Collaborative research in action

ReMediES

RE-configuring MEDIcines End-to-end Supply

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Authors[1] and expert contributors[2]:
Dr Clive Badman[1], Dr Jagjit Singh Srai[1],
Andy Dwyer[2], Dr Stewart Mitchell[2],
Catherine Hunter[2], Dr Markus Schober[2],
Liz Meehan[2], Heidi Keeling[2], Tim Marsden[2]

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Collaborative research in action

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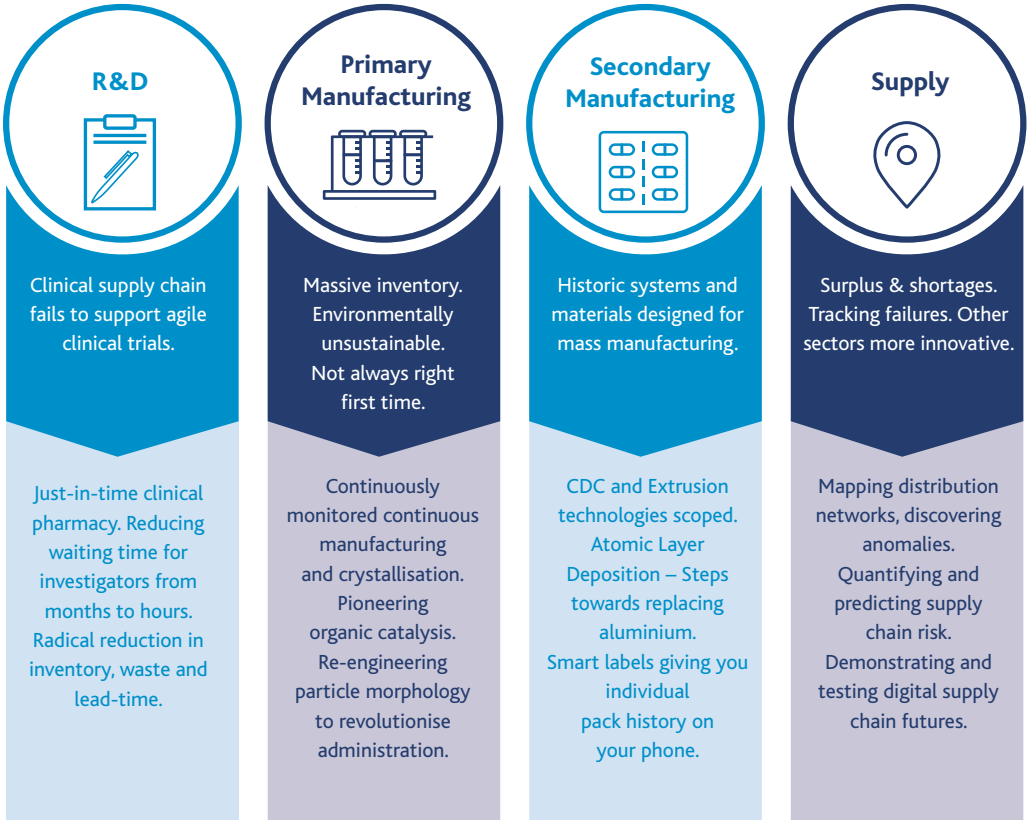
Introduction

Medicines manufacturing is an important part of the UK economy, employing 40,000 people and generating $33 billion in exports.

As recently commented by Andy Evans, Chairman of the Medicines Manufacturing Industry Partnership (MMIP), it is 'the most productive element of the most productive part of the UK economy.' In many respects, therefore, medicines manufacturing is a success story.

But there is work to be done. Product development cycles are long and attrition rates are high, leading to development costs of around $2.6 billion per product. Clinical trials often take place many months after the trial drugs have been manufactured resulting in significant stock write-offs of 50% or more. The sector also suffers from a cumbersome, inventory-heavy commercial supply chain. If the UK is to remain competitive, medicines manufacturing needs to embrace change and become faster, more responsive and more cost-effective. It also needs to be ready for the future, for the new personalised medicines that are on their way and which will revolutionise healthcare delivery.



"The UK is already one of the best places in the world to research and develop exciting new medicines for hard-to-treat diseases, but needs to improve when it comes to manufacturing and packaging them, ready to go to patients."

Andy Evans, Chair of the Medicines Manufacturing Industry Partnership (MMIP)

"Pre-competitive collaboration has accelerated technological development as investments leverage expertise and resources across a consortium of partners. Successful collaborations can have a flywheel effect as technologies develop quickly, and relationships build, providing confidence for further collaborations."

Dr Jag Srai, University of Cambridge

To date, pharmaceutical companies have not found it easy to innovate in manufacturing. The sector is highly regulated which instils caution in all parties. The underlying science, the manufacturing processes and the supply chains are complex and need major investment if real progress is to be made. In short, the hurdles are just too high for a single company to clear on its own. The solution: pre-competitive collaboration, with the active participation of the regulator.

In 2014, the ReMediES project was launched, bringing together 22 industrial partners including global pharmaceutical companies, major contract manufacturing organisations, equipment manufacturers, international logistics specialists and a global pharmacy. The Universities of Cambridge and Strathclyde provided expertise in supply chain and pharmaceutical product and process engineering.

Together, these organisations set to work on some of the key challenges facing small molecule medicines manufacturing. Can we run our clinical trials more efficiently, reducing waste, inventory and lead-times? Can we adopt advanced technologies to make both our primary and secondary manufacturing processes right first time, more flexible, more environmentally sustainable and capable of responding to changing demand? Can we apply science to create more soluble medicines? Can we package medicines in ways that will reduce wastage and help with patient compliance? And can we get better at delivering drugs to the people who need them, when they need them?

Over the last four years, the ReMediES partners have worked together to tackle these fundamental, cross-sector, cross-functional challenges, making real changes today to how medicines are made and supplied – and ensuring the sector is well placed to deliver the medicines of tomorrow.

Dr Clive Badman, OBE
Vice-President Pre-competitive Collaboration, GSK, Project Director, ReMediES

Dr Jagjit Singh Srai
Head of Centre for International Manufacturing, Institute for Manufacturing, University of Cambridge, Research Director, ReMediES

£11.5
million government* funding & £11.5 million industry funding

22
industry partners + Universities of Cambridge and Strathclyde

83
jobs created

405
safeguarded

4 year programme

8 workstreams

100+
individual projects

*through the Advanced Manufacturing Supply Chain Initiative (AMSCI) and the Scottish Funding Council.

Executive Summary

The aim of the ReMediES project was to improve the manufacture and supply of medicines by tackling inefficiencies across the end-to-end supply chain, developing faster and more responsive production processes, deploying smart packaging technologies to support tracking and compliance and redesigning delivery models.

Through collaboration, the partners were able to take fundamental and applied research through to prototype or commercialisation.

Highlights

Clinical supply chains

A new 'Just-in-Time' clinical pharmacy has been prototyped that can provide drugs to support complex drug trials, reducing costs, increasing responsiveness and enabling a more flexible and exploratory approach to clinical research.

Primary manufacturing

Through a number of related projects, ReMediES has made significant progress in developing new chemistries and processes that support the move from batch to continuous manufacturing, shrinking factory scale, increasing speed and reducing cost.

It has resulted in:

- *new equipment for continuous processing with immediate commercial applications that support right-first-time manufacturing, yield improvements and inventory reduction.*
- *the development of a new GMP supercritical fluid manufacturing facility in the UK.*
- *significant advances in biocatalyis and the use of enzymes in flow.*

Secondary manufacturing

A major, three-part project in secondary manufacturing has piloted new equipment for continuous drug isolation, continuous direct compression and, for hot-melt extrusion, capabilities that enable shorter production cycles and volume flexibility. Substantial reductions in the cost of production will result, estimated for one company alone at £10m per year once fully implemented.

