (radical) as opposed to incremental innovation and is punching significantly below its weight.

More worrying is the deterioration between the two CIS surveys (CIS2 was carried out in 1997, covering 1994-96, CIS3 was carried out in 2001, covering 1998-2000):

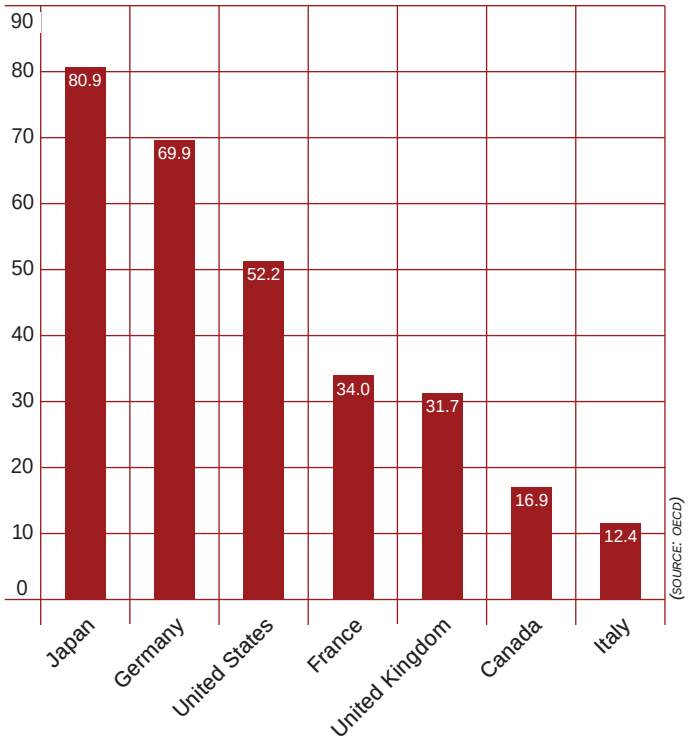
Once again, applying intelligent HTT in product and process development should go some way to redressing the above under performance across a similar set of sectors ie pharmaceuticals & biotech, oil & gas, food processing, beverages, chemicals, health and personal care.

The third measure which is seen as a gauge of invention is patenting. Here the UK is significantly behind the leading industrialised nations:

Output measures of UK innovation in CIS2, CIS3 and changes



Number of "triadic" patent families per million population 1998 (see OECD publication DSTI/DOC (2004) 2)



There are interesting sector differences in the investment per patent where, for example, in pharmaceuticals the number of patents per £10m is low. By contrast trademark performance is significantly higher in the UK, which is interpreted as showing that "innovation in the UK may be more focused on achieving incremental improvements in new product and product quality which justifies new brand names but no patents". There is also evidence that UK business tends to prefer informal rather than formal methods of protecting IP which may reflect studies that show that only 5-10% of patents account for half European value. It is clear that in some countries such as US and Japan, HTT is being exploited to capture significant patent families in fields such as catalysis. The UK could be significantly disadvantaged if it does not respond to this competitive threat. HTT should also benefit product testing and approval procedures to reduce cycle times and speed up time to market, for example, rapid toxicity testing.

Utility and benefits in Industrial Sectors

In broad terms the benefit of any technology base or organisational approach to industry lies in the ability to improve its competitive position: either to catch up with competition so it can stay in the game, or to gain competitive advantage.

Either way, the benefits can be expressed as either:

- Efficiency improvement: ie to be able to enhance R&D efficiency or optimise product design and process of manufacture
- Enhanced innovation: indicated by introduction of new products into the market or developing IP to protect market share

HTT and R&D efficiency

In simple terms there are three avenues to exploit HTT capability in an R&D environment.

i) Doing things more quickly and cheaply

There is clearly benefit in improving R&D productivity using this technology approach. The impact of R&D on value added (VA) is discussed in the above section.

The Pharmaceutical sector is traditionally viewed as the first to adopt HTT methodology, in using high throughput bioassay to increase the screening of discovery compounds and in combinatorial chemistry to significantly enhance the rate of chemical synthesis of small molecular weight organic molecules.

The reasons for adopting the technologies are dependent on the economics and risk/benefit balance of the industrial sector. Pharmaceutical discovery clearly identified the need to explore a much wider range of chemical structures faster and with greater resource efficiency because the ratio of lead chemistry to final marketable medicine is so great (typically millions to one).

It also held the potential to reduce the elapsed time required to identify lead chemistries – promising faster time to market: each day saved in R&D gives an extra day of sales under patent coverage. For a global "blockbuster" drug that could be £2m per day sales.

ii) Doing the "right things" – ie doing things differently

An important factor in HTT approaches within R&D is the ability to carry out the work in a markedly different way and hence respond to escalating challenges associated with R&D i.e. the need to:

- make/measure a wider variety of properties to fulfil more demanding targets
- achieve more robust or more precise effects
- unpick and understand complex, multi-factorial dependencies
- manufacture a larger range of novel, differentiated/tailored products

The ability to carry out product optimisation during the development phase of any product is critical to competitive advantage in the marketplace. This advantage could include product performance characteristics, ie giving the consumer the best performance at a competitive price.

However, the optimisation of product design also ensures that the manufacturing process can be optimised to reduce costs and be robust to variation in process and raw materials. Typically, the ability to explore and understand the "operating" envelope for acceptable product quality requires exploring a very large parameter space – often only accessible through HTT capability in the development phase.

HTT may also allow much more efficient product optimisation by the evaluation of a variety of products against otherwise prohibitive regulatory requirements.

iii) Doing what has been inconceivable

Complex, multi-factorial, dependencies are often a feature of performance of any real-world product. At present, the prevalence of "one variable at a time" experimentation does not allow sufficient ranges of parameter space to be investigated to deliver empirical relationships in these types of problem, let alone populate predictive mathematical models or enable investigation of underlying mechanisms.

As discussed in more detail in the section on academic science, there is real potential for the enormous improvement in data generation by HTT to address this issue for complex, real-world problems. One consequence of this will be improved correlative or mechanism based predictive models, which are likely to provide potential for paradigm-shifts in product design, particularly in formulated products.

This, coupled with the potential to intensify manufacturing processes, opens up opportunities to develop tailored, unique products, optimised for specific purposes to maximise the value of sales into differentiated markets.

High Throughput Technologies for Drug Discovery

In pharmaceutical companies the capability to improve R&D drug discovery efficiency, reducing direct costs and also increasing speed to market is critical to the future of the industry. To achieve even a 10% annual growth rate, leading Pharmaceutical companies need to bring 3–5 major new products to market each year. Average annual new drug approvals in the U.S. doubled from the 1970s to the 1990s, while R&D costs more than quintupled (i.e., the industry is spending incrementally more than double for what it delivers). Currently, it is estimated that 75% of the total cost of research to discover and develop a successful new therapeutic product is expended on products that ultimately fail.

Use of high throughput capability in drug discovery has been estimated to reduce Pharmaceutical R&D costs by up to a factor of 10. Future capabilities will allow faster and more robust early stage screening of complex whole cell physiology for early identification of unacceptable metabolism or toxicity, reducing R&D costs lost on failed drug candidates. There is also longer term potential to develop early stage screening methods for disease targets.

On the supply side, direct sales of instrumentation products and services (including contract R&D and analytical services) constitutes a $1.2 billion market supporting drug candidate discovery. New technologies such as microfluidic chips could also target a projected 2005 global market value of $1bn in research tools, $20bn market in clinical diagnostics and a $7bn market in analytical applications.

There is as increasing demand for early stage screening and evaluation of toxicology of new and existing chemicals in a variety of sectors other than the pharmaceutical sector. This promises to boost demand for HT technologies.

HTT and industrial Innovation

In addition to improved efficiency, there is also a key role in harnessing the capability of HTT to strengthen innovation.

It is clear from the above examples that this approach should enhance the ability to generate novel and differentiated products. Similarly, by allowing relatively low-cost exploration of a much wider composition, reaction or parameter space, it is more likely that unpredictable properties or materials will be discovered. Coupled to the data capture, visualisation and process control of HTT, it is also likely that conditions giving rise to such unpredictable results can be detected and reproduced.

A related source of potential innovation is that automating experimental methods frees up much more "thinking" time for industrial research scientists: long a criticism of the increasing pressure for improved R&D efficiency in the chemical industries.

Equally, patent protection can be strengthened by being able to define, with minimal additional technical effort, the range of chemical composition or performance properties protectable by the invention. This may be critical in the decision on how much risk of disclosure may result from the patent publication process, allowing patent protection for areas which previously have been held as "know-how".

Utility and benefits in Academic Science

In general terms, industrial users have been in the vanguard of developing and applying high throughput methodologies. In most cases, these have been driven by the need to enhance experimental efficiency, for example, to be able to make much larger numbers of compounds for drug discovery.

However, there are a variety of advantages to the use of this approach in academic science. This applies to scientific groups who are not, themselves, researching the core area of high throughput methodologies. It can readily be used as a tool in any investigative scientific programme.

Use of automated experimentation releases highly skilled staff from "mundane" experimentation which would otherwise provide little opportunity for training or scientific or intellectual discovery.

Some of these deliver the same type of benefit, eg improving the efficiency with which routine experimentation can be carried out and providing opportunities to explore a greater range of experimental space within the lifetime of a given project. This may provide opportunities to ask a wider range of "questions" within a given research project, or provide better quality data with which to test hypotheses or populate predictive models.

Perhaps more importantly, the ability for experimental determination of a very large range of parameter space can provide a paradigm shift in the approach to a number of investigative science areas. In traditional scientific methodology, experiments are ideally set up to follow a well defined observable while changing a single control parameter in order to determine the cause-effect relationship. In many systems, this is not achievable because the system under study does not lend itself to the scientist being able to fix all important variables but one.

It is particularly problematic to apply this methodology in programmes investigating complex systems, ie those in which the observable end-point depends simultaneously on multiple parameters, and these parameters are themselves interdependent. Multi-factorial experimental design can be used to investigate these multi-functional dependencies, but typically require very large experimental programmes to fully understand the interdependent relationships. Often, traditional experimental methods do not allow researchers the capacity to carry out such investigations.

Clearly, high throughput experimentation can provide the capability to investigate such systems, by allowing the very large numbers of experiments required to be carried out within a realisable time and cost. This opens the possibility of being able to understand phenomena which simply could not be sensibly investigated by traditional experimentation.

Another category of investigative experimentation which can also benefit enormously from increased numbers of experiments is that involving cause-effect studies involving biological systems. In addition to the multi-factorial nature of such systems, there is also a recognition that such systems are much more susceptible to "random" noise than physico-chemical systems. Typically this is dealt with by applying statistical averaging of data to obtain correlations within a confidence limit which is highly sensitive to the repeat number of the experiment (typically confidence improves as the square of the number of repeated observations). Therefore, being able to carry out 10,000 readings, rather than 100, doubles the confidence of interpreting a cause-effect correlation.

There are many examples where the ability to understand correlations in biological systems depends on better quality of data: HTT offers a means of obtaining this improved data quality which could provide significant new insight into biological mechanisms and functionality.

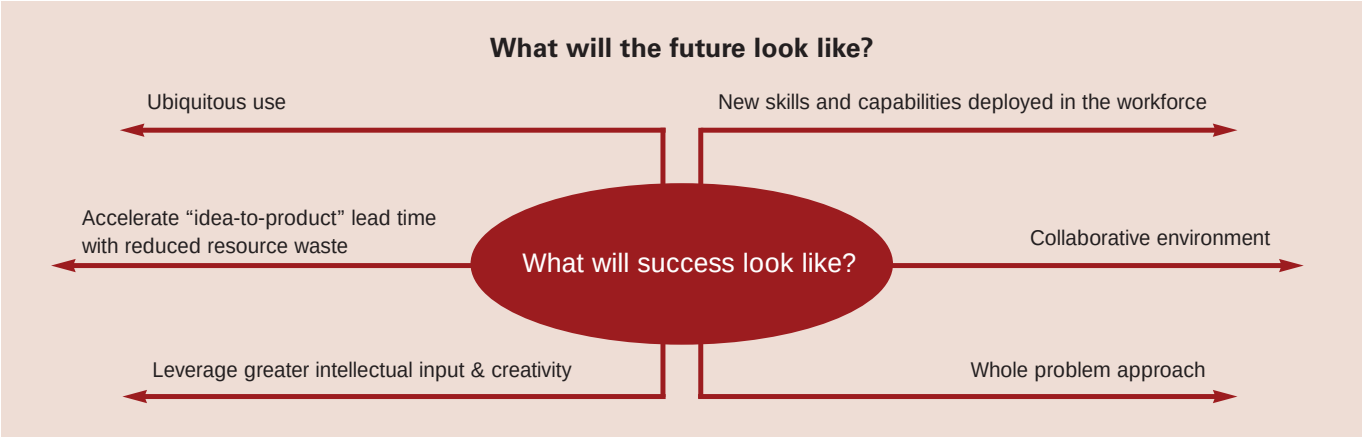
A vision of a successful future

Clearly, there are significant potential benefits from successful implementation of this technology in the R&D stages of many industrial sectors. What are the features of this future landscape by which we will know that this approach is being successful?

The ultimate measure, in commercial terms, is clearly that companies will gain substantial competitive advantage by improving their R&D efficiency and rate of innovation.

