

Jagjit Singh Srail, Clive Badman²

1. Centre for International Manufacturing, Institute for Manufacturing,
Department of Engineering, University of Cambridge, United Kingdom

2. Business Engagement