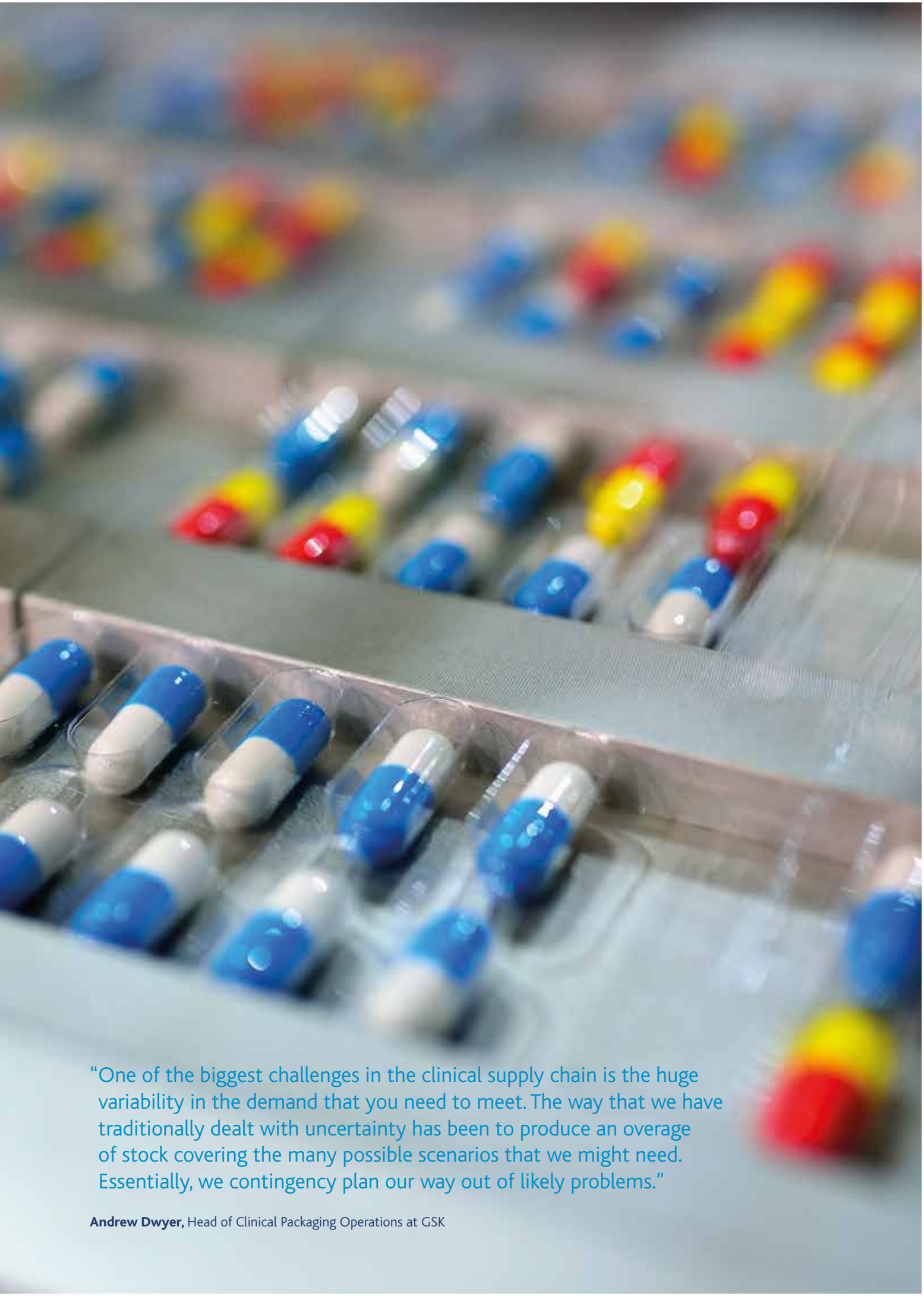
Packaging

Smart labels using printed electronics have been developed to enable product tracking, monitoring and supporting patient engagement. Commercialisation opportunities are being pursued with leading packaging manufacturers. New pack formats have also been introduced, significantly reducing cost and waste. Encouraging steps have also been made in identifying more sustainable and cost-effective packing materials.

Commercial supply chains

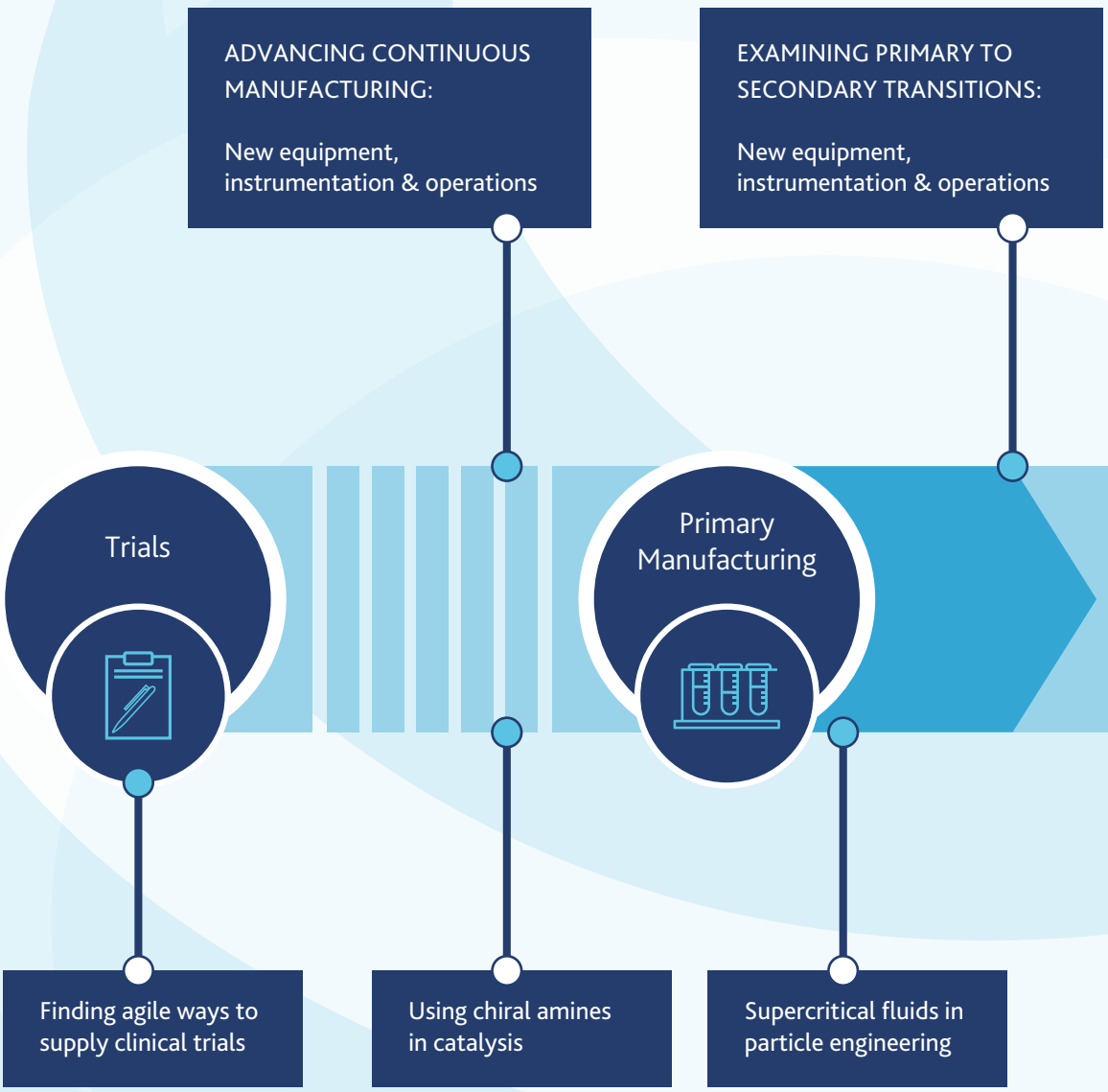
An end-to-end supply network design, analysis and modelling platform has been developed to help manufacturers understand the opportunities that these technologies present to reduce inventory and increase speed-to-market. Alongside this is the development of a digital factory demonstrator which is allowing a ReMediES partner to use a control tower platform to improve service and delivery for one of its major product lines.

As well as delivering real breakthroughs, the project has given supply chain partners a much clearer understanding of each others' knowledge and capabilities, roles and requirements. This can only serve to strengthen the UK's supply chain and foster future collaboration. Establishing a supportive regulatory context for these emerging technologies was also fundamental to the success of the project. ReMediES was able to engage with the UK regulator every step of the way, allowing for rapid review of the regulatory implications of these new technologies.