However there are a number of "component" factors which are also useful measures of how successfully this capability is being exploited:

- there should be clear indications that these high throughput tools unlock and leverage greater creativity in both academic and industrial research:
- the approach, as described above, provides capabilities to solve complex, interdependent, problems holistically – and this research can be integrated across the classical R&D stages:
- HTT methodologies should become commonplace and beneficially deployed in the workplace – by analogy with the spread of computational capability from the 1970's to the position we have today, high throughput "tools" and approaches change from being a highly expensive, rare, centralised, bespoke, facility to become an integral part of laboratory and workplace practice:
- which in turn will lead to a change in the spectrum of skills and capabilities deployed in the workforce:
- in the interim, there is a need for ready access to specialised capabilities and facilities in order to accelerate uptake and fuel improvements in capability;
- due to the complex range of supply-side skills and companies, there is clearly a need to develop flourishing collaborations between organisations: creating new innovation & supply networks

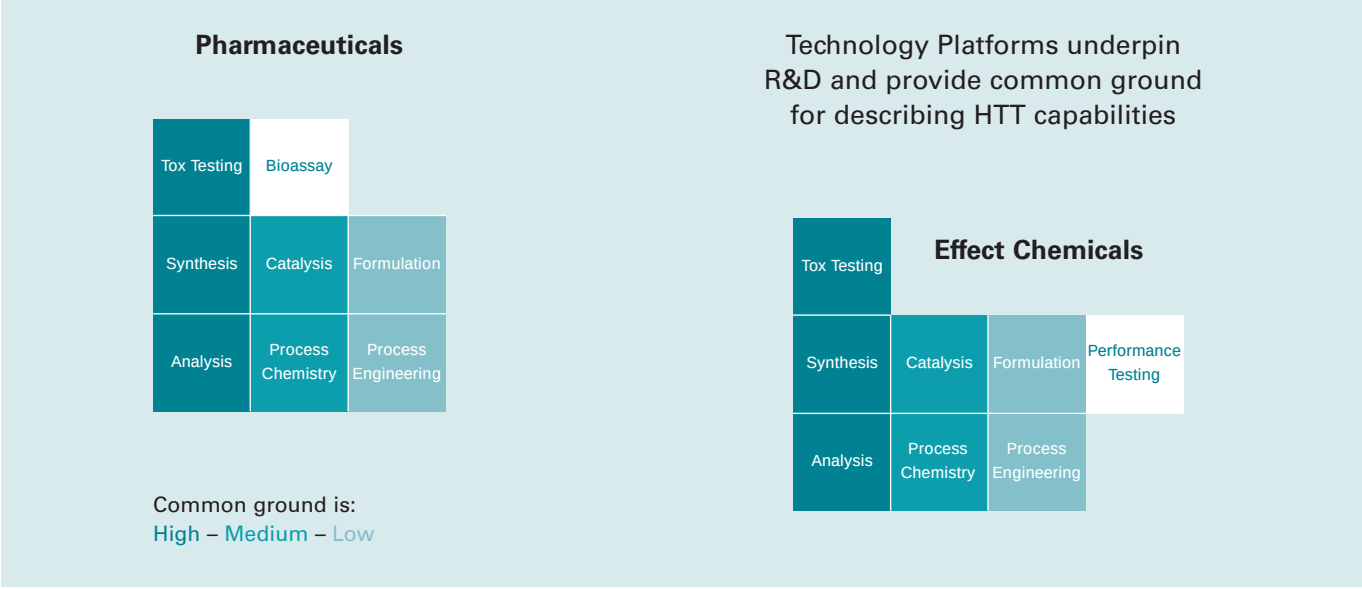


Technology Platforms to Deliver Benefits

The primary focus of this report is to understand what needs to be done to deliver benefits of using HTT to a wide range of industrial sectors, including pharmaceuticals, biotechnology, clinical diagnostics, foods, fine chemicals, effect chemicals, cosmetics and personal care products, household products, polymers, composite materials, ceramics and catalysis.

We have also reviewed the different needs and opportunities for HTT in various phases of R&D and manufacturing within these sectors.

Over this spread of applications, it has become clear that the HTT science and technology which underpins use in these industries is best described by categories based on the underlying technological operations or technology platforms as described below:



Using this approach, it is also clear that there is significant common science and technology between different industrial sectors, and therefore this approach also helps to identify potential routes to collaboration and technology transfer between non-competitive companies.

The relative importance of each technology platform to a range of user-industrial sectors is shown in the table on page 14 along with an indication of the key supply-side industrial sectors needed to develop and supply new capability to service the technology platforms.

Impact of HTT on Industrial Sectors

H = High HTT impact M = Medium HTT impact	Synthesis	Catalysis	Bioassay	Formulation	Analysis	Materials	Process engineering
Industrial user sectors							
Aerospace					M	M	M
Automotive		M		H		M	
Agrochemicals/Biocides	H	M	H	H	H	M	M
Biotechnology		H	H	M	H		M
Contract analytical			H		H	M	
Ceramics	H			H	M	H	H
Chemicals	H	H	M	H	H	M	H
Computing						M	
Energy, oil and gas	H	H		M	M	M	H
Effect Materials/molecules	H	H	M	H	H	M	H
Electrical and Electronics						M	
Environmental		M	H		H		
Food and Drink	M		H	H	H	M	M
Household			M	H	M		M
Personal Care and cosmetics	H	M	M	H	H		H
Healthcare			H				
Composite Materials	H			M	H	H	M
Medical devices or diagnostics			H				
Metals or minerals	H	H		M	M	M	M
Pharmaceuticals	H	M	H	H	H		M
Plastics	H	M		M	H	M	
Security			H			H	
Speciality Chemicals	H	H	M	H	M	H	H
Textiles and fibres	M	M		M	H	H	
K= key capability to meet technology needs of this platform S= supporting capability provider							
Supply-side sectors							
Instrument suppliers	S	S	K	S	K	S	S
Automation/robotics	S	S	S	K	K	K	K
Software developers	S	S	S	S	K	S	K
IT/hardware	S	S	S	S	K	S	K

Benefits to Industry from Exploiting HTT

UK industry has identified a diverse range of potential gains from the effective exploitation of HTT. The benefits, aligned with each of the above technology platforms, are summarised below. In this context, short term implies a timescale of 1-3 years, medium term approximately 5 years and long term approximately 10 years.

	Short term	Medium term	Long term
Synthesis	• Faster throughput • Improved recording • Explore inaccessible chemistries • Understanding of scale factors • Cheaper facility costs	• Better information flow • Tailor new chemistries • Virtual chemistry screening • Stronger IP position • Compliance with REACH	• Artificial Intelligence + HTT to produce optimum process • More versatile chemistry • In-silico screening
Catalysis	• Process optimisation • Easy access to legacy data • Novel catalytic structures	• Renewable energy applications • Processes which are more robust to feedstock variability	• In-silico catalyst screening • Integration of R&D processes
Bioassay	• Pharmacogenetics target identification & validation giving new IP • Efficient protein separation	• Toxicogenomics, minimising animal testing • Integrate synthesis and bioassay	• Personalised medicines • Assay systems for multiple protein-protein protein-ligand systems
Formulation	• Mapping of phase boundaries • Rapid compositional specification for robust products	• Novel compositions & new IP • Optimised multi-factorial performance	• Better prediction of complex behaviour • Stronger IP • Product differentiation for market segmentation
Analysis	• Immediate feedback on efficacy, composition or structure • High information content to guide decisions • “Fail early”	• Evaluation of product performance from property measurements • Ability to visualise and make decisions from large data sets	• Faster, more valid measurements • Reliable information from nano and micro scale samples
Materials	• Fast corrosion/stability testing • Automated sample preparation • Secure data management	• Fast screening of materials for electronics, batteries, coatings, implants	• Integration of R&D processes • Structure Activity Relationship knowledge creation
Process Engineering	• Rapid data generation on unit operations • Utility of process models • Increased process knowledge for optimsation and troubleshooting	• Rapid whole process data generation including SHE and green technologies • Process flexibility for novel products	• Rapid process prototyping through integration of data generation and process simulation • Systems integration for mass customisation

Synthesis

Industrial sectors

Synthesis, the making and manipulation of chemical substances into more complex and desired target materials, is ubiquitous throughout the chemical and applied chemical industries. Synthesis is a key activity and frequently the bedrock of R&D operations within these industries and is strongly supported by UK academic institutions, furnishing research organisations with the prospect of discovery and exploitation of new molecules and materials.

There is scarcely a single aspect of 21st century living that is not affected in some way by chemical synthesis: from bulk commodity materials such as synthetic oils and additives, through food additives and supplements, electronic materials, constructional materials, cosmetics, dyestuffs, inks, artificial polymers, explosives, preservatives, packaging, agrochemicals and the high value products such as pharmaceuticals and healthcare products.

Definition of Synthesis

In simplistic terms synthesis can be encapsulated as the process of producing a compound by a chemical reaction or series of reactions from simple or commonly available starting materials. Within this section the term compound is used to cover any well-defined molecular entity – hence it would include polymers, but would not include formulations, a topic which is covered elsewhere in this roadmap.

The range of compound types covers non-natural organic materials, inorganic and organometallic substances and derivatives of these in all physical states. Other than as a laboratory reagent, these carefully synthesised compounds are scarcely ever encountered as products in their pure forms. They usually appear in commercially useful products formulated with other components such as diluents, carriers, fillers, moderators etc.

Synthesis within the R&D and manufacturing activities incorporates the discovery of new compound structures, the invention of new ways (routes) to make compounds and the actual manufacture of the compound itself.

Typical benefits from application of HTT capability to synthesis

Compound discovery – synthesis and screening

A key activity for all those engaged in synthesis is to make new compounds and compound classes. The discovery of a new compound allows the organisation to seek and secure wide patent protection and other IP rights on the use of that compound. For a new drug substance this could easily result in commercial revenues of massive proportions, e.g. blockbuster drugs now bring in >£1b/annum of revenue.

Synthesis and molecular discovery is still a key criteria for academic success, eg the Nobel Prize has often been won by the discoverer(s) of new compounds or synthetic methodology – buckminsterfullerene being a recent example.

Often associated most strongly with organic synthesis, continuing advances have now blurred the distinction between organic-inorganic, organometallic, macromolecules and of course the rapidly expanding bio-areas: 21st century chemists are to be found looking into every kind of available chemical domain.

Within the last 30 years or so (driven by the advent of cheap and rapid computation) the theoretical contribution to understanding synthesis at a molecular level has advanced dramatically. Predictive modelling of some aspects of chemistry is really very good indeed, particularly those aspects related to structural elucidation of molecular frameworks. Prediction of bulk properties of compounds is not perhaps so well advanced and is still a strong candidate for development, e.g. polymorphic form stability. While for IP and patent purposes an unambiguous molecular structure is essential, the commercial use of a compound is critically dependent on the form in which it is presented as well as its intrinsic molecular structure.

The drive for novel compound discovery, more than any other factor, has been the dominant feature of the introduction and acceptance of the combinatorial approach to synthesis within the pharmaceutical, catalyst and electronics areas. The desirability and commercial benefits of finding and bringing new entities to the market has pushed these industries into looking for ever greater diversity of structural type and for doing it quicker. Initially their efforts were directed at producing very large numbers of compounds in an automated fashion. These combinatorial production rates can be several orders of magnitude higher than by conventional means. The quantity of the output, however, was not matched by the quality of the large numbers of compounds produced and it has taken some time to

get both these attributes attuned to get the benefit of the approach. The current trend is to ease back on the large numbers produced but to provide high quality compounds that are well characterised and understood.

Specific areas of technical benefits accruing from the application of HTT in the discovery phase include:

- Exploitation of new domains of compound structure and not just more of the same. HTT allows the rapid examination of large areas of structural types that have previously been inaccessible to investigate.
- Speeds up the identification of new compound targets for commercial exploitation. HTT synthesis can deliver orders of magnitude improvements in compound preparation and evaluation of their performance.
- HTT can enable the exploration and discovery of new chemistries that have simply not been available previously. This in turn leads to new ways of synthesis and new types of molecules with new properties.
- HTT can now be harnessed to provide more extensive and better quality data for compound description and definition.
- It is an ideal tool for rapidly screening new molecular entities for effects. As compound library preparation grows a wider range of effects can be explored.

Chemical Development and Manufacture

Following the initial discovery of a new compound the perennial problem then has to be addressed of how to exploit it.

Having got it and decided, via initial screening, that it is with pursuing it is then necessary to make it and make it in worthwhile quantities by a robust, repeatable process from available starting compounds...as quickly as possible. In this arena (process or chemical development) HTT can be employed to good and immediate effect. At this stage, commercial costs of developing a potential marketable product escalate dramatically and time is of the essence. Patent life is now running and competitors are not standing idly by. What is required now is to find ways of making the compound, reliably and of good quality from available commercial building blocks. Inevitably, once a target structure is identified there will be multiple optional ways to make it. Which way is best? Is there a "best" way? What's the most economical, safest, easiest to manufacture and quickest synthetic route?

(It should be noted that Discovery HT methodologies are frequently not suitable for making other than test quantities of new compound. These methods cannot be scaled-up for subsequent needs. A new approach, described elsewhere in this report however does offer some scope for a seamless transition from discovery to manufacture, that of the technique of numbering-up or scaling-out.)