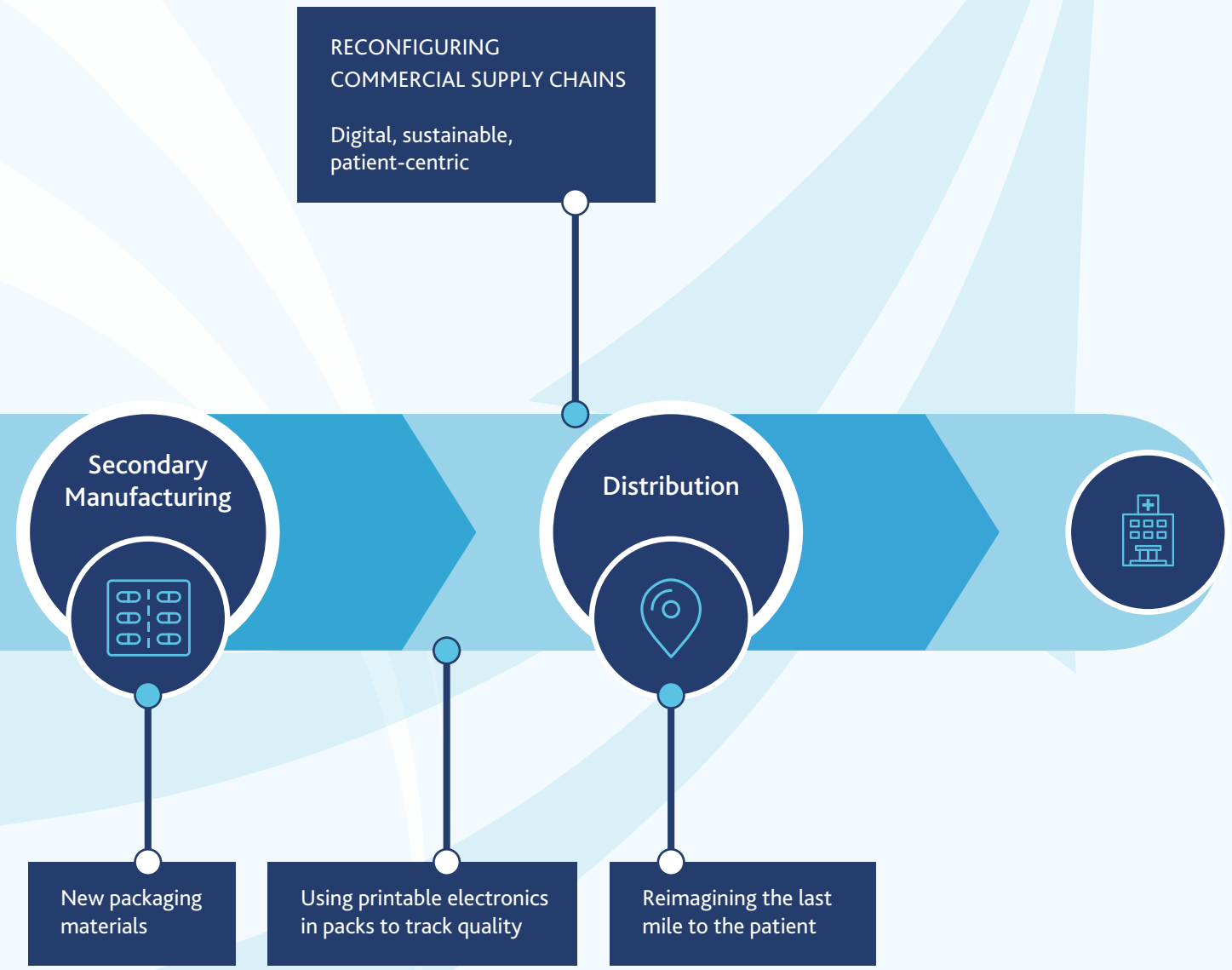


"One of the biggest challenges in the clinical supply chain is the huge variability in the demand that you need to meet. The way that we have traditionally dealt with uncertainty has been to produce an overage of stock covering the many possible scenarios that we might need. Essentially, we contingency plan our way out of likely problems."

Andrew Dwyer, Head of Clinical Packaging Operations at GSK



The ReMediES project: collaborative research in action



ReMediES has made significant progress in tackling some of the key challenges facing medicines manufacturing in the UK. It has done this by bring together a multidisciplinary team from across the pharmaceutical sector along with research expertise from two of the UK's leading universities. Together they have made some real breakthroughs along the end-to-end supply chain, advanced some early-stage technologies and collectively provided a solid foundation on which medicines manufacturing and supply can continue its transformation.

R&D: reinventing clinical supply chains

PROJECT LEAD:
Andrew Dwyer, Head of Clinical Packaging Operations at GSK

PARTNERS:
GSK, AstraZeneca, University of Cambridge, InterSys Risk

Clinical trials are a critical part of pharmaceutical R&D. As medicines become more specialised and the regulator more demanding, these trials are becoming increasingly complex to manage, often involving thousands of patients at hundreds of sites in different countries. At the same time, the sector wants to bring new medicines to market more quickly and more cheaply.

The current system is both expensive and inefficient. It costs in excess of £75 million to run the clinical trials for a new drug and up to 75% of drugs trialled never make it into commercial production.

Because the sector is still reliant on high-volume production techniques it has to manufacture a trial drug in large quantities, often before the patients have been recruited, sometimes without confirmation that the trial is going ahead. Clinical teams are therefore required to decide the doses of the drugs they are trialling – and hence how much needs to be manufactured – 12 to 18 months before they expect to use it. As a result, more drugs are made than are needed to cover contingencies.

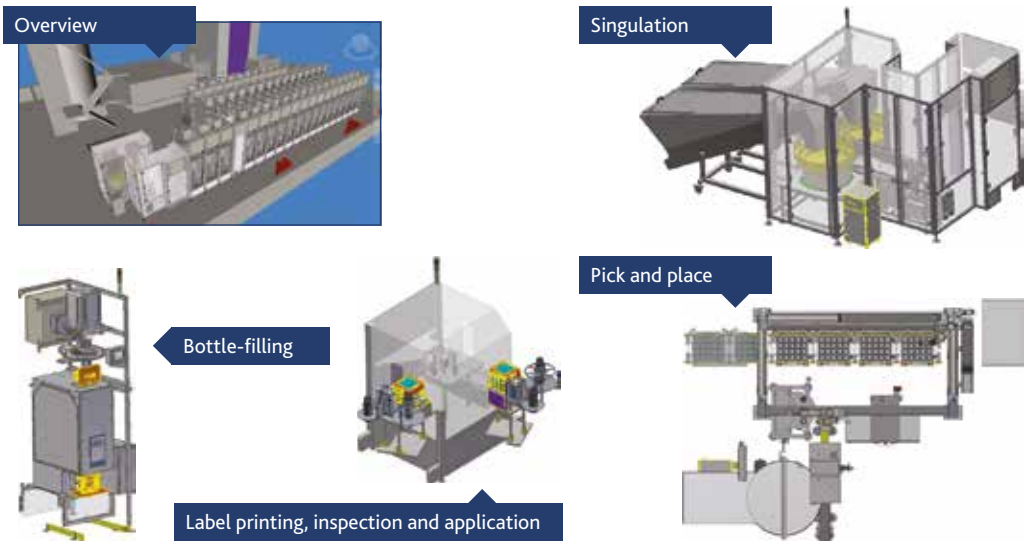
The process is also not sufficiently agile to respond to the changing circumstances inherent in any trial. For example, early results might suggest altering dosing or randomisation strategies. Or there may be an issue with recruitment and a sudden need to expand the trial into a different country with a different set of regulatory approvals, different packaging rules and different languages on the labels.

These eventualities are difficult, if not impossible, to deal with in the current supply model.

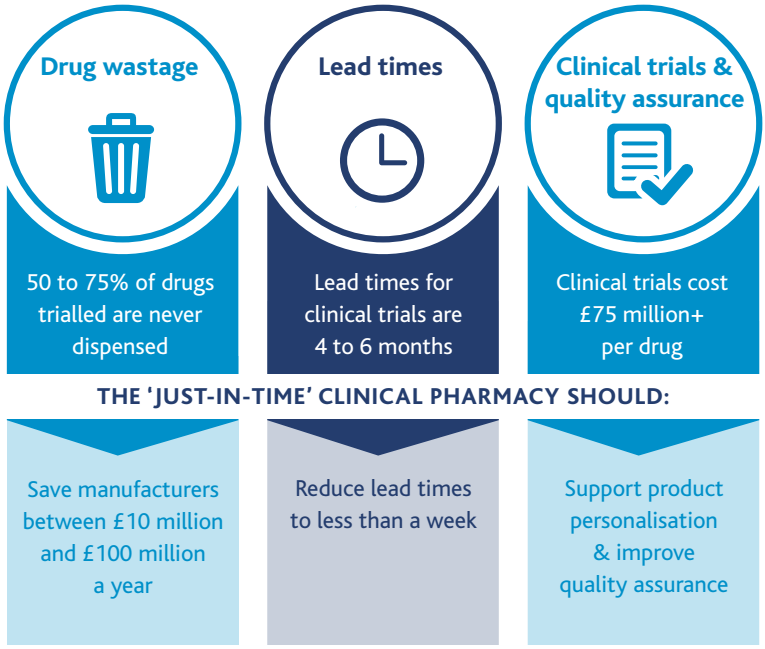
A more agile supply chain would allow researchers to be more exploratory in the early stages of clinical development and to respond to the data as it is generated during the trial. But the stakes are high when introducing change to the clinical supply chain. Clinicians need to be reassured that they will have a secure and uninterrupted supply of medicines to trial patients in the right place at the right time.