Specific areas of technical benefits within the development phases from application of HTT include:

- Exploring reaction conditions more extensively for making compounds rapidly by optimising chemistries and identifying bottlenecks.
- Providing capabilities to rapidly explore alternative more efficient syntheses – channelling every effort into a poor route or poor chemistry is seldom a wise strategy
- Rapidly exploring reagent selection (e.g. solvent, catalyst, base, acid) and reaction condition choices (isolation, drying methods and handling requirements).
- Quickly exploring alternative and extensive chemistries that are (patentable) ways of protecting the commercial life of a putative product.
- Rapidly and extensively determining the best final stage compound isolation options. (This is crucial as this operation produces what will become the marketed product. It may need to be dried, purified, crystallised or treated in some way to make it useable, e.g. the right polymorphic form is an absolute requirement for many drugs, liquid crystals etc).
- Testing of processes to scale up to manufacturing and providing extensive information on reaction conditions and boundaries that need to be observed to provide acceptable quality product in a safe and efficient manner.

Having passed through some kind of development phase any new compound will need to be manufactured in substantial quantity. Scales of production vary according to product type and intended use. These range from perhaps a few 10's of kg for some high value potent fine chemicals to perhaps $>10^9$kg for commodity products.

What these products share are the needs for well understood and defined processes that are safe to operate, tolerate as wide a reagent and raw material variability as possible, tolerate a wide range of operating conditions, are economical, robust, consistent, give low waste and an excellent quality final product. The current worldwide economic and regulatory climate makes all these requirements mandatory and not just desirable options!

The present situation is one of increasing capability, complexity and sophistication in synthesis. All this has to be operated against a background of increasing demands from ecological, regulatory and marketing groups. The use of HTT coupled with powerful data handling and knowledge based systems are essential to address 21st century expectations.

None of these things can be achieved without a well trained and retrained technologically dynamic workforce.

Key needs to deliver these benefits

A variety of common "needs" has appeared including the following:

Equipment

- Familiarity with what HTT is currently available and can do.
- More versatile material handling operation in new equipment, e.g. viscous liquids, sticky solids.
- Robust and generic equipment that is (much) easier to use and learn to use.
- Standardised connectivity to different types of equipment
- Extended scope of HTT capabilities, e.g. rheology, surface properties monitoring, difficult solids handling.
- How can the best use be made of existing equipment, technical back-up and retraining needed.

Operations

- Explore a wider range of chemical structure (diversity) and methodology.
- What is the smallest scale of equipment operation to allow for max experiment/unit mass AND be reproducible?
- Lack of engineering scale-up criteria established, e.g. micro litres to litres.
- Develop multiproperty screens relevant to product properties.
- Synthesise from discovery to large scale, scale-out or multiply-up?
- Standardise R&D approach using HTT methodologies to widen sector use.
- Faster throughput of experiment BUT without sacrificing quality of output.

People

- Too many scientific (+jargon) barriers across disciplines, e.g. maths, chemistry, biology and certainly IT.
- A range of skills is now needed for newcomers to HTT. Cultural change in attitudes is needed.
- There are no clear cut mechanisms for adequate training in HTT.
- Current (academic and commercial) mindsets are not conducive to embrace HTT workflows.
- SMEs need access to people with the necessary skills. They can't always afford to buy them in.
- Promote skills and information flow to link the Discovery, New product development and Process Engineering interests.
- Look to influence University education on a 2-10 year out basis.

Integration

- Data flows and operations need to be linked more easily and seamlessly using standardised connectivity's
- Use HTT as a means of connecting to and leveraging legacy data sets.
- Establish real-time monitoring of multi-parameter quality attributes.
- Establish compliant data/sample tracking to appropriate regulatory requirements.
- Standardise equipment and data collection software for better and more consistent connectivity.

New Approaches

- New informatics' approaches are needed for dealing with large design spaces
- Computer aided synthesis (integrated with HTT) should be promoted.
- Create diverse experimental data sets to generate in-silico models for prediction of reaction parameters.
- Use HTT with real-time online monitoring of processes to operate and control complex synthetic processes.

Requirements for new or improved capabilities in support of synthesis

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Modular cheaper equipment • Link Synthesis to processing • Small scale operations • Guides for scale-out or number up	• Plug and play • Multi sensor control • Link discovery and process • Multi step synthesis	• Whole process integrated in one HTT "device" • Large design spaces with modelling and Artificial Intelligence • Apply to route selection

Catalysis

Definition & Industrial Sectors

Over 80% of commercial chemical processes involve catalytic steps. Catalysts can be heterogeneous (usually solids in a liquid or gas reactant feed) or homogeneous (dissolved species in a liquid feed). In Europe alone the catalyst market is worth €10 billion/year, and products made using catalytic processes are estimated at €2000 billion/year. Catalyst technology is central to a large number of UK industry sectors including bulk chemical, petrochemical, home & personal care and pharmaceutical businesses.

Despite the immense range of applications for catalysts, the fundamental knowledge of structure-activity relationships is lacking and the discovery of successful catalysts is somewhat a 'black art'. This lack of scientific understanding and the multitude of factors affecting catalytic behaviour make the combinatorial approach to catalysis R&D particularly attractive.

Benefits and challenges of applying HTT to catalysis R&D:

HTT in catalysis R&D will not only speed-up routine experimentation in this field, but the capacity to investigate much broader ranges of parameter space than feasible with classical experimentation methods will yield considerably higher rates of innovation and new process discoveries. The large amounts of high quality empirical data obtained from screening catalytic processes are also expected to yield useful structure-activity relationships that will form the basis of predictive models and lead to a deeper understanding of catalyst science.

Training in the application of HTT in this field is a priority, and it is recommended that this should be included in courses ranging from undergraduate science to professional continuous development. Cross-disciplinary collaboration is also central to the realisation of emerging new concepts in scientific instrumentation and data management necessary to address the specific needs of high-throughput catalyst research.

High-throughput approaches promise to accelerate the full R&D process: From catalyst synthesis, activity screening and lifetime evaluation through to the generation of high quality calorimetric data useful for process modelling prior to scale-up and pilot plant evaluation. Specific areas in which HTT promise to yield step change developments for catalyst markets include:

- Fast methods for catalyst bench life screening
  Enabling catalyst manufacturers to label products with precise 'use by' dates and ensure the highest product quality for customers, whilst reducing 'time-to-market' for commercial catalysts.

- Discovery of new catalysts for sustainable energy applications
  Catalysts are expected to play a central role in future energy production technologies such as fuel cells, catalytic combustion, reforming reactions, coal gasification and gas storage applications. HTT will enable the fast discovery and development of these catalytic processes.

- High-throughput kinetic data collection during early R&D
  Using HTT to measure quality kinetic data and produce models for process design so that potential scale-up issues can be identified early in the catalyst development process.

- Environmental and toxicity screening
  Screening catalytic species for their accumulation and potential damage to the environment

- Valorisation of alkanes
  Discovery of catalytic routes for the conversion of light alkanes (currently flared at oil fields) to useful and easily transportable liquid precursors for other petrochemical products.

- Rapid catalyst lead generation and structure activity relationship determination

- Mass screening experiments can be used to identify generic catalyst activity trends, using readily available library precursors and reaction feeds. In combination with characterisation data, structure-activity relationships (SARs) can be identified and this will provide a valuable source of information for the design of experiments for other applied catalyst discovery programmes.

- Virtual Chemical Development (VCD)
  This implies a shift towards knowledge generation and management, IP ownership and away from the requirement to own manufacturing capability. This concept fits the EU's vision for Europe being the leading 'knowledge based economy' by 2010. Processes will be discovered through HT screening and modelling within VCD companies, whilst process development for 'hits' will require access to generic affordable libraries of substrates and external testing facilities (10g+ scale).

Summary of key requirements for this technology platform

These capabilities are seen as being particularly challenging targets in this sector

Application	Capabilities
Materials Handling	• Precision solids dispensing • Solid sampling to obtain representative composition of mixed or impure ingredients • Static powder dispensing
Characterisation	• New fast 'inferential' measurements • Small-scale solids characterisation • In-situ reaction monitoring
Standards	• Establish common protocols and standards to ease the implementation of HTT, reducing the number of bespoke HTT systems required.
Process discovery	• Libraries of common precursors and reference catalyst processes
Data management	• Data acquisition and modelling capabilities • Storage of legacy pilot plant or laboratory data • Connection/harmonisation with other data sources

Requirements for new or improved capabilities in support of catalysis

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Accelerated ageing tests • Data management solutions • Solids handling solutions	• HT kinetic data collection • Catalyst/precursor libraries • SAR library creation	• Handling complex mixtures • HT characterisation methods • Harmonised e-language

Bioassay

Industrial Sectors

This is a very broad area of technology utilised by a variety of industry sectors. The analysis in this report is therefore limited to those applications which either operate in close connection with other related activities, e.g. high throughput screening coupled to combinatorial chemistry in pharmaceutical or bio-effect molecule discovery or where the application of the assay is core to the business activity, eg in contract bio-analysis for forensic identification, environmental monitoring or determination of food quality and safety. It will also include some reference to healthcare applications, for example in the development of toxicology screening and clinical screening, e.g. for disease or pathogen screening.

There is a $20bn global market in clinical diagnostics, a $7bn market in contract analytical markets with bio-determination end-points, a $1.2bn global market in instrumentation supporting pharmaceutical R&D and a $1bn+ market biochip products as basic or applied research tools.

Definition of bioassay

Broadly there are two, somewhat overlapping, categories of assay: those primarily focused on determining properties of bio-molecules, cells or tissues and those used to measure or understand the effect of exposure of chemicals to bio-systems.

Sampling from tissue, cell sorting and manipulation, tissue based bioassay and evaluation is also seen as a key area for future development. Typically these operations have not been targeted for automation, but robotics systems are emerging,

coupled to intelligent materials handling and recognition systems, which could revolutionise these operations. Applications cover a variety of tissue types, e.g. human (or surrogate) tissues for pharmaceutical discovery, pharmaco-kinetics and metabolites screening, toxicology testing (and replacement of animal testing), development of biocompatible materials, forensic analysis, foodstuffs (animal and vegetable) for regulatory approval or quality assessments, plant material for biocide or pesticide development or control, microbial tissue for bioprocessing or clinical applications.

Separation and characterisation of biomolecular components cover a wide range of technologies including polymerase chain reaction (PCR) amplification, PCR purification, liquid handling, protein purification, protein assay, protein microarray, drug screening, genomic DNA purification, RNA purification, plasmid DNA purification, DNA microarrays. Many of these have been highly automated and miniaturised.

Typical benefits arising from application of HTT capability to bioassay

Due to the diversity of biomaterials being handled in these different applications, there is a very broad range of challenges to which high throughput capability can be brought to bear.

Gene-based assays

The human genome project has opened up the opportunity to explore a much greater variety of potential health and disease states. By way of illustration, the full range of current drugs are thought to mediate the products of about 500 genes, from an estimated 30,000 genes which could theoretically be encoded from the human genome.

Genomics approaches are being used for target discovery which can then identify protein targets for screening and lead discovery. There is ongoing pressure to explore these new targets more quickly in order to gain intellectual property which will allow some degree of exclusivity in exploring lead chemistry against these targets.

Pharmacogenetics approaches are being increasingly used to optimise drug leads and validate the target. This is providing greater understanding of the variation within populations to the efficacy of treatment and longer-term potential for more personalised medicines.

Toxicology is an increasingly important assay for all chemical industry sectors, both for registration of new chemical compounds, re-registration of established compounds (e.g. the EU REACH legislation) cell-based assay (eg hepatocyte or microsomal analogues) and toxicogenomics are increasingly used to minimise the requirement for whole animal tests.

Protein-based assays

The use of protein activity assays, screening compounds against individual proteins, is well established in the discovery stages of R&D in a range of life-science industries eg generating biocidal agents or in the pharmaceutical agents. Current estimates suggest that the proteome (the range of proteins expressed by the human genome) might comprise up to 500,000 proteins, each of which can also undergo a range of chemical modifications which could mediate its function. Clearly, this is creating demand for very high capacity automated separation and analysis.

Typical protein separation methods include for example, precipitation and centrifugation, filtration and ultrafiltration, chromatography, dialysis: many of these have been adapted to automated methods but there is still a need for further developments, particularly in the integration of separation methods and the measurement method used to select the candidate proteins.

There is an increasing interest in being able to integrate synthesis and bioassay within the same device, with fast feedback and “smart” experimental design to identify and optimise lead chemistries.

Increasingly there is pressure to be able to investigate multiple protein-protein and protein-ligand interactions in bio-systems. This is a challenging target and driving development of new methods as many of the experimental protocols which were developed for single protein separation and characterisation are not easily adapted to this type of investigation. Proteomics in this fuller sense will require step-change developments in e.g. protein separation methods, smaller scale sample handling, labelling chemistries.

Key needs to deliver these benefits

In broad terms, these can be grouped according to the type of activity that the bioassay supports:

Gene-based assay:

- Pharmacogenetics for genotyping: methods are already well advanced but there is ongoing pressure to increase throughput rates in lower cost, automated, assays. There are also significant benefits from development of systems combining multiple assays. As the use of this approach is extended into later stages of drug development, e.g., clinical trials, there is a need for greater accuracy and also regulatory acceptable data generation.
- Sample extraction is often a complex process of cell lysis, DNA or RNA isolation via centrifugation, adsorption onto a matrix or binding to a magnetic particle, repeated cycles of washing and elution. While very high throughput is achievable with "well behaved systems" e.g. 200,000 DNA preparations per day from automated plasmid purification has been reported from a paramagnetic bead-based system in the Whitehead Institute, there are still major needs for robust recovery methods from, for example, partially degraded samples (e.g. forensics) or more fragile, e.g. RNA, systems.

Protein-based assay

- Sample handling to extract material from tissue
- Separation processes operating in high throughput mode capable of extracting picomolar amounts of protein (and remove high-abundance proteins)
- Detection methods capable of selectivity and sensitivity to these quantities of material
- Integrate protein binding/activity assay and chemical synthesis into fast-cycle unit operation (in-chip integration)
- Extend and integrate activity-assay to include pharmaco-kinetic properties, e.g. adsorption, partitioning, selectivity, uptake
- Extend bio-response end-point to include toxicity, metabolism, and population or species differences
- Integrate bio-molecule physico-chemical characterisation by direct read or "inferential" measurement capability
- Integrate bio-molecular physico-chemical determination within automatable platform –e.g. as has already been demonstrated for protein crystallisation in situ in multiwell format

Requirements for new or improved capabilities in support of bioassay

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Increase throughput genetic assay	• Smart sample extraction • Handling difficult samples • Kinetic protein-based measurements	• Extend assay beyond binding constants e.g. pharmacokinetics, toxicity • Integrate bio-molecule physical characterisation

Formulation

Industrial Sectors

Formulation, the creation of multi-component, often multi-phase, products is a recognized R&D component of a wide range of manufacturing industry including for example personal care products, cosmetics, household products, foods, fine chemicals, effect chemicals, polymer composites, coatings, inks, dyes, and pharmaceuticals.

Definition of formulation

Formulation within R&D activity covers: ingredient selection and manipulation, product design & composition, performance evaluation and optimisation, process definition and scale up. Formulated products can comprise a range of materials including, for example: organic or inorganic solids; liquids (aqueous and non-aqueous, of a variety of viscosities, Newtonian and non-Newtonian); dissolved or self-aggregating molecules; electrolytes; surfactants and polymers (as latices, solubilised chains or particulates). These are often multi-component mixtures in non-equilibrium multi-phase structures, with domains of length scales in the 10nm – 500 micron range.

Typical benefits arising from application of HTT capability to formulation

A key technical driver in formulation is to be able to select the most appropriate product composition and process. Since product performance is typically dependent on significant interplay between product composition and manufacturing process, the compositional design space is large and interactions between different parameters can be complex. Many areas of underpinning science which can be rigorously interpreted in model systems can only be qualitatively applied to "real-world" systems. Traditionally this has meant that the formulation selection process has been heavily dependent on the experience of skilled practitioners, using complex, often un-stated or unrecognized, "fuzzy" logic and intuition in combination with the underpinning scientific framework.

Therefore, it is an area that presents some unique challenges for application of automated experimentation, but also an area where the capability of HTT can provide some unique advantages in extending the underpinning science into complex, multi-factorial, real world dependencies.

Specific area of technical benefits accruing from application of HTT include:

- Better optimisation of product design and performance by being able to obtain empirical data on a much greater range of the very rich and complex "design space" inherent in multi-component materials. Broadly there are two approaches to this: to carry out selective "one-off" scoping studies which develop a database of dependencies to guide future product design. The second is to develop "bespoke", ongoing screening or in-depth study of optimisation for specific applications). Typically a combination of both will be required to develop knowledge in this field. In either case, the advantages of using HTT approaches include:
  - Doing more –greater scope and better mapping of complex data "topology". A simple example would be to map the composition-temperature phase diagram of a commercial surfactant:water:electrolyte mixture, a complex example would be to select active ingredient:formulation vehicle combination optimised for maximum bioefficacy and robust manufacturability.
  - Doing it faster – by scoping specific solution to a particular problem or application e.g. for market segmentation or "bespoke" solutions
  - Doing it smarter – by using experimental design algorithms (e.g. genetic algorithms) combined with fast feedback to obtain "best compromise" solutions as quickly and with as few experiments as possible
  - Better prediction: since many formulation properties change during process, storage and use, the ability to predict behaviour either through mechanism-based rules, phenomenological correlations or mathematical modelling and simulation can be greatly enhanced if based and validated on richer, more comprehensive, empirical data sets
  - To generate better correlation between laboratory based measurement and real-world performance characteristics
  - To correlate whole product performance characteristics to product micro-structure: this could include: storage stability; product application; delivery of effect; post-application performance (e.g. in coatings)

- Development of stronger IP protection on product design and process

- Production of differentiated array of product options e.g., for market segmentation, personalised products, robust transfer of production to distributed facilities

- Integration of formulation stages into active ingredient discovery, whole product performance optimisation and manufacturing process (e.g. personalised medicine)

- More robust compositional and process parameterisation for scale up and definition of manufacturing operating windows e.g. in specification of allowable composition variation, products will become more robust to variation in raw ingredient specification or process parameter variation

- In addition to optimising product design there is a unique opportunity offered by high throughput experimentation to carry out investigative and mechanistic studies of complex systems governed by multi-factorial dependencies –
  - Being able to address problems which are simply not tractable with traditional experimental approaches because the number of experiments required by the statistical design is too great for traditional methods. This also provides the ability to investigate and deconvolute co-dependent phenomena, for example, where one component of a mixture governs more than one performance property (e.g. surfactant altering both solubilisation of an active ingredient and spreading of deposit on a substrate) and that property is mediated by another component (e.g. a solvent).
  - Being able to support simulations and phenomenological modelling by providing richer, more comprehensive "training sets" of empirical data. While many model systems can be quantitatively predicted from current theory, these solutions become approximate in complex (real-world) systems. Simulation or correlative modelling can be used to enhance the predictive capability of such models if "validation" data can be generated from experiment. The accuracy of the prediction can be significantly enhanced by increasing the size of the "training data".

- Being able to handle complexity
  - of composition, e.g. a surfactant of a “notional” chemical identity typically comprises 2000+ different chemical species within a “chemical family”.
  - of dependencies, e.g. one component of a product may govern a number of product properties – optimisation of whole product performance being a compromise between them – rheology of paint or adjuvant in an agrochemical.

Key needs to deliver these benefits

Characterisation methodologies relating to material properties are a key area for future development.

This covers a very wide variety of properties. However, many of these are applicable to most formulation-related activities in a range of industrial sectors.

- Rheological measurement – to measure a wide variety of viscosities and time dependencies, capable of operation at non-ambient temperatures and pressures
- Particle size or phase separation, e.g. rheology, time-of-flight ultrasonic measurements etc relating to particle or domain sizing, incipient flocculation as indicator of longer storage properties, particle or crystal growth, process dependent microstructure changes. Organic or inorganic crystal structure, e.g. polymorph analysis, crystal size, shape, morphology, mechanical properties. Micron to nm-scale sampling or spatial discrimination to examine compositional variation.
- Solids or composites material properties, e.g. porosity, sorption capacity, surface properties, local vs. bulk compositional variation, mechanical properties of composites, e.g. modulus, tensile strength, gelation.
- Surface and interface-mediated properties, e.g. surface tensions, extensional rheology, spreading characteristics, film formation, adhesion, optical properties.
- Chemical stability or degradation – during processing, storage or in-use.
- Imaging methods, to integrate with intelligent machine image analysis, and techniques combining imaging and other characterisation methods – e.g. spectroscopies. Development of non-invasive depth profiling methods, e.g. confocal or tomographic (e.g. NMR imaging) methods.

In addition, there is significant potential to use “inferential measurements” – i.e. measurements which are simple to operate in high-throughput mode, but which can be correlated to more complex material property performance (e.g. near IR spectroscopy correlated to polymer tensile strength). This area may be able to extend HTT formulation capability into a very wide variety of application-specific correlations dependent on industrial sector.

In addition, there is potential to develop a database approach to correlations of generic properties in this field of relevance to a number of industrial sectors:

- Correlation of formulation vehicle to bioavailability, e.g. relationship to DMPK for effective drug delivery (pharmaceuticals), mitigation of toxicology or environmental impact (all effect chemicals), specificity of biocidal or pesticidal activity.
- Correlation of formulation property to customer tactile perception, e.g. rheological and surface properties to customer acceptability/preference (personal care, cosmetics, household products, foods).

Versatile materials handling: current capability is available for Newtonian, low and medium viscosity fluids, and “well-behaved” powders, but there is a widely recognised need for systems to dispense and handle viscous materials, semi-solids, amorphous solids, gels, and “sticky” materials. Because of the “impure” nature of many formulation ingredients, representative sampling (in preparation or characterisation processes) are critically important and challenging as the scale of sample handling is reduced.

The microstructure of these systems is typically highly dependent on the preparative methods used. Therefore, it is important to have scaleable “make” processes, e.g. shear, grinding, mixing, extrusion, heating, pressure variation etc which correlate to scale-up and manufacturing scale processes.

Development of informatics approaches to deal with very large multi-parameter design spaces including:

- flexible, user-friendly experimental design tools (DoE)
- smart algorithm development for intelligent (self-optimising) search and optimisation tracking
- data handling to allow complex cross-correlation of “hard” and “fuzzy” data sets
- manageable data handling to extract key correlations in multi-functional dependencies
- ability to address both screening and investigative/in-depth approaches

Ensure compatibility of process and results to fit regulatory requirements – e.g. of analytical standards, quality procedures (eg ISO 900x), data recording procedures suitable for regulatory and licensing authorities (e.g. electronic records not acceptable for some IP processes).

Training of formulation staff to approach problems using different paradigms.

Integrated approach to optimisation across organisational boundaries.

Access to capabilities – equipment and skills, particularly for SME’s via a network of national facilities for example?

Summary of key requirements for this technology platform

These capabilities are seen as being particularly challenging targets in this sector:

Application	Capabilities
Handling difficult materials	Viscous fluids and semi-solids Accurate dosing of sticky or “intractable” materials Solid sampling to obtain representative composition of mixed or impure ingredients
Representative preparative methods	Controllable shear regimes Scaleable energy input-shear, heat etc. Grinding and milling Crystallization methods for reproducible nucleation and growth Extrusion or melt processing Particle size selection Temperature serration and controlled temperature cycling
Characterization methods	Particle/domain sizing in concentrated dispersions (or representative sampling into dilution methods Rheology Surface properties, morphology, tribology, wetting, interfacial tension Mechanical properties, stress testing, fracture behaviour, hardness

Requirements for new or improved capabilities in support of formulation

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Viscous fluids • Crystallisation methods • Interfacial tension	• Solid sampling, accurate dosing • Controllable and scaleable shear, milling, extrusion • Rheology, particle size	• Sampling impure components • Particle size selection • Materials properties

Analysis

Industrial Sectors

Analysis is important to all process industry sectors and at all stages of R&D, process development and manufacturing. In particular analysis is a critical element of any HTT system, wherever it is applied. There is no point in making large numbers of compounds, materials or formulations if they cannot be reliably screened and characterised with an acceptable degree of accuracy and reproducibility, on a timescale which is compatible with the overall process.

Different industry sectors have a different balance of requirements in terms of the relative importance of the analytical techniques which they need. In the pharmaceutical industry there is a need to understand composition and structure of new molecular entities. Here separation and spectroscopy techniques tend to dominate. In the specialty chemicals, materials and home and personal care sectors there is a greater demand for physical measurements to quantify the desired effect of the product. In most sectors there is interest in the possibility of making simple inferential measurements which are capable of providing information on composition or properties where direct measurement is difficult or impossible.

As the development of HTT progresses it is likely that there will be a demand to adapt all the techniques which we have become accustomed to using in support of R&D so that they can operate effectively within a HTT environment.

Definition of Analysis and Characterisation

In the context of HTT there are two basic levels:

Screening

This normally implies a simple test which can be carried out quickly and automatically. In its most basic form it might deliver a yes/no response to indicate whether the compound, material or formulation concerned is worth any further attention. In many cases however, screening can produce richer information about the effects of the material in question.

Characterisation

This implies a more detailed analysis of the material concerned, aimed at providing much more quantitative information. This can take many forms, such as:

- a full chemical and structural analysis (e.g. by NMR) in the case of a new drug
- a range of physical properties in the case of materials or formulations and
- information on the morphology or structure of solid materials

Benefits from high throughput analysis

If analysis and characterisation form part of an integrated process, from synthesis through to data analysis and feedback, the benefits are:

- immediate feedback on the efficacy of the material
- where possible, the ability to screen against key product performance properties
- where possible, the use of integrated chemical and biological screens providing richer information on potential new products
- acquisition of large quantities of information (provided these can be processed and understood) which can be used to guide future experimentation or product design
- the ability to “fail early” – i.e. to avoid spending further development time on products which are unlikely to display the necessary characteristics.

The are a number of further developments which would increase the benefits arising from analysis in the context of HTT. These include:

- better integration with synthesis or material preparation, such as in situ measurements using sensors
- development of more accurate, precise and reliable measurements on nano and micro scale samples
- cheap measurements (of the order of pence per sample, or better)
- better integration with other elements of the process, i.e. data handling, informatics and predictive modelling.

Some of the important developments required to deliver these benefits are as follows.

Key needs to deliver these benefits

- The ability to carry out representative measurements rapidly on small samples
- Development of multi-property screens relevant to product properties
- Techniques to interpret complex spectra of multiple compounds (chemometrics, simulation)
- Integration of measurement with chemistry (e.g. in situ measurements)
- Transfer of characterisation and screening methodology between industrial sectors
- Techniques and instruments designed for “make and measure”
- Rapid and non-invasive techniques, for example for screening pharmacogenetic matching for personalised pharmaceuticals

System integration

One of the priorities for library characterisation is to integrate analytical techniques with the reactors performing chemical synthesis. This integration would result in more rapid, and probably more accurate and reproducible, characterisation of large numbers of samples. This is likely to occur through the development of sensors and other tools to support rapid analysis on a small scale. This concept might be extended to include real-time tools to measure equilibrium conditions in reactors and to microfluidic systems with in-built measurement devices.