The ReMediES ambition

The project addressed two related issues: reducing the cost of running trials while creating a more agile and responsive system that will allow clinical researchers to adopt more exploratory practices and hence, potentially, bring a wider range of medicines to market.



Just-in-time clinical pharmacy.



The approach

By mapping existing clinical supply chains, visualising new ones, looking into novel equipment and automation technology and carrying out risk assessments, the team developed the concept of a 'just-in-time' (JIT) automated clinical pharmacy for use in drug trials. This represents a completely new approach to supplying clinical trials and one which could respond to orders and supply patients in days rather than months. Its new supply and rapid quality release capabilities were evaluated by analysing field data from previous clinical trials and simulating a proof-of concept inventory profile. This allowed the team to explore scenarios in which the level of inventory was reduced while enabling the system to cope with the dynamics of uncertain patient recruitment and deliver enhanced service levels.

By integrating robotics with control systems and data management the team was able to conceptualise an automated system for dosing a drug substance into a capsule, accurately dispensing a given number of those capsules into a bottle, completing the packaging with the appropriate clinical label, releasing, certifying and dispatching within a 24-hour time frame.

Replacing slow, manual, made-to- stock processes with rapid, automated, made-to-order processes will increase speed in the supply chain, enable product personalisation, increase quality assurance, improve efficiency and allow for the development of 'dose-to-order' innovations which should lead to better medical outcomes.

Outcomes

The team has developed a detailed engineering design model which is ready to prototype. The modelling of stock implications for a made-to-order facility has demonstrated that the potential benefit of an automated clinical pharmacy could be savings of tens of millions of pounds per year per company. This work will be taken forward by the new Medicines Manufacturing Innovation Centre (MMIC) in Glasgow and represents one of the 'Grand Challenges' of this new facility.

"If we can flexibly manufacture and supply clinical trial medicines to clinicians in days rather than months then we will offer researchers the opportunity to rethink how they design and operate their studies, potentially enabling the development of new medicines sooner and/or more cheaply than is currently possible."

Andrew Dwyer, Head of Clinical Packaging Operations at GSK

Transforming primary manufacturing

Within the commercial supply chain, primary manufacturing typically takes place in high-volume, batch processing manufacturing plants designed in the era of large-volume / low-product-variety operations.

However, in today's more complex product portfolio, this plant configuration results in inflexible operations and the production of too much intermediate stock. The sector has long been bedevilled by its high levels of inventory – typically it has 18 months' of stock available at any one time.

The challenges at this stage of the manufacturing process are similar to those facing the clinical supply chain: a reliance on the overproduction of stock to mitigate a lack of agility in the downstream supply chain. The sheer scale of batch manufacturing means that mistakes are expensive. If something goes wrong in a 10,000 litre vessel, the waste of energy and materials is significant. In continuous manufacturing, on the other hand, the process supports greater scale flexibility, amenable to low and high throughput operations that can be constantly monitored through advanced process-analytical technologies to ensure quality.

Quality is another area of challenge for medicines manufacturing. To put that in 'Six Sigma' terms, the sector's quality levels remain at 3 to 4 sigma. In other words, quality control is used to manage quality defects in manufacturing processes that can be as high as 6.7% or as low as 0.62%. In a six sigma environment the target is to reduce defects to below 0.00034% or 3.4 defects per million.

Other sectors have been faster to adopt advanced manufacturing technologies and reaped the twin rewards of greater efficiency and better quality. The pharmaceutical sector has targeted a number of advanced manufacturing technologies, particularly in continuous processing, identified as being particularly attractive for both small scale and very large scale manufacturing. It is also the case, that continuous manufacturing is not appropriate for all types of API production and that batch processing still has an important role to play in manufacturing certain medicines.

However, the sector now has achieved real momentum in the adoption of continuous manufacturing and ReMediES has played an important part in making that happen.

The ReMediES ambition

To drive right-first-time quality and reduce the high levels of stockholding while developing innovative techniques and processes that will reduce both cost and environmental impact.

The approach

ReMediES focused on a number of related areas that together would have a significant impact on primary manufacturing processes, support the move to continuous manufacturing where appropriate and make efficiency gains elsewhere.

The approach involved exploring specific technology areas: the development of organic catalysis through the use of enzymes in continuous flow reactors, developing plug-and-play continuous manufacturing equipment to support a range of chemistries, and taking supercritical fluid particle engineering to the next level with GMP facilities in the UK.

BlackTrace: Continuous Processing (including reaction, separation and particle formation).

Towards continuous manufacturing

PROJECT LEADS:
Dr Stewart Mitchell and John Mulgrew, CMAC Future Manufacturing Research Hub, University of Strathclyde

PARTNERS:
AstraZeneca, GSK, Robinson Brothers, Thomas Swan, Blacktrace, PSE, IntensiChem, Mettler Toledo, C-Tech Innovation, Cambridge Reactor Design, Perceptive Engineering, University of Cambridge

The aim of this project was to develop different types of mobile continuous process equipment that could be used by major manufacturers and contract manufacturers for a range of chemistries while developing knowledge and capabilities across the supply chain.

Its ultimate aim was to improve quality, increase the speed and reduce the cost of manufacturing medicines.

This workstream created a shared platform for process technologies which brought together a number of technology companies and their end users to develop and prove high-tech application technologies in areas such as mobile continuous processing, higher pressure hydrogenation and crystallisation.

A range of continuous manufacturing technology platforms has been developed. Two of these are ready for commercial production, and the others have moved out of the laboratory and into piloting.

Blacktrace has developed a complete continuous processing scale-up platform including reaction, separation and particle formation which will be available commercially in 2019.

Cambridge Reactor Design built three new technology platforms:

- *A continuous system for pilot-scale manufacturing, with heated reagents, highly corrosive reagents and products. This equipment has been trialled and purchased by Thomas Swan Ltd.*
- *A continuous mobile hydrogenation unit for lab-scale operation which has been tested by Robinson Brothers.*
- *A mobile continuous crystallisation platform capable of being located within a GMP facility geometry platform.*

Intensichem developed and built high-pressure flow hydrogenation test and scale up rigs and full-scale development (cGMP) and production. Full-scale proposals are being discussed with RBL and GSK.

C-Tech developed and built a continuous microwave reactor. This has resulted in improved yield and purity analysis on MW reactor trial runs for Robinson Brothers with a step change in rate from days to minutes.

PSE & Perceptive Engineering Ltd delivered a laboratory system to demonstrate process modelling, experimentation and model predictive control at CMAC on continuous processes.

A, B and E: Cambridge Reactor Design for continuous crystallisation and reactors.
C and D: C-Tech microwave flow reactor.
F: Intensichem commercial flow hydrogenation.

Transforming particle engineering

PROJECT LEAD:
Catherine Hunter,
Director, CrystecPharma

PARTNERS:
Juniper Pharma Services,
AstraZeneca, CMAC

Supercritical Fluids (SCFs) have been widely used in sectors such as chromatography and separation science but have yet to realise their full potential for medicines manufacturing. Given recent developments in scalability and simplicity of engineering, SCF represents a significant opportunity to streamline product development in key areas such as enabling optimised respiratory drug delivery and processing of biological medicines.

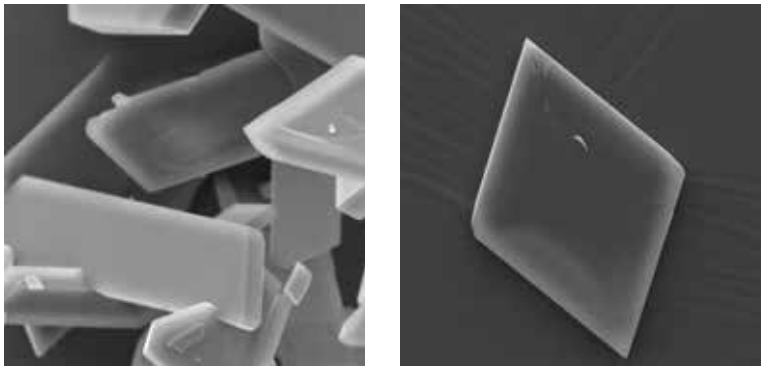
One of the key characteristics of using SCFs to engineer particles is the high level of control that they offer. It is also a single step, and so high yielding, operation offering the potential to significantly reduce manufacturing costs.