Separation and spectroscopy

There has already been substantial progress in the area of chromatographic and spectroscopic measurements. For example technology is now available to perform multiplexed vibrational spectroscopy and there is scope for further incremental improvement and product development in order to operate in higher throughput and miniaturised regimes. It is also attractive to develop these techniques to produce inferential measurements which can be correlated with other properties which are difficult to obtain directly.

Structural and physical properties

More fundamental work is needed to develop approaches for analysis of effects and performance, particularly involving physical properties. This is particularly relevant to the growing area of HTT for formulation. The ability to carry out a battery of different screens on the same sample, simultaneously and predicatively if possible, is seen as an important requirement.

The range of techniques which require development to operate in an HTT environment is as follows:

physical properties, including
- rheology
- particle size
- porosity
- optical properties
- electrical properties

mechanical properties, including
- adhesion
- abrasion
- tensile tests
- tribology

structural and morphological characterisation of solids, including
- x-ray structure analysis
- polymorph identification
- grain structure and anisotropy
- image analysis

surface properties and composition

accelerated ageing and weathering

Sample preparation

In order to underpin all the above measurement techniques the problems associated with sample preparation need to be addressed to ensure that measurements really are representative and reproducible – as well as accurate. In particular this requires miniaturised techniques for preparing and presenting difficult materials – particularly powders, soft solids and viscous fluids.

Summary of key requirements for this technology platform

These capabilities are seen as being particularly challenging targets in this sector.

Issues	Capabilities
Sample preparation and presentation	Small but representative samples Difficult materials – solids and viscous fluids
Measurement integrated with reactors	In-situ measurement devices such as probes or sensors Multiplexed or multi-parameter measurements for high content screening and analysis Non-invasive techniques
Physical measurements, including morphological, mechanical and structural properties	Flexible tools for the measurement of physical properties in miniature or high throughput mode Specialised probes for physical property determination The development of inferential techniques for determining physical properties via easy-to-measure parameters
Data handling, informatics and modelling	Techniques for visualising and understanding large quantities of analytical data The provision and organisation of data for QSAR and QSPR The use of artificial intelligence and related techniques to optimise measurement parameters
Skills and capabilities	Need some staff who are multi-skilled in measurement and screening techniques (and in related instrument and automation issues) Need flexible and intelligent instruments, adaptable to the skill level of the users

Requirements for new or improved capabilities in support of analysis

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Sample Preparation for difficult materials • High content screening • Miniaturisation	• In-situ measurements • Physical properties • Mechanical properties • Structures and Structure Property Relationships	• Specialised probes for physical properties • Inferential measurements • Non-invasive techniques

Materials

Industrial Sectors

The manufactured materials industry is vast and highly diverse. It is continuously evolving and currently represents one of the most dynamic advanced technological markets for both Europe and the US/Japan. Considerable chemical and engineering technology lies behind a multitude of products competing for applications: metals and alloys, ceramics, plastics, composites, glasses, fibres, carbons etc. Areas of application include construction, electronics, transportation, energy, art, medicine (e.g. implants), textiles, optics and containment.

Definition of materials

Synthetic materials can be categorised as inorganic, organic, metals, carbons or composites and are generally solids under the conditions specified for their application. R&D work is usually aimed at the discovery or development of materials with outstanding properties e.g. strength, (re)activity, chemical stability, biological compatibility, electrical properties, visual appearance or texture. Heterogeneous catalysts are classed as advanced functional materials but these are covered in a separate section in this report.

Benefits and challenges of applying HTT to materials R&D

High throughput technologies (HTT) can be applied to materials synthesis, characterisation and testing, and some sectors have already started to capitalise on the increased rates of innovation that HTT deliver. However, the application of laboratory automation for materials research is somewhat slower than in other areas of R&D such as chemical synthesis or proteomics. The principal reasons for this are technical difficulties with reliably automating and multiplexing key processes such as solids handling (particularly for small quantities of solids) and lengthy characterisation procedures, as well as the inevitable high costs associated with purchasing bespoke automation.

One application of HTT that is expected to benefit a large proportion of industrial sectors and clearly lends itself to mass screening concepts is stability testing. This could be applied to product storage stability testing and more generally to material lifetime evaluation (e.g. monitoring corrosion or material degradation). The number of commercial products or development materials that would benefit from this application of HTT is considerable, and the widespread application of such stability tests could yield long term commercial and ecological benefits to the UK as a result of improved product reliability and reduced wastage. The key challenge with this application of HTT will be the development of fast assays. Technologies for solids handling, data management and interpretation will need to be developed, and to achieve full benefit from HTT the costs will need to be manageable for a large proportion of end user industries.

In the field of sustainable and renewable energy HTT can be applied to discover new materials for gas storage (e.g. hydrogen), components for fuel cells or for photovoltaic cells. This is an area where automation technology is still lacking for the reliable synthesis of libraries of advanced microstructured materials on the milligram scale, and fast characterisation methods need to be developed.

True combinatorial approaches would be useful in materials synthesis. Although some automated systems exist, the miniaturisation of material syntheses is currently limited by problems associated with mixing, solids handling and materials characterisation. The drawback here is the limited availability of characterisation techniques which are sensitive to the response of individual components of complex mixtures (rather than just measuring average values). Fast materials characterisation is an area of considerable technological development. There are promising developments in high throughput calorimetric methods which need to be further tailored to materials use. Classical characterisation methods such as X-ray crystallography and surface analysis (XPS, BET, electron microscopy etc) could potentially be replaced by a panel of fast 'inferential' spectroscopic techniques (NIR, nmr, Raman etc) in combination with multivariate statistics software tools for the purpose of deconvoluting complex spectroscopic patterns. There is also a need for new preparation or characterisation methods where the key properties are delivered by the final product form, e.g. separation membranes.

There is also great scope for the application of HTT in the area of biomaterials. The capacity to synthesise large libraries of ceramics, polymers or composites and then test their toxicity or bioactivity in high-throughput mode (*in-vitro*) for a range of different tissues could considerably increase the rate of discovery of new improved implant materials. The use of *in-vitro* screens for the widespread determination of toxic effects of commercial or pre-commercial products promises to be a very large application area for HTT, particularly with the adoption of REACH legislation in the next 2 to 3 years. High-throughput technologies for toxicology tests already exist and are actively applied by the pharmaceutical industry to test biological responses to active pharmaceutical ingredients. Improvement in biological cell-processing procedures are desirable primarily to reduce assay time but also to eliminate user variability, minimise contamination and permit complete data tracking. Standard HTT method development would benefit several industry sectors in providing robust and faster automated processes for toxicity or bio-activity screening, and ensuring high quality reproducible results.

Summary of key requirements for this technology platform

These capabilities are seen as being particularly challenging targets in this sector

Application	Capabilities
Materials Handling	• Precision solids dispensing • Solid sampling to obtain representative composition of mixed or impure ingredients • Static powder dispensing
Characterisation	• New fast 'inferential' measurements • Small-scale solids characterisation
Standards	Establish common protocols and standards to ease the implementation of HTT, reducing the number of bespoke HTT systems required.
Toxicology	Development of fast screening technologies (in-vitro)
Stability testing	Accelerated stability/corrosion tests with automated monitoring
Processing technologies	Understand effect of process on material structure and property development Adaptation to more intensive processes

Requirements for new or improved capabilities in support of materials

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Accelerated ageing tests • Data management solutions • Solids handling	• HT screening methods for new functional materials • HT toxicity/environmental tests	• Handling complex mixtures • HT characterisation methods • SAR library creation

Process Engineering

Industrial Sectors

All manufacturing sectors involve processes in production. Those of specific interest to HTT are often grouped under the so-called process industries, which involve manipulation of materials including inorganic and organic compounds and formulations in solid, particulate, colloidal, liquid or gaseous form. In some sectors, such as bulk chemicals, new process plants are now rarely built and the focus is on optimisation through advances in individual unit operations and control. In others, such as specialised organic chemicals, process flexibility is key to enabling a broad range of new molecules to be produced on demand. In some, such as pharmaceuticals and food processing, regulatory issues are critical.

Definition of process development & process engineering

Processes are normally the principal domain of chemical engineering, which views them as constituted from a variety of unit operations linked together. Traditionally, process development spans the translation of a new transformation (chemical, biochemical and/or physical) from the laboratory, often through a pilot plant stage, into production at commercial scale. This is called scale-up, as the commercial facilities are often an order of magnitude bigger than those at pilot scale and some two orders of magnitude bigger than laboratory scale. However new intensified technology and more active materials are bringing scale-out opportunities, where the pilot and even laboratory scales can deliver commercial production. Process development can also cover optimisation of an existing process or assessment of a new production technology. It can include

intermediate and final product storage during which various desirable changes e.g. curing/fixing or undesirable changes e.g. caking/degradation, can occur. In addition to achieving the transformation economically, there are safety, health and environmental criteria that the process must meet before it can be approved and constructed.

Detailed process engineering is now largely computer aided (CAPE) with steady state and dynamic stimulation of a broad range of unit operations requiring large amounts of high quality data. Simulation of solids, particulates and more complex fluids processing can still be difficult. The early process definition stage, including process flowchart design and equipment selection, can be improved by using methodologies such as Britest (http://www.britest.co.uk/). Britest is seeking to define data requirements and acquisition methods including HTT, which are also called high output technologies.

Typical benefits from application of HTT capability to process development

The following is a list of potential benefits which could be gained from applying HTT to process development:

- Accelerate lab to commercial production through boosting the productivity of process development to deliver marketable product at a cost that will win market share or develop new markets. In particular, the final unit operations can be key to achieving the required product specification (see synthesis section).
- Increase use and utility of predictive process models such as the Britest methodology and commercial process simulators by providing comprehensive, high quality data sets.
- Increase flexibility to manufacture a larger range of novel, differentiated/tailored products
- Accelerate assessment and response to regulatory requirements and changes e.g. safety, health and environmental and validation of processes.
- Accelerate and improve response to challenge of sustainable development through rapid assessment of so-called green technologies.
- Intensify processes linked to rapid realistic assessment of commercial risk.
- Make processes more robust to variability of raw materials and process parameters improving quality and stability (links to synthesis section).
- Improve cost-effectiveness in terms of repetitive and conditional processes.
- Enable stronger IP protection of process technologies.
- Make optimisation and troubleshooting more effective by providing comprehensive data to build a fundamental understanding of unit operations and processes (in many existing processes there is very limited data available and hence lack of process knowledge) (links to synthesis section).
- Enable data gathering during manufacture for optimisation through improved development of HTT on-line analysis.
- Handling complexity through understanding product property/process interactions and interdependencies eg formulation and gene and protein processing (links to synthesis section).
- Improve systems integration for mass customisation e.g. personalised medicine.
- Delineate boundary conditions for use in plant equipment and prepare models, by which processes can be defined, tested and predicted.
- Ensure optimum efficiency of each stage of synthesis.
- Test alternative “new” plant procedures, particularly with a DoE approach to multifactorial problems.
- Rapidly explore trouble shooting options.

HTT may also be able to help in the manufacture of compounds by addressing the question of whether to opt for batch or continuous processing. For many bulk type materials there will be no debate or option; the economics will dictate HT continuous processing. For other products e.g. fine chemicals, drugs, agrochemicals etc the choice is not so clear cut. There are HTT approaches to both continuous and batch processing. In many organisations the choice is not an easy one. Once a synthetic transformation is known it can be evaluated in the laboratory in the batch vs. continuous modes. Predictive models and/or good testing equipment for this comparison would assist this type of investigation.

Key needs to deliver these benefits

There are some key areas where advances are needed to realise some of the benefits listed above.

Scale – Data acquisition versus process design

Scale factors which need to be addressed include:

- Scale-up of wide range of physical properties across nano, micro and bulk scales, particularly for non-Newtonian, colloidal, crystalline, particulate and film materials (links to formulation, catalysis and materials sections).
- Scale-up of wide range of unit operations, particularly novel reactors, separators and product formation devices e.g. crystallisers, filters and dryers.
- Numbering-up or scaling-out rather than scale-up.

This will require intelligent HTT models, for example, to manage development of chemistry and catalysis simultaneously with engineering design of critical unit operations e.g. reactors/crystallisers to speed and enhance process development programmes to produce robust technology with reliable and large scaling (10 and greater)

Specific opportunity statements related to scale are listed below:

A radical reduction in the time taken to generate kinetic data for process design is needed so that potential scale-up issues can be identified earlier in the development process and appropriate processing technologies adopted (i.e. avoid the time cost of having to react retrospectively). This could be achieved using HTT to make this practical to do on an every reaction basis rather than only when absolutely necessary.

It would require harnessing key HTT capabilities such as: ability to measure; integration of experimental tasks including analysis and extraction of key response data and mathematical fitting. However, the following constraints must be overcome:

- ability to monitor reaction
- ability to run reaction
- may need reaction sampling
- reagent charging
- design of kinetic experiments and translation into system
- extraction of response data from analytical data
- ability to take response data and fit kinetics
- integration of data flows from sampling/data capture into response into kinetic analysis

Note: Newcastle University has been successful in an EPSRC HTT proposal on the automation of mechanism determination for chemical process development which addresses a number of the above constraints.