The process is 'bottom up' (with particles grown from solution) and so generates particles which have well defined physical, chemical, structural and surface characteristics. In many cases, these features can be altered by modifying the processing conditions, such as temperature, pressure, solvent choice and fluid flow. This level of control means it is possible to design particles to achieve a Target Product Profile. It could, for example, improve the stability and storage of medicines, generate particles that are more soluble and so act more quickly in the body, and enable the development of products that can administered in a more patient-friendly way through an inhaler rather than by injection.

The goal of this project was to establish if Crystec's mSAS (modified supercritical anti-solvent) SCF technology could represent a more cost effective and potentially higher-quality approach to product manufacture, whilst also offering flexibility of scale, through the establishment of a robust SCF-based pharmaceutical manufacturing supply chain in the UK. To achieve this the team focused on a range of case study compounds to demonstrate the versatility of the platform in handling a wide range of different molecules. The throughputs were then also considered and increased where possible. In addition, some of the programme focused on whether mSAS SCF technology could form an integral component of other continuous crystallisation approaches in order to provide further opportunities to streamline the end-to-end supply chain.

Success stories

A commercial scale supercritical fluid particle engineering plant has been built in the UK resulting in the reshoring of this high value manufacturing capability from China. This will support the rapid acceleration of this technology from exploratory research to full-scale commercial manufacture for clinical supply. In addition, a scaled supergeneric product has been developed which offers a ground-breaking treatment for a condition which affects the quality of life of 8 to 12% of the global population.



Particles optimising oral delivery (left) and nasal delivery (right).

"ReMediES came at exactly the right time for us because we were, as a small company, having to make some tough decisions as to where GMP manufacturing would have to be. We already had an R&D centre in China. We had an opportunity to locate GMP manufacturing in China. Then ReMediES came along and gave us the opportunity to do that manufacturing and create additional value in the UK as well as to better meet the needs of our customers worldwide."

Paul Thorning, CEO, CrystecPharma

Innovation in processing: biocatalysis in flow

PROJECT LEAD:
Dr Markus Schober
Investigator, Synthetic Biochemistry, Advanced Manufacturing Technologies, GSK

PARTNERS:
GSK, AstraZeneca, Johnson Matthey

Pharmaceutical companies have been interested in biocatalysis for some time, recognising its potential as an economical manufacturing process which could significantly reduce the industry's reliance on metal catalysts. But developing these new catalytic processes at industrial scale is a complex task.

This project focused on combining the technologies of flow and biocatalysis using transaminases, a class of enzymes widely used in the production of APIs. The goal was to determine if continuous processing was feasible for these enzymes, by solving such common problems as product inhibition and unfavourable equilibrium as well as reducing the manufacturing footprint by minimising downtimes and inter-batch cleaning.

The team also investigated immobilisation supports for enzymes to increase their long-term stability and compatibility with organic solvents. It also identified simpler and more efficient separation methods for biocatalytic processes to improve manufacturability and reduce the waste streams generated.

The prize for getting these technologies to an industrial scale is significant. Ultimately, it would mean that steps could be removed from the synthesis altogether, making the process considerably faster and more cost-effective. Biocatalysis also helps API manufacturers reduce their reliance on rare and expensive transition metals, replacing them with catalysts that are easily and sustainably produced through fermentation processes.

The project made considerable progress in developing this technology but further work is needed to commercialise it.

Success stories

For both GSK and Astra Zeneca the use of enzymes, especially in flow, will become a greater part of synthesis in the future leading to more environmentally sustainable and more efficient processes.

At GSK a platform for continuous enzymatic processes has been established.

The immobilisation of a transaminase being considered for use with one of AstraZeneca's compounds has significantly improved the stability of the enzyme. Work continues to improve its compatibility with organic solvents, thereby leading to increased solubility which will benefit continuous manufacturing.

Johnson Matthey, a specialist chemicals company, has built a reactor prototype to address both the manufacturing of the immobilised enzyme and the use of the supported material in continuous flow. It plans to launch a proprietary range of 'off-the-shelf' immobilised enzymes.

Automated system for enzyme immobilization as designed by Cambridge Reactor Design.

Advances in secondary manufacturing

PROJECT LEAD:
Dr Liz Meehan, Pharmaceutical Technology & Development, AstraZeneca

PARTNERS:
Perceptive Engineering Ltd, PSE, GEA, Britest, GSK, Cogent Skills. Alconbury Weston Ltd, AstraZeneca, University of Stathclyde

The implementation of advanced (continuous or additive) manufacturing processes for both drug substance and drug product is fundamental to creating a more flexible and agile medicines supply chain.

This requires either the development and commercialisation of new equipment not yet available to the pharmaceutical sector or the ability to deploy nascent manufacturing technology platforms in an increased number of pharmaceutical products.

This part of the ReMediES programme set out to create a set of technology platforms that can support both clinical trials and commercial supply, whether in large volumes (for blockbuster drugs) or for niche patient populations. By taking a multidisciplinary approach, this project has shown how the implementation of advanced manufacturing technologies can be accelerated.

It had three core stands:

01

CONTINUOUS DRUG SUBSTANCE ISOLATION

This project was about designing new equipment for the continuous washing, filtration and drying of drug substance which can reduce processing time, improve linkage to continuous drying and improve control over particle properties making them easier to process using new secondary manufacturing techniques such as continuous direct compression and hot melt extrusion.

The flexibility of the CFD system enables rapid process optimisation during development to deliver an API that is high purity, solvent-free and is presented as a free flowing powder with no agglomeration (increased particle size) or significant attrition (reduced particle size) of the isolated material.

CFD laboratory-scale prototype.

02

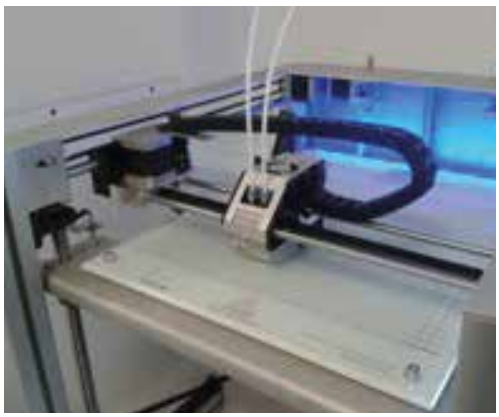
CONTINUOUS DIRECT COMPRESSION (CDC)

CDC has the potential to become the first choice for manufacturing tablets. Its benefits include simplifying the manufacturing platform for tablets so that there are fewer components in the formulation and fewer unit operations and it can cope better with raw material variation. These benefits can apply equally to newly developed drug products or – when switching from batch processes – to existing drugs.

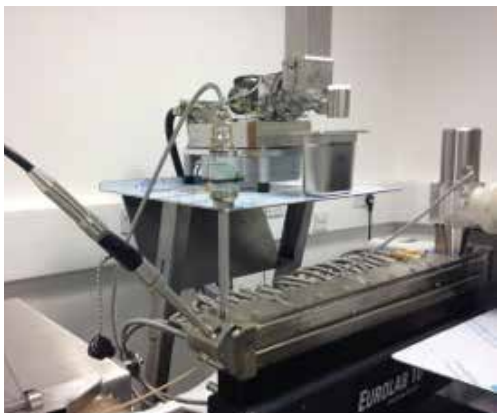
CDC throughputs can be adjusted so that it can be used in process development and clinical trial supply as well as at commercial supply volumes. The process is constantly monitored to ensure consistent quality over extended run times.

The project team designed the process for the implementation of continuous blending and direct compression and showed how it could be applied across clinical and commercial supply chains.

The output from this ReMediES CDC work will form another Grand Challenge initiative in the new MMIC facility with the aim of further developing the technology to industrial commercialisation.



3D printer.



HME system.

"If we look at other industries we are probably a bit behind the curve and are playing catch up. All sorts of industries use continuous manufacturing and utilise the same principles as we are trying to do now." **Liz Meehan,** AstraZeneca

03

HOT-MELT EXTRUSION AND 3D PRINTING (HME)

This strand demonstrated that hot melt extrusion (HME) technology is able to produce oral solid dosage forms in one continuous process. It also sought to demonstrate the potential for the wider application of hot melt extrusion and the subsequent benefits for clinical and commercial supply chains.

Hot melt extrusion is a specialist platform technology for the processing of amorphous solid dispersions that are most often used for the commercial manufacture of solid oral dosage forms. The technology helps to increase bioavailability when the drug substance has very low solubility. This is a problem that the pharma industry increasingly faces as innovative new drugs are coming forward which have poor solubility. HME is therefore an emerging technology for which there is likely to be a growing demand in future supply chains.

The team was able to confirm that HME is a sufficiently robust manufacturing process for the production of amorphous solid dispersions, a leading platform technology for improving the oral bioavailability of poorly soluble drugs.

Modelling of HME can be used to derisk scale up to larger volume extruders for commercial scale manufacture. When used in conjunction with 3D printing technologies, HME could also provide a viable option for extremely flexible dosing to patients in early clinical studies with all the benefits of rapid prototyping, optimised product design, low material usage and on-demand supply.

3D printing (3DP) in medicines manufacture is still in its infancy and remains largely an academic pursuit. Personalised medicine has the potential to change that and, in the process, to revolutionise the supply chain. However, despite successful demonstrator projects, we are still a long way from it becoming a reality.

ReMediES explored 3DP in order to add to the collective knowledge in this area, particularly the impact of formulation and structure on release properties as well as filament characterisation. The 3D printing output from this project will be valuable in supporting the development of a business case to progress further strategic pharmaceutical R&D investment in this emerging technology.

The ReMediES projects are about developing capabilities along the supply chain to support the adoption of new technologies.

ReMediES partner, Britest, has developed an e-learning platform supporting technology selection, providing regulatory information and a decision support tool to help firms assess the viability of a particular technology based on supply chain drivers. It also supports the development of a business case for the early adoption of ReMediES technologies.

Cogent Skills, working with project partners and the MHRA, has compiled three GMP guidelines on: *Continuous Manufacturing, Quality by Design (QBD) and Development of a Continuous Manufacturing Process – Regulatory Considerations*. These have been incorporated into the Britest e-learning platform.

Getting the medicines to the patient: rethinking packaging

PROJECT LEAD:
Heidi Keeling, Project Director, Global External Sourcing, AstraZeneca

PARTNER:
GSK

Packaging is another area of both challenge and opportunity for the sector. Medicines require robust packaging that keep them dry, secure and free from contaminants.

However, the materials and production processes used to make these packs are expensive. At the same time, advances in technology allow manufacturers to augment the properties of the physical packs with 'smart' components which have the potential to transform the management and control of medicines throughout the supply chain.

Developing new types of packaging

Blister packaging is used for many types of medicines. For those medicines which need high levels of moisture protection, manufacturers have relied on aluminium laminate, a highly effective but expensive and resource-consuming material.

Finding an alternative is a priority for the sector. This project explored a number of options before identifying atomic laser deposition (ALD) as a potentially viable option. Its moisture protection is approximately half as good as aluminium and ten times better than low-cost alternatives. If it can be successfully scaled up and commercialised beyond ReMediES it could replace aluminium as the standard material for a wide range of medicines which do not require the very highest levels of protection, thereby delivering major reductions in cost and environmental impact. The initial findings are promising.

© AstraZeneca

Rotary blister tooling.

The team also looked at using a new material and processing techniques to make the blisters in packaging smaller and by doing so make significant cost-savings and reduce environmental impact.

Working with material suppliers and blister pack manufacturers, the team has developed a new process which makes a blister smaller by around 30% and therefore allows for more blisters per strip.

This production process is going to full trial. For one company alone it could mean:

- *A reduction in C02 emissions of 700 tonnes annually.*
- *Savings of around $500,000 for materials, $50,000 on electricity, $2million on distribution.*
- *A productivity increase of 25%.*

Agile packaging

This team also explored how augmented reality technologies could be used to improve some manufacturing processes. The approach was tested by digitising five standard operating procedures so that operators can see the instructions in front of them while looking at the equipment. When this was applied to threading long reels of material through a machine, the time spent on this intricate procedure was reduced from 12 minutes to three.

Smart labelling using printed electronics

PROJECT LEAD:
Tim Marsden, CPI Innovation Services

PARTNERS:
GSK and AstraZeneca

One of the critical challenges for the supply chain is getting medicines – particularly those that need to be stored at low temperatures and particular levels of humidity – to the patient without having compromised their usability.

At the moment, any faults tend to be discovered only when the drug has got all the way to the end of the supply chain, causing both maximum wastage and delays in supply.

This project successfully trialled the use of printed electronics to create smart labels that can monitor temperature, humidity and shocks, together with a time-stamp. The work involved a number of progressive developments, migrating from battery technologies through to the use of NFC technologies that provide data access and retrieval at selected points across the supply chain. Manufacturing equipment to produce these printed electronic labels at scale has been used to demonstrate the commercial feasibility of the technologies.

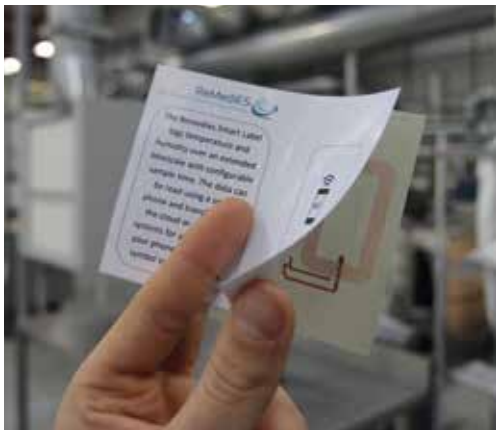
Success stories

The process has been trialled and commercialisation discussions remain ongoing.

CPI is engaged in a future European project, 'InScope', funded under the EU's Horizon 2020 scheme. The project seeks to create a pan-European pilot-line, incorporating the best of European printing and integration techniques. GSK is participating in this EU project, with the aim of producing 10,000 smart labels for development.

"You're not just building in tracking of where [the drug] is, but also how it has been handled. You can say whether it has been dropped, whether there has been a change of pressure or temperature or, perhaps, whether something has come loose during shipment. So, you can look at a whole host of supply chain issues around handling and environmental conditions and assess the integrity of the product as a result of how it has been handled."

Tim Marsden, CPI



Left: The R2R integration tool integrates electronic chips on to a flexible substrate.
Right: The ReMediES NFC smart label.

Next generation supply chains

PROJECT LEAD:
Dr Jag Srai, Head of Centre for International Manufacturing, IfM, University of Cambridge

PARTNERS:
GSK, AstraZeneca, SAP, CPI, Intersys, DHL, WBA (Alliance Healthcare)

End-to-end supply chain segmentation

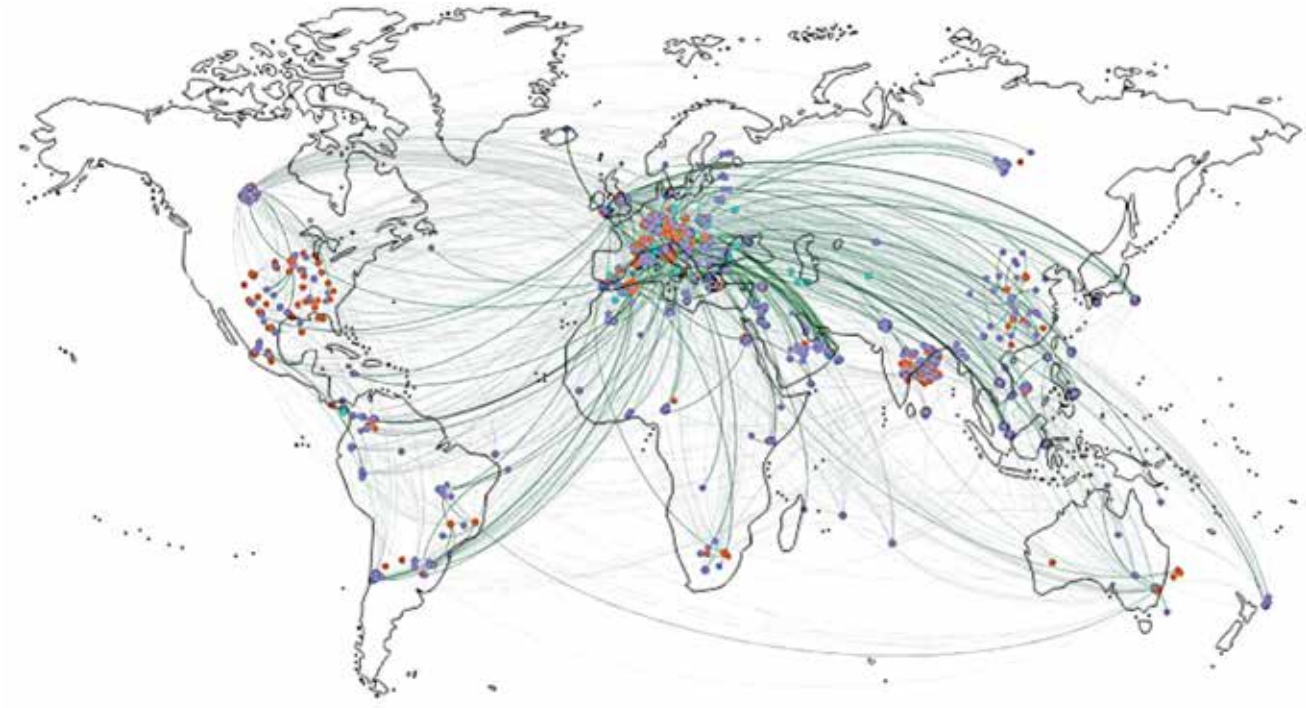
Making good decisions about supply chain design depends on a deep understanding of each product. In supply chain terms, for example, a 'flu vaccine administered at GPs' surgeries at the height of an epidemic looks very different from a mass market analgesic sold off the shelf in supermarkets. This project used supply chain analytics to analyse 'segment' supply chain data relating to different products, identifying those products where speed and responsiveness to market demand is critical, and those that are most important from a supply security perspective. The flow of goods through the supply network also improves our understanding of critical nodes within the supply chain and where best to hold inventory.