Another important but often neglected area is the scale up of the mechanics of the processing. This comes to the fore when on-scale up the products of the chemistry don't do what is expected of them and block the transfer pipes or scour and corrode the vessels or swell up so they don't filter or dry etc. For HTT to have a role in allowing these factors to to be tested during scale up equipment development is needed, as it is not readily available for such evaluations.

Product/Process interactions

Many products are becoming more sophisticated, for example, through formulation or more complex chemistry/materials science. The link between product properties and processing conditions requires a deeper understanding of these potential interactions and there are many more processing options to explore. Quality, stability or degradation (physical, chemical and biochemical) factors during processing, including storage must be rapidly assessed. In addition, there is a need to link product/process data analysis outcomes with higher level business processes and decisions i.e. cost modelling, candidate selection etc.

Specific opportunity statements related to product/process interactions are listed below:

1 Maximum product quality and performance (existing or new product scale up) could be achieved by using HTT to assess process parameters and derive understanding and quantitative models, including identification of critical variables. This would require harnessing a parallel small scale mimic of the preparation/manufacturing process. It will also need integration of process operations and data acquisition in process measurement, plus product analysis and characterisation to aid rapid interpretation of test data, modelling and parametric analysis. However, there are several constraints which must be overcome including:

- accurate, automated small scale solids handling, and general handling of dry and wet solids

- control of pH at small scale – and scalability of mixing to achieve similar pH distributions at large scale
- characterisation of solids: porosimetry, chemisorption, surface analysis, bulk composition
- in situ measurements – temporal resolution, for HTT and manufacturing units
- off-the-shelf data acquisition systems, applicable at small and manufacturing scale – enabler.

2. For complex processes, there is a need to accommodate multiple streams of raw materials of variable quality without compromising quality or consistency of process product, thereby reducing cost and environmental impact through eliminating failed batches. This could be achieve by using HTT to allow real time online monitoring of multi-parameter quality attributes in multiple raw material and product streams simultaneously.

3. Dramatically reduce the lead time for developing new process plant to make novel food products by further understanding of the processing characteristics of multiple ingredients in solid substances to improve the design of processing equipment. This could be achieved by using HTT to comprehensively define the relationship between product formulation and process design. It would require research into the effects of multiple ingredients in a complex food structure, including testing of product properties of ingredients to build up a knowledge database of ingredients and their effects on product characteristics. The experimental work would need to be complemented by using predictive modelling techniques for product properties. This would require close working within company to link NPD and Process Engineering departments.

4. Achieve the identification of novel biocompatible polymers with specific properties coupled with the need to manufacture economically and to secure a robust IP position. In this case, process definition has much less need for rapid make and measure capability and less reliance on system integration but both are still essential.

Systems integration

Systems integration of make and measure is needed to rapidly iterate to solutions for the optimum commercial route e.g. production of drug substances (see synthesis section). One opportunity raised during the roadmapping workshop was the development of new alkane-based routes to petrochemicals rather than more expensive olefin based routes, thereby simplifying the manufacturing process and reducing dependency on thermal cracking. This could be achieved by using HTT to screen a broad area of catalytic space for those compositions for alkane conversion. This will require new adaptive development and implementation approaches to existing petrochemical process/units which will challenge current industry practice.

While not a technology or software itself an equally important factor for success is people integration. Integrating the engineering approach with the lab (HTT) chemist approach and getting them to agree some common language and critical factors to be understood is crucial to ultimate commercial success.

Simulation, modelling and control

There is a need for further development of informatics approaches for significantly expanded process data sets and properties modelling for processing of complex materials. This would also advance the need for improved and more effective control systems in processing including new intensified processes.

Requirements for new or improved capabilities in process engineering

Short term (1-3 years)	Medium term (5 years)	Long term (10 years)
• Reaction and separation monitoring e.g. kinetics and rheology changes	• Miniaturisation of novel reactors and separators	• Real time multi-parameter monitoring in HTT set-up • Full sensor/Artificial Intelligence feedback for process control • Exploit Process Intensification and HTT

Summary

The key areas requiring research and/or development to fill some of the identified technology gaps or remove existing constraints are summarised below, aligned with the technology platforms.

Requirement for New or Improved HTT Capabilities

	Short term	Medium term	Long term
Synthesis • More versatile & robust equipment • Synthesis, process & isolation integration • Easy to use, cheaper, modular equipment • Efficiency gains	• Modular cheaper equipment • Link Synthesis to processing • Small scale operations • Guides for scale-out or number up	• Plug and play • Multi sensor control • Link discovery and process • Multi step synthesis	• Whole process integrated in one HTT “device” • Large design spaces with modelling and Artificial Intelligence • Apply to route selection
Catalysis • Accelerating in full R&D cycle: catalyst synthesis to process development	• Accelerated ageing tests • Data management solutions • Solids handling solutions	• HT kinetic data collection • Catalyst/precursor libraries • SAR library creation	• Handling complex mixtures • HT characterisation methods • Harmonised e-language
Bioassay • Faster, more targeted assays	• Increase throughput genetic assay	• Smart sample extraction • Handling difficult samples • Kinetic protein-based measurements	• Extend assay beyond binding constants eg. pharmacokinetics, toxicity • Integrate bio-molecule physical characterisation
Formulation • Handling difficult materials • Representative preparative methods • Characterisation methods	• Viscous fluids • Crystallisation methods • Interfacial tension	• Solids sampling, accurate dosing • Controllable and scaleable shear, milling, extrusion • Rheology, particle size	• Sampling impure components • Particle size selection • Materials properties
Analysis • Sample preparation & presentation • Measurement integrated with make • Physical property screening	• Sample preparation for difficult materials • High content screening • Miniaturisation	• In-situ measurements • Physical properties • Mechanical properties • Structures and Structure Property Relationships	• Specialised probes for physical properties • Inferential measurements • Non-invasive techniques
Materials • Accelerating the full R&D cycle for materials development	• Accelerated ageing tests • Data management solutions • Solids handling solutions	• HT screening methods for new functional materials • HT toxicity/environmental tests	• Handling complex mixtures • HT characterisation methods • SAR library creation
Process Engineering • Handling difficult raw materials • Monitor kinetics,equilibria • Rheology, heat & mass transfer	• Reaction and separation monitoring eg. kinetics and rheology changes	• Miniaturisation of novel reactors and separators	• Real time multiparameter monitoring in HTT set-up • Full sensor/Artificial Intelligence feedback for process control • Exploit Process Intensification and HTT

Capabilities required to underpin all platforms

There are some generic "cross-platform" capabilities which apply across all the technology platforms used for the above analysis. These are described as:

- Instrumentation
  currently available from suppliers or new requirements
- Automation and Robotics Engineering
  generic or bespoke technology for automating operations
- Data Handling and Interpretation
  ways of handling large quantities of information from HTT experiments so that human beings can use it to make decisions
- Integration – standards and inter-operability
  in an ideal world all HTT hardware and software would communicate with each other; additional protocols and specifications are also required to ensure high quality results from HTT.
- Organisational Implementation
  HTT is a disruptive technology for many laboratories and requires organisations and individuals to adapt in order to gain the full benefits

Instrumentation

At present a range of instrumentation exists, much of which has been developed to satisfy the drug discovery market within the pharmaceutical sector. This is well suited to the synthesis of new molecules and subsequent purification and analysis. However it often needs substantial adaptation to be used in other applications in different business sectors.

The range of instruments includes:

- various types of reactor for the synthesis of new compounds or materials
- instruments and reactors for high throughput screening
- analytical instruments for the characterisation and measurement of compounds and materials
- various techniques for determining physical properties and characteristics
- equipment for the production and analysis of images
- instruments for purifying compounds and materials

Ideally, the equipment available to scientists and technologists working with HTT should be:

- robust, with intuitive and user-friendly operation
- versatile and easily adaptable for use in different applications
- able to operate in different modes, depending on the skill of the user
- equipped with standard hardware and software interfaces – for linking to other equipment and to databases used for data mining, QSAR, QSPR etc.
- available in resistant materials to handle corrosive substances

There is a clear trend towards miniaturisation. Laboratories are using microtitre plates with larger numbers of smaller wells – as many as 3,456 or more wells in a single plate. This leads to the inevitable trade-off between speed and throughput on the one hand, and the need to manipulate, and make reliable measurements on, ever smaller quantities of material on the other. This also highlights the need to understand physical phenomena, such as mixing, in small wells and the need to have models or rules to understand scale-up.

There are also some specific demands on measurement capability. Instruments need to be designed to make representative, reproducible and meaningful analytical and physical measurements on small sample sizes. This is particularly challenging for physical measurements, such as rheology or viscosity, where it would be desirable to have specialised probes or sensors. The concept of having a battery of measurements on the same sample and the use of chemometrics to deconvolute the data in order to produce high information screening is very attractive, as is the development of in situ measurements, perhaps using intelligent sensors, to produce immediate feedback on a reaction or process.

Automation and robotics engineering

The application of HTT is critically dependent on robust and reliable automation and robotics. The current range of equipment available ranges from straightforward carousels for introducing samples into instruments, to complex sequences of automated processes using a series of robots controlled from a remote computer. As with instrumentation, much of this is well suited to pharmaceutical applications but often needs substantial adaptation to be applied in different business sectors.

In this context automation encompasses a range of robots and peripheral devices but also the use of automated systems in the laboratory, including continuous flow systems and dedicated automated systems such as those that might be used in clinical and other laboratories. Automation has also been applied to chromatography, spectroscopy and related measurement

systems. Other facets of automation include the use of artificial intelligence, neural networks, and related systems to automate experimental processes, potentially without human intervention, and various forms of data analysis (see page 39) which could be applied automatically to data sets, Human-computer interfaces, to ensure both integrity and ease of use, are becoming increasingly important, as is the interface between automated processes and Quality Assurance systems in industrial applications.

Automation of laboratory operations is highly dependent on sensors. Many of these are well established devices for sensing parameters such as temperature or position. As HTT systems develop however there is a growing demand for sensors which can operate in situ or non-intrusively, and in miniaturised environments. Examples include the use of specific chemical sensors to indicate the completion of a reaction or the use of proximal probe devices to measure surface forces on a micrometre or nanometre scale.

Perceived requirements for automation and robotics include:

- data systems and hardware components capable of straightforward integration
- scalability issues, particularly
  - the ability to produce samples on a microgramme scale which can yield representative measurements
  - the ability to control conditions (for example in microplate wells) and make measurements in situ
  - an understanding of rules and models to scale up from laboratory to process scale
- reliable and robust operating procedures, coupled with intuitive user operation
- flexible management software
- methodologies for handling difficult materials, such as viscous fluids, sticky materials, fine powders, solids in flowing streams etc., particularly on a small scale
- the development of multi-purpose screens relevant to product properties
- the availability of staff trained in the operation and application of automation and robotics.

The most significant new platform to impact on robotics and automation is microsystems, or lab-on-a-chip technology.

This has potential for application in the pharmaceutical, life sciences and specialty chemicals sectors. If successfully applied in these sectors it could significantly increase the rate of synthesis and screening of potential new products and reduce the inventory of chemicals used (and wasted) in the process. Fundamentally there is further potential to use microsystems in any application which can exploit the advantages offered by the unique properties of these systems, including laminar flow, diffusive mixing and surface-dominated physical effects.

Applications of microsystems include drug discovery (and potentially drug manufacture), formulated product development (for example home and personal care products) and diagnostic devices for medical or environmental monitoring applications.

The emergence of this technology will generate over the coming decade the need for basic research into applications on this scale but will also require the development of robust technology to integrate microfluidics modules into total systems. This is analogous to the development of integrated robotic systems in current use but will generate new challenges in terms of introduction of materials into microsystems, the control of flow, mixing and system parameters, and the generation of valid screens and measurements at this scale.

Data Handling and Interpretation

One obvious consequence of increasing experimental throughput is the generation of high volumes of data. However, there are other aspects of data handling and interpretation which arise from adoption of HTT, for example: what are the optimum experiment protocols to generate data e.g. via multifactorial experimental design; what quality of data is required for meaningful interpretation; how can experimental data generation be used to best effect in developing predictive models; etc?

The specific answers to these questions are obviously dependent on the research activity in question, e.g. a screening process for drug discovery research will be different to a synthetic route optimisation for process development. However, there are some generic issues, discussed in the sub sections below, which raise both significant opportunities for improved processes and also point out important targets for development of new capabilities.

Statistical experimental design

Traditional scientific training teaches “one-variable at a time” experimental methodology, i.e. set up experiments to limit variation in everything except systematic variation of one parameter and measure the effect of this variation to determine a cause-effect relationship.

In many systems, particularly complex, interdependent systems, this is not the most efficient experimental methodology and indeed in some cases, particularly biological systems, is not practically possible.

Statistical experimental design (SED, or statistical Design-of-

Experiment – DoE) methodologies are well developed and proven alternatives to this traditional approach, and, while familiar to many bioscientists, are perhaps, less well used or understood by those from the physical and chemical sciences.

There is clearly a need to have training for scientists to develop their understanding of such approaches – as part on ongoing professional development for those in the workplace and also to ensure greater exposure within undergraduate courses.

There is also a desire within industry to be able to access software systems which both make the set-up stages of experimental design "easier" for practitioners, and also, to have systems which are "smarter" or more intuitive, e.g. perhaps by having a front-end input system which allows the scientists to define the purpose of the experiment in natural language, and the software then translates that into a rigorously designed statistical experimental methodology.