Developing an asset library for use by industry

One of the challenges for medicines manufacturers is their lack of awareness of the capabilities that exist along the supply chain and of the research taking place in UK universities and innovation centres. If the UK pharmaceutical sector is to remain competitive, it needs to leverage these assets more effectively. This team created a web-based 'capability matrix' for small molecule pharmaceuticals, housing data from 138 companies and 34 research organisations. This resource is available to companies and to trade bodies promoting the UK pharmaceutical industry. The dataset was further augmented by a web-based platform incorporating transactional data from industry databases, allowing for partner-based enquiries on supply networks for given products or technologies.

Understanding digital transformations and making the business case for the adoption of continuous manufacturing

All industries are addressing the issue of how best to harness new technologies to develop a truly digital supply chain and the pharmaceutical sector is no exception. The team used a model developed at the Institute for Manufacturing to frame its thinking about what a digital supply chain comprises and what sort of infrastructure it needs.



Visualisation of a manufacturing and distribution network.

The Supply Chain Reconfiguration Laboratory at the Institute for Manufacturing, University of Cambridge.

Using this framework, it developed a series of scenarios across the supply chain from the digital factory, through smart packaging, smart distribution and, ultimately, to connecting with patients.

A key part of the commercial platform was to look at the business case for adopting new production technologies such as continuous manufacturing: understanding what it can deliver and under what circumstances. This was achieved by developing a multi-layered modelling platform. The modelling platform links previously disconnected analyses – often reflecting the technology silos of process technology, manufacturing footprint and downstream distribution and service – into an end-to-end supply chain perspective. A number of projects were also conducted in the use of digital technologies across the end-to-end supply chain.

These include:

- *Developing the case for digitally reconfigured 'care pathways' between various stakeholders, including the patient, healthcare professional and product supply chain.*
- *An electronic patient-information leaflet, potentially replacing the paper version used in medicine packs, was developed in consultation with the MHRA, with a prototype mobile phone app providing patients with electronic access. Additional functionality was explored to demonstrate the utility of a digital interface in terms of patient information, compliance and outcomes.*
- *Understanding the potential implications of product serialisation on the future of digital supply chain efficiency, product provenance, and inventory management.*

The team has developed an operational toolset based on use cases for specific products, enabling the quantification of the benefits of using a particular process for a given product.

As part of this project, GSK further developed a digital factory demonstrator. This has led to the implementation of a control tower platform across a major product line, which is already improving service and delivery.

"We are seeing new capabilities in design and supply chains, and in how digitalisation can support major strides in productivity and, potentially, in the operating model. The ability to integrate new chemistry with novel production processes, smart packs, lean distribution models and patient data – using mobile-phone apps and diagnostics – offers a more 'end-to-end' view of a sector that is traditionally a rather fragmented network of isolated centres of expertise."

Dr Jag Srai, Institute for Manufacturing, University of Cambridge

"As yet, we do not have a fully developed means of predicting the impact on a supply chain of a new technology. That work has been advanced significantly by the Institute for Manufacturing and I'm sure will bear fruit to help companies understand how innovation will impact not just at the unit operation level, but at the supply chain level."

Clive Badman, ReMediES Director

Understanding risk

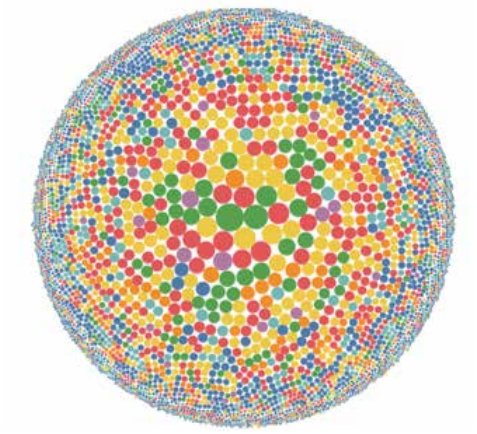
This project looked at identifying, quantifying and predicting supply chain risk, and understanding the relationships and interdependencies between risks. This has led to two new tools to support risk management within pharmaceutical supply chains. The first is an enhanced risk tool, the development of which was led by Intersys, to quantify risks across different product groups and regions.

The second tool, led by Cambridge, evaluates the interdependency of risks, where the dependencies can drive a network level risk beyond that of a single event or risk category. Both tools are being commercialised.

Downstream supply

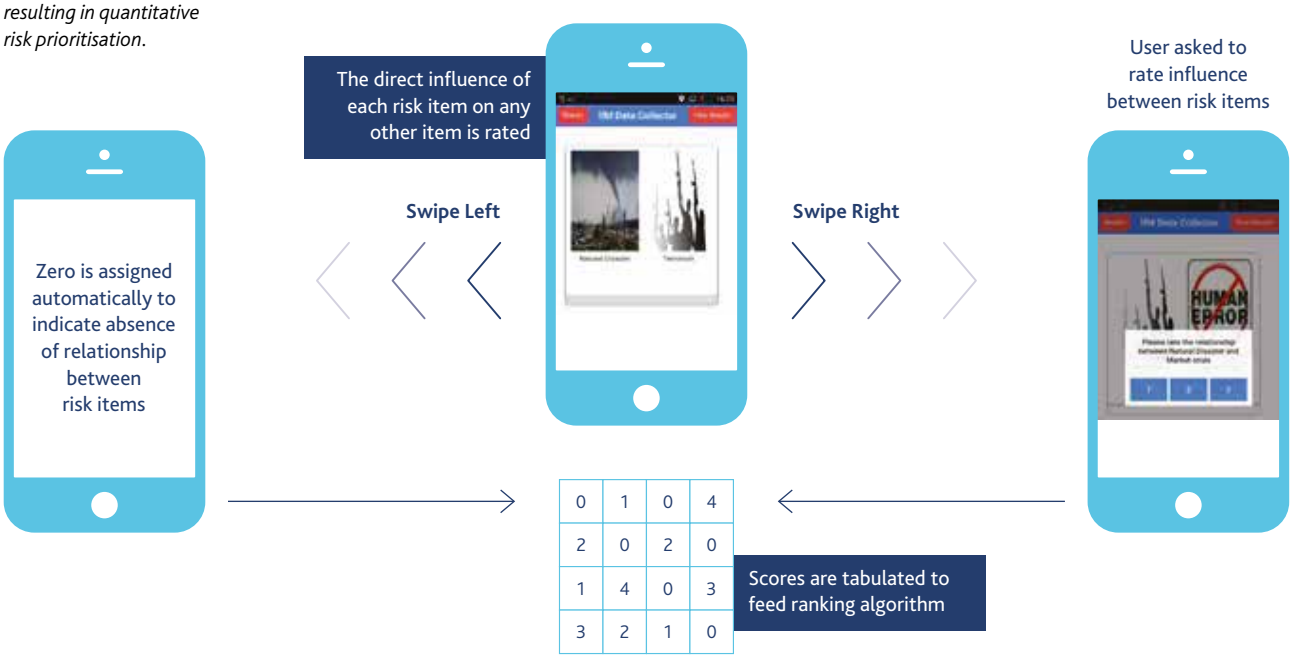
In order to address issues of surpluses, shortages and tracking failures, the team mapped distribution networks, looking particularly at the connections between existing wholesale pharmacy distribution networks and hospital networks to identify where a lack of alignment is causing problems with supply.

The global pharmacy, Alliance Healthcare, and life sciences logistics specialist, DHL, joined the ReMediES project, enabling the development of a new strand looking at downstream integration. Adopting approaches used in FMCG and retail, the team modelled direct supply to patients and its impact on supply networks.



Above: Visualisation of numbers of prescriptions being processed by pharmacists in selected postcodes over the course of a month.