A particular strength of high throughput experimentation is that it allows practical assessment of a much greater range of experimental parameter space and as such has great potential to allow robust investigation of multifactorial dependencies. This is particularly valuable in investigating complex systems, which, without this capability, are simply not amenable to investigation with traditional experimental methods.

The consequence of this is that there is a need for both training and for user-friendly software systems to allow industrial scientists to be able to set up experimental methods on their particular systems and to be able to interpret the results in a meaningful way. At present, this often requires the intervention of a trained statistician – a resource which is increasingly rare not only in an industrial research group but is a key skill shortage within the UK skill base in industry and academia.

Data capture and analysis

Clearly a consequence of higher experimental capacity is the need for informatics for dealing with very large design spaces. For screening activity with relatively simple yes/no selection, or identification of data points well outside of the norm, there are a number of systems for data handling and visualisation. However, where complex correlations between data sets is required, particularly in cases where trend analysis or quantification of interdependencies is required, then many *de facto* standard software packages do not provide easy analysis and new visualisation approaches are very valuable. An example of this is in analysis of data on the kinetics of chemical reactions – to be able to identify key response parameters and ability to fit them mathematically: which are key to developing robust process scale-up.

Another example of current importance in developing integrated assays to link drug discovery and medicine optimisation in pharmaceutical research or meet toxicology assay demands (e.g. to allow industry to respond to the EU REACH legislation), is to be able to integrate and correlate data on multiple bio-assay end-points e.g. P450 inhibition, metabolism, protein binding, DMPK, formulatability. Correlations of low cost or simple bio-screens with in vivo data is a challenge in this area.

As high throughput approaches are being applied to more complex materials, e.g. polymer design, composite materials, formulated materials, there have been valuable improvements in the use of chemometrics to determine correlations between "easy to accomplish" measurements (which can be readily integrated into a high throughput system) and more complex, but more "directly interpretable" methods (which give direct information on complex behaviour). For example, the use of inferential measurements like using Raman spectroscopy of polymer solids to correlate with the fracture behaviour of materials allows the Raman spectroscopy to be applied in high throughput screening of optimised materials.

Data mining and intelligent pattern matching are increasingly used on more complex data sets. This, coupled to the ability to generate much richer experimental data, can provide validation of algorithms for data interpretation and prediction.

There is still a perceived need for off the shelf data acquisition tools – which can be readily integrated with instrumentation, experimental design software and corporate databases via standard data protocols (XML is perhaps becoming a *de facto* standard but data formats still often a key problem, requiring time consuming data set corrections e.g. is the date format standardised between the data systems).

Algorithms are required to make selection decisions on complex or fuzzy data are required to enable the use of this approach in optimising performance properties, e.g. rheology or storage stability of a complex fluid.

Data streaming and interpretation from remote operations (distributed sensors, point of care diagnostics, remote centralised laboratories) are likely to become increasingly important, requiring development of standards, internet compatibility and middle-ware developments.

Data modelling and prediction

There are a number of both phenomenological and theoretical modelling applications which heavily dependent on having good quality experimental data to "fit" the correlations. Once populated, these models can then be used predictively. Typically, the scope of the parameter space over which predictions are valid is sensitive to the input data, and clearly, the use of high throughput experimentation can provide data from a wider range of parameter space than a traditional approach.

This becomes really valuable in populating multivariate models, where the interaction between different parameters cannot be assumed to be simply additive, and where experimental determination of a complex web of interacting parameters is required to produce a useable model. This is particularly true in optimisation of performance properties of products where different performance characteristics depend on a complex interplay of composition and manufacturing process e.g. the rheological properties of a foodstuff need to be tailored to give optimum flavour-release and mouth-feel as well as long shelf-life and good visual presentation.

The opportunity to generate data using standardised high throughput methods opens up opportunities to generate databases for common usage –e.g. reaction kinetics, toxicity assays, stability properties, behaviour of complex raw materials (e.g. commercial mixtures of surfactants, ingredients in foodstuffs).

This, in turn, opens up the opportunity of much more robust computer modelling to guide search in product design space across a range of industry sectors, particularly if integrated with *ab initio* and empirical models.

Data systems for operational support

In addition to handling experimental data to deliver R&D end-points, the use of high throughput technology engenders the need for software systems to facilitate the logistics of this type of experimentation, e.g. scheduling software to maximise use of robotics equipment, sample tracking (in process and also through storage and distribution chain) and audit trails for regulatory of process control applications.

There is opportunity to enable much more effective use of automation assets using systems for optimising workflow logistics which are coupled into the experimental design stages of the operation. Clearly this has implications on the interfaces between DoE, instrumentation and robotics control software and data capture and analysis systems.

Integration – Standards and inter-operability

As illustrated above, there are some major issues in the industry on effective integration of DoE and analysis software with data capture/transfer from instrumentations. There is a relative paucity of IT or hardware standards in this field, and no major supplier who might set a de facto standard as the supply side market is relatively fragmented.

This is a particular issue in adoption of systems which allow for iterative feedback – i.e. where integration of DoE and data analysis and data interpretation must be done "on the fly" – requiring methods for fast correlation in live data streams.

There are also some significant hurdles regarding regulatory acceptability of data generated by highly automated experiment systems. Data format acceptable to regulatory bodies and for audit of invention for filing IP are not yet fully defined and accepted.

Training and education is required to change cultural approaches (and open up the opportunities to exploit a potential paradigm shift in experimental methodology) and also to engender systems for greater cross-discipline skills use (and also address issues regarding the shortage of statisticians). In the medium term, this can also be addressed to some degree by further developments in easy-to-use front end systems to allow customisation of software functionality without re-programming.

In the short term there may be some pragmatic approaches worth pursuing in order to address the issue of standards in data representation. As stated above, XML is becoming the de facto standard for data representation and it should be possible to use XSLT to expedite data transfer between robotic systems and software packages (Spotfire, XL etc.). This should also allow data to be represented on a variety of computing platforms.

There is also a perceived difficulty in interfacing different suppliers' hardware. This issue is less straightforward to address due to the fragmented nature of the equipment suppliers. One approach would be to work alongside a trade association of relevant suppliers (e.g. ELRIG, the European Laboratory Robotics Interest Group) to establish an initiative aimed at agreeing and implementing standards within the UK, while maintaining links with and awareness of similar bodies in the USA or Europe.

Organisational implementation

It has been argued that HTT is a truly disruptive technology – the introduction of which will lead to radical changes not only in unit operations within a research or development group, but in the way organisations operate as a whole and even how they do business. An interesting analogy is the adoption of computer and IT systems into organisations in the 1970's.

Successful exploitation of benefits accruing from the use of HTT is dependent on the availability and further development of the science and technology capability, as outlined above.

However, there are additional criteria for successful implementation:

- availability of suitably trained scientists and engineers
- their acceptance of the value of adopting different methods of working
- organisational change to overcome barriers to realising the benefits of new ways of working
- cost-benefit and risk-benefit criteria can be established and justify adoption

It is clear that the "early-adopter" industrial sectors, e.g. drug discovery in pharmaceutical companies, implemented high throughput technologies in well-defined and compartmentalised sections of their R&D chain, i.e. in high throughput screening and combinatorial chemistry for drug discovery. It could be argued that while this has been successful in exploring far greater numbers of compounds, this has not, as yet, yielded the expected business benefits in delivering marketable medicines that were originally envisaged. While the reasons for this are complex, a key element to examine is that the discovery process is only the start of a long R&D chain, and high throughput technologies have made relatively much smaller in-roads into drug optimisation stages required to translate intrinsic activity into bio-available medicines, i.e. pharmacokinetics, toxicology, process chemistry, manufacturability, formulatibility and clinical assessments.

Partly this is due to scientific and technical limitation in the art, but other major issues are the benefit/risk evaluation required to make the investment in new approaches, and the cultural change required within organisations to adopt new approaches and deliver their benefits.

It is important to recognize and find routes to address these issues in any planned implementation of high throughput technologies.

Internal issues

While practicalities of real organisations limit the rate and scope of change that is achievable, it is critical to recognize the potential for change implicit in adoption of HTT throughput the organisation. Case studies of change management and innovation are helpful in providing frameworks to address these issues, and case studies specifically addressing high throughput capability implementation are being developed by InsightFaraday in conjunction with collaborators in management schools. In broad terms these cover two areas:

Cultural change – the recognition that effective exploitation of HTT will only be achieved through shifts in organisational boundaries, work patterns, skills and capabilities within the workforce. It is also apparent from some studies that the introduction of new technology can be an engine for cultural change as well as a necessary consequence.

Business model change: the starting point for companies engaging with HTT is often to deliver efficiency improvements within R&D –either doing the same things faster/cheaper or doing more things to make products or processes better. However, the ability to integrate product design (traditionally R&D) with flexible, high throughput manufacture (process intensification) can open up opportunities for radical changes in business models. For example, rather than making a "generic" product in bulk in a large manufacturing facility and shipping it globally, it becomes economically viable to make "bespoke" products in low volumes at globally distributed facilities servicing globally differentiated markets or even "personalised" products.

External issues

There are a number of issues which suggest that companies also have to have a carefully developed view of interactions outside their own organisation to develop the best approach to evaluation and adoption of high throughput technologies.

In addressing the potential value of new technology like high throughput technology, organisations typically need to address some common hurdles to adoption and implementation:

- the technical staff within the organisation are often not fully expert in the new technology, are increasingly under time pressure to deliver their current remit and have decreasing time to develop and implement new technologies
- multidisciplinary skills are required to encompass the range of capability to deliver business benefit, and either skills are not available in-house, or if they are, they do not have established

working practices to allow them to operate effectively together
- there is often a paucity of information or case studies which allow management an analysis of cost/benefit based on other companies experience
- the supply-side organisation required to service the industrial need is highly fragmented and requires co-ordination and adaptation to deliver the right products into the company
- the technology base is spread globally, and the UK may not be in a position to service all needs

This combination of factors suggests a very strong need to adopt a collaborative network among users and between users and suppliers, with global reach and integration into academic centres of excellence.

This can mitigate many of the hurdles listed above and also deliver a number of additional benefits:
- lowering the entry cost for both evaluation and adoption of technologies – this is particularly important in HTT adoption by mid cap companies and SME s. In addition to improving the in-house development of high throughput capability, this approach should also allow evaluation of contracted-out activity where high throughput elements of work would best be done via third-party expertise, e.g. if the in-house capital or running costs or skill development costs are not cost effective, or the rate of improvement of technology is too high to risk fixing on capital investment at that stage of technical evolution.
- sharing knowledge between non-competitive companies with common technical needs – both for higher quality risk benefit evaluation and also sharing development costs of new capability
- international benchmarking to determine strategic government policy and investment in industrial support and academic support programmes
- develop platforms for consultation and implementation of technical standards and best practice, improving effectiveness of the technology and, in the longer term aiding integration of automation and data systems and ultimately lowering costs and prices

Summary

Cross-platform HTT Capabilities Required

	Short term	Medium term	Long term
Instrumentation	• Miniaturisation • Robust and adaptable • Multiple measurements for high content screening • Cheaper entry level equipment • Easier equipment access	• Physical property measurement • Specialised probes and sensors • Synthesis and measurement integrated • Wiidespread use in universities	• Multiple measurements with integrated chemometrics and Artificial Intelligence • Exploitation of microfluidics and microarrays • Structured re-skilling
Automation and robotics engineering	• Multi-disciplinary training to include automation • Miniaturised sample handling, dispensing and presentation	• Techniques for handling and dispensing difficult materials • Flexible management software	• Artificial Intelligence built in for experimental design and interpretation • Incorporation of microfluidic components into integrated systems
Data Handling and Interpretation • Statistical Experimental Design • Data capture and analysis • Data modelling and prediction • Data systems for operations • Process modelling and simulation	•Greater training in DoE: more access to statisticians • Handling very large design spaces • Multivariate factorial modelling • Standards & connectivity to allow cross-platform use	• User-friendly “intuitive” software • “Live” data interpretation on large data sets • Algorithms for inferential correlations • Prediction for complex product performance • Integrate scheduling into DoE and data interpretation feedback	•Cross-correlate numerous end-point effects • Standards for data transfer: data streaming from remote networks • Self-optimising “whole-process” feedback algorithms
Integration • Standards • Interoperability • Product-process interactions	• Regulatory acceptance of HTT generated data • Identify and agree *de-facto* data format standards	• Data integration across platforms • Hardware integration via standardised common interfaces	• International formal standards
Organisational Implementation	• increased training in HTT methodology • Interdisciplinary project management • Better quantified case studies for cost/benefit • Sharing best practice • Improved understanding of HTT capabilities	• Strategic implementation across functional barriers in company • Business model diversification • “Shared cost” entry	• Cultural acceptance of different “experimental method” • Supply chain development

Barriers to Utilisation of HTT

So what is stopping companies being able to utilise HTT to deliver economic benefits?

Too often UK companies are accused of being risk-averse, and delaying adoption of new capability until a competitor has shown its advantage. While fast-followers can sometimes gain competitive advantage over first-adopters, e.g. if the capital cost of technology falls or efficiency improves, all too often late adoption leads to the catch-up rather than competitive advantage scenario. In other cases, the entry cost of building a fully in-house capability is too high to justify the potential return for an individual company –particularly mid-cap and SME companies.

In broad terms these can be addressed by activity to overcome two major barriers:

- awareness
- cost-effective access

Awareness of what is possible and where to find it

Outside of the pharmaceutical discovery activities, a key issue for exploitation of this approach is the relatively limited knowledge within companies on what is available now and what that might be able to deliver for them.

This is partly because the capabilities required to deliver HTT encompass a very broad range of scientific disciplines, so there is relatively little exposure to the approach in traditional undergraduate and graduate science courses and in addition, there are relatively few academic centres of excellence from which industry can understand the issues involved.

The UK Knowledge Base in HTT

Suppliers of HTT Equipment and Services

HTT laboratory equipment and software is available from a large number of UK-based suppliers. British-made automated laboratory platforms and software products compete for a relatively small market with leading US and European products. The costs of automated laboratory systems are too high for mass adoption and bespoke solutions are often required. A large number of British engineering firms, mainly SMEs, specialise in customised laboratory automation or in integrating products from other suppliers to produce bespoke automated laboratory solutions.

There is a case for action to help boost this sector by creating user networks and stronger supply chain relationships.

The UK Knowledge Base in HTT

Universities

There is a growing number of university departments in the UK actively developing and applying HT approaches to specialist research areas, including:

Cambridge University – *synthetic chemistry, chemical biology and theoretical chemistry*
Southampton University – *inorganic thin films, polymer science and bioscience*
Liverpool University – *materials synthesis, process chemistry*
Newcastle University – *chemical engineering*

Several other UK universities have research interests in the design and application of *microfluidic* devices in *synthetic, biological* and *analytical chemistry*.

Industry can gain access to HTT expertise in these centres through collaborative research programmes. The centres are a useful source for training in HT methodologies as well as trained personnel.

Where companies have developed in-house capability it is seen as a source of competitive advantage, and also difficult to patent, and this imposes a significant degree of confidentiality in the industrially used capability, which limits industry to industry technology transfer.

Therefore it is important to develop information dissemination platforms and networks or “communities of practice”, to inform and train industrial (and academic) researchers on the potential benefits and the capabilities required to deliver them, to allow organisations to make informed, high quality risk/benefit and cost benefit decisions on adopting the approach.

Cost-effective access to currently available technology

It is clear that for there to be significant increase in the utilisation of HTT approaches in industrial R&D, there are two major initial hurdles to be overcome:

- Lower entry cost – current capability is often bespoke, tailored to narrowly defined needs and requires significant resource to implement into a company's working practices. The supply chain is not well established, often requiring "integrator companies" to pull together a diverse supply network and build into a utilisable platform. This is exacerbated by the patchy coverage of industry standards to allow easy integration of component parts into a system. The market is still growing, from a relatively low base: making economies of scale difficult in some technology areas.
- Access to skilled personnel to specify, evaluate and make best use of the facilities: many companies find that the R&D staff have diminishing time to develop and implement new technology –the technology might be available, but no internal resources are available to implement it in the company.

Clearly, a system to create and structure access to commercially operated shared facilities is potentially an attractive route forward. Such facilities could provide a range of services:

- As a hands-on introduction to HTT
  To allow initial investigation of potential opportunities

- For training personnel and developing good practice
  For many HEI's and small companies resource restrictions mean that they do not have up to date equipment, trained staff or facilities to use HTT approaches in their operations.

- As an entry level exploration of the utility of HTT to a company/academic group
  To allow exploration of benefits to companies low on the learning curve –to allow them to take first steps towards building their own HTT capability. Particularly useful for "slow" follower and medium size companies. They have sufficient critical R&D capability to build in house expert users but are constrained by capital cost of entry or do not know the level of use capacity they require until they have experience of using facilities. Academic user groups may also find this useful.

- Ability to run a commercial project in HTT mode without investment in in-house capability
  This would allow companies unable to meet current entry cost for in-house capability to use HTT. This particularly applies to small and medium companies, who may have sufficient expertise in house to run kit, but current views on cost/benefit preclude in-house investment. It could also apply to larger companies where part of R&D chain needs less frequent access to a wider variety of capability.

- Ability to evaluate next-generation capability or share costs of developing new capability
  This would apply to larger companies wanting to run "real world" evaluation of the next generation technologies before investment; would benefit from consortia to test and build new capability and academic user groups.

Facilities in Germany and Switzerland – a benchmark to aspire to

In October 2003 a UK Global Watch Mission was organised to assess the position of HTT development and exploitation in Germany and Switzerland, particularly for performance evaluation. The report of this mission was published in January 2004 (see www.insightfaraday.org).

The mission team found a cluster of activity in HTT situated along the Rhine Valley. This geographic area has the largest concentration in the world of industrial users, universities and high technology suppliers of HTT equipment. The capabilities were created with the support of the Federal Ministry for Research and Technology, leveraged with further regional, national and European funds. One of the best examples was the University of Freiburg which provides research, a range of technology platforms, equipment and trained personnel. This centre offers facilities and expertise to companies throughput Germany and Switzerland and has clearly catalysed a step change whereby HTT methods have become the norm for product and process development.

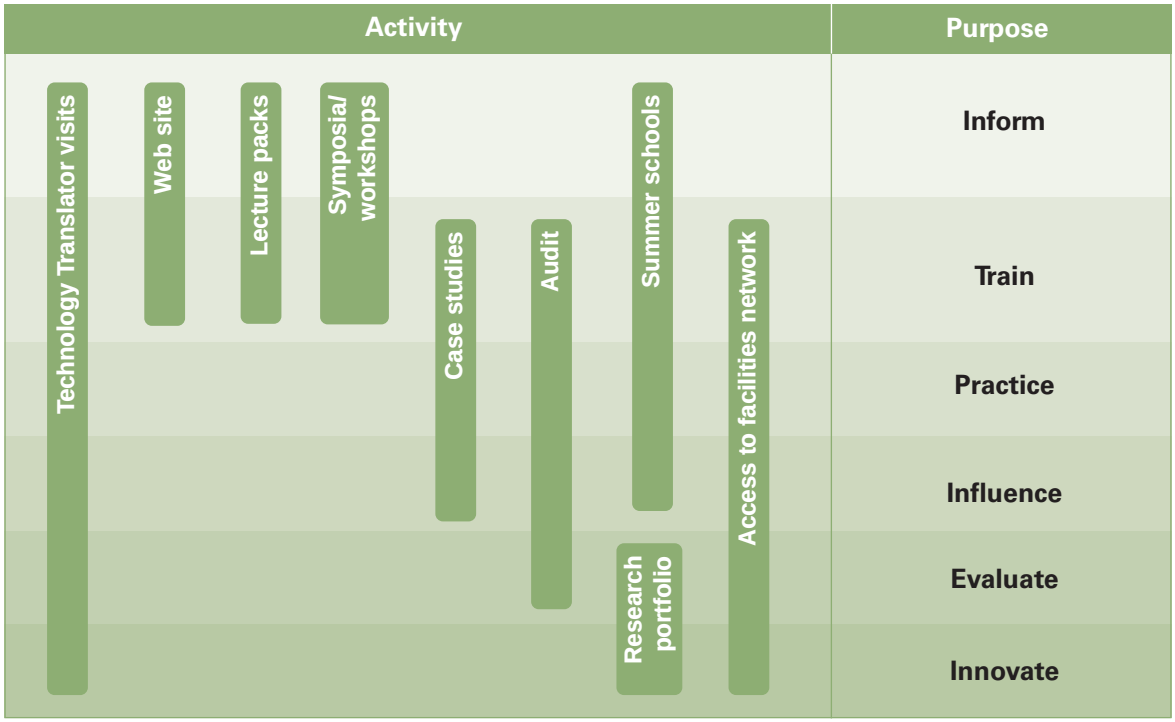
Action plan and recommendations

What has Industry asked InsightFaraday to do

InsightFaraday's role is to encourage appropriate use of high throughput capability, focused primarily on R&D stages of business activity, but recognising the importance of this approach in process intensification and manufacturing.

This roadmap and the consultations which have contributed to it provide some clear messages from industry on what it regards as the action priorities for InsightFaraday in order to encourage the exploitation of HTT in the UK. These are:

- provide advice to industry on HTT implementation
- enable UK industry to gain access to facilities and centres of expertise in the UK or elsewhere
- influence the relevant government bodies, using the roadmap, to allocate funding aimed at encouraging the uptake and development of HTT
- establish networks of practitioners with common interests, and organise meetings and conferences on specific topics, to encourage the sharing of knowledge and experience
- stimulate new research and development to address technology gaps hindering the delivery of the next generation of HTT
- engage in technology transfer activity to address the shorter term issues which are inhibiting the take-up of HTT
- commission training and development offerings, aimed at students and current practitioners, to increase the supply of knowledgeable, multi-disciplinary people available to UK industry.



InsightFaraday will develop its range of services focused on these requirements

What InsightFaraday can help make happen with additional partners & resources

There are many ways in which InsightFaraday can leverage its effort through working with partners from

- industry, both users and suppliers of HTT
- academic centres, focusing on both research and more immediate services to industry
- other suppliers of services which are complementary to those of InsightFaraday
- professional bodies, trade associations and similar consortia where aims and objectives overlap
- national and regional government, to gain support and appropriate funding

Some of these, which have emerged from the technology roadmap consultations, are shown in the table below.

InsightFaraday Interactions and Activities

Industry	Academic Centres	Service Suppliers	Professional Bodies	Government
Identify user industry's needs Encourage suppliers to address key issues Publicise case studies Engage in technology transfer and longer term research	Stimulate research to address needs and gaps Establish high throughput facilities Set up regional centres to provide access to industry Training material for degrees, masters courses and summer schools	Joint product development and marketing: eg. Chemical Faradays, PICME, Britest and others Co-ordinated approach to improved process development, including CPACT, Britest, academic centres	Align efforts with the Chemistry Leadership Council/Chemistry Innovation Centre Networking and events, jointly with RSC, SCI, CIA, ELRIG Develop training products in collaboration, eg. with RSC	Funding and sponsorhip from DTI Collaboration with research councils on longer term priorities Collaboration with regions to set up centres of expertise to support industry

What Companies can do

In the light of this technology roadmap it is recommended that companies should review their HTT strategies. More specifically

- companies who are current or aspiring users of HTT should examine their implementation plans and if appropriate seek advice from InsightFaraday on their options, the costs and the expected benefits
- companies who supply HTT equipment should consider how to extend their product range to meet the level and type of demand
- companies should articulate their own requirements for
  - networking
  - training and recruiting
  - technology transfer
  - long term research
- companies should encourage their HTT practitioners to participate actively in networks which are of value to them

InsightFaraday is well placed to assist companies in considering their requirements and to establishing networks, products and services to meet their needs.

What the Government can do

This technology roadmap, and the events which produced the information collated within it, demonstrates that

- the potential value to UK plc from implementing HTT to improve new product and process innovation is very significant
- there is a clear role for managed assistance to ensure that the UK draws the maximum benefit from these technologies and their contribution to innovation and world competitiveness.

The most obvious means of achieving this is through funding priority areas, for example:

Research Councils

- Longer term research on new platforms and critical underlying science
- Establishment of training and education vehicles, such as Masters courses
- Incentives and encouragement to second academics into industry and vice versa

Department of Trade and Industry

- Take into account the key messages and themes in this roadmap when formulating its Technology Strategy
- Provide assistance, through its Business Support Solutions, to enable companies, particularly SME's to gain access to this technology
- In particular provide support to applied research projects that align with the key short and medium term requirements identified

The Regions

- In sectors where there is a fit with the regional innovation strategy, provide assistance to companies to encourage the take-up of HTT
- Encourage the establishment of academic HTT service centres with the potential to offer world class facilities and expertise for research and industry access.

It is further recommended that the above actions should be co-ordinated nationally to ensure that they support and complement each other.

Acknowledgements and sources of information

Information was gathered from a number of activities. Insight Technology translators have made over 50 in-depth consultations with companies and academics. There have been two major, focused, consultation exercises during 2003 with active practitioners of high throughput technologies, and a highly structured roadmapping workshop in March 2004 to obtain a reasonably detailed view of how HTT may be of benefit to user organisations. Delegates for the workshop were chosen to represent a broad cross-section of users, bringing experience of a range of R&D stages from different industry sectors. There were also representatives of supply-side companies including instrumentation, automation and robotics, data analysis and IT as well as experts in high throughput science and technology from academia.

Delegates were asked to classify themselves/their companies to understand where issues are different or common in different industry sectors, or at different points in the R&D & manufacturing chain.

Questions	% of respondents
Familiarity with HTT	
Expert	60
Aware	40
Where do you sit in the Innovation Chain (Multiple answers allowed)	
Enabling Research	60
Product Discovery	40
Product Optimisation	44
Process Definition	30
Product Manufacture	14
After Sales/Tech Service	8
Other e.g. overall management covering several areas	32
'Materials' being created/analysed/manipulated/studied (Multiple answers allowed)	
Biological material/macromodules	40
Catalysts	34
Ceramics	4
Formulated Material-i.e. complex mixtures or physical forms	48
Inorganics	12
small molecules (<1000)	34
Metals	6
Polymers and Fibres	32
Surface Treatments or coatings	20
Other	20
Type of company/industrial sector (Multiple answers allowed)	
Automation/Robotics	18
Agrochemicals/Biocides	18
Contract analytical	8
Catalysts	10
Energy	8
Effect Materials/molecules	8
Electronic Devices or Displays	6
Foods	10
Home and personal Care	8
Instrument Supplier	10
Life Sciences	22
Materials	16
Pharmaceuticals	40
Speciality Chemicals	22
Software or IT	14
Other	22

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GlaxoSmithKline
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Infineum
Johnson Matthey
LGC
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Insight

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