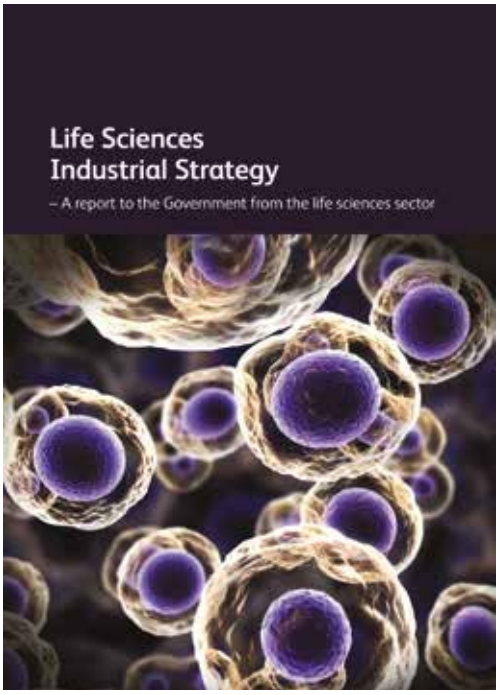
Below: A mobile application designed to elicit knowledge from risk management experts resulting in quantitative risk prioritisation.



What next for medicines manufacturing?

Medicines manufacturing is vital to the UK. The ReMediES project has played a critical role in bringing some new technologies to market, propelling others up several technology readiness levels and in helping the sector as a whole move towards a new, more streamlined, patient-centric supply model that will be able to respond to the demands that will certainly be made of it in the years ahead.

The work of ReMediES will continue through the new £56 million Medicines Manufacturing Research Centre (MMIC), located in Glasgow, which is jointly funded by Innovate UK, Scottish Enterprise, GSK and AstraZeneca. MMIC is designed to help both start-ups and multinational pharmaceutical companies adopt novel processes and technologies and customise them to integrate with their own manufacturing processes. Just-in-time clinical pharmacy and continuous direct compression are MMIC's first 'Grand Challenges', taking forward the work of two of ReMediES's core projects.



In 2017, CMAC secured a further £10 million from EPSRC to establish a continuous manufacturing hub in the UK, building on the initial successes of the EPSRC CMAC Centre for Innovative Manufacturing established in 2012. This current seven-year programme, led from the University of Strathclyde, comprises academic investigators and research staff across seven leading universities, with the University of Cambridge leading the work on future supply chains. In addition, CMAC has secured £30 million industrial funding from its Tier 1 Industrial partners, GlaxoSmithKline, AstraZeneca, Novartis, Bayer, Takeda, Lilly, Roche and Pfizer and a wide range of technology companies. Emerging projects from ReMediES will continue within CMAC (fundamental science), some under the wing of MMIC (translational projects) and others are being developed as part of the Industrial Strategy Challenge Fund Wave 3.

A representation of the new Medicines Manufacturing Innovation Centre (MMIC).

MMIC will take forward two of ReMediES core projects.

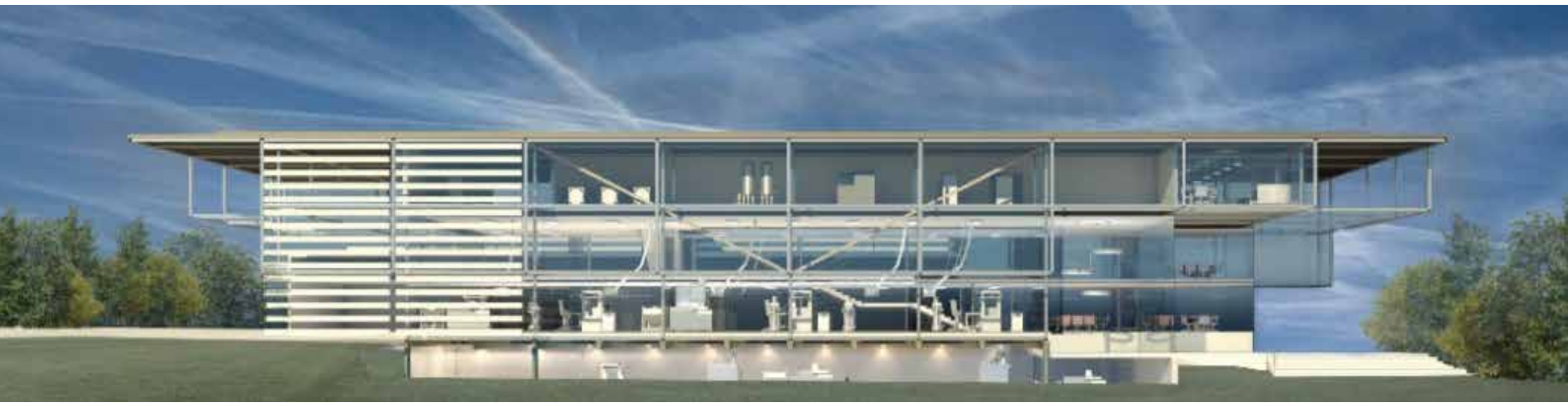
"ReMediES was one of the early examples of the pharma industry working together in collaborative R&D, something it didn't have a record of doing before. The project, even in its early stages, started to show the value of such collaboration, that you don't have to share your crown jewels and that there are a lot of non-competitive or pre-competitive areas where companies can work together if they choose to, which can benefit the whole UK pharmaceutical industry."

Will Barton, OBE, Technical Adviser, ReMediES

ReMediES has demonstrated unequivocally that pre-competitive collaboration works. Previously, companies were reluctant to engage, concerned about the return on their investment and the impact on their IP. But ReMediES has shown that by working together it is possible to bring about step changes in the development and adoption of new technologies to the benefit of manufacturers, healthcare providers and, ultimately – and most importantly – the patients.

If we are to build on its success, we need industry to be more open to partnership models, government to incentivise collaboration through its funding mechanisms and academia to provide more technology support across fundamental and applied research.

Below: MMIC.



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The ReMediES team

Clive Badman, OBE
Vice-President Pre-Competitive Collaboration, GSK
Project Director, ReMediES

Jag Srai
Head of the Centre for International Manufacturing, Institute for Manufacturing, University of Cambridge
Research Director, ReMediES and Commercial Supply Chain project lead

Andy Dwyer
Head of Clinical Packaging Operations, GSK
Clinical Supply Chain

Stewart Mitchell
Project Manager, CMAC Future Manufacturing Research Hub, University of Strathclyde
Continuous Manufacturing

Catherine Hunter
Director, Crystec Ltd
Supercritical Fluids in Particle Engineering

Markus Schober
Investigator, Synthetic Biochemistry, Advanced Manufacturing Technologies, GSK
Biocatalysis in Flow

Liz Meehan
Pharmaceutical Technology and Development, AstraZeneca
Primary to Secondary Pharmaceutical Processing

Heidi Keeling
Project Director, Global External Sourcing, AstraZeneca
Next Generation Packaging Materials

Tim Marsden
Project Manager, Printable Electronics, The Centre for Process Innovation
Printable Electronics and Intelligent Packaging

The ReMediES partners

22 industrial partners from global pharmaceutical companies, major contract manufacturing organisations, equipment manufacturers, international logistics specialists and a global pharmacy plus two universities, Cambridge and Strathclyde.

ReMediES partners March 2018.

ReMediES partners

Alconbury Weston, Alliance Healthcare, AstraZeneca, Blacktrace, Britest, Cambridge Reactor Design, Centre for Process Innovation Cogent (the Sector Skills Council (SSC) for the Chemicals, Pharmaceuticals, Nuclear, Life Sciences, Petroleum and Polymer Industries), CrystecPharma, C-Tech Innovation, DHL, GEA Engineering, GSK, IntensiChem, Intersys, Johnson Matthey, Juniper Pharmaceuticals, Mettler-Toledo, Perceptive Engineering, Process Systems Engineering, Robinson Brothers, Thomas Swan, University of Cambridge, University of Strathclyde.

WITH THANKS TO THE CORE MANAGEMENT TEAM

Clive Badman, OBE, Vice-President, Pre-competitive Collaboration, GSK

Jag Srai, Head of the Centre for International Manufacturing, Institute for Manufacturing, University of Cambridge

Craig Johnston, Operations Director, CMAC Future Manufacturing Research Hub, University of Strathclyde

Joe de Sousa, Director Science & Technology, Global Product Development, AstraZeneca

Minesh Shah, Finance Manager R&D Finance, GSK

AND TO THE EXPERT ADVISORY GROUP

Will Barton, OBE, Technical Advisor ReMediES

Andy Green, Investment Director, FinanceBirmingham

Alastair Florence, Director, CMAC Future Manufacturing Research Hub, University of Strathclyde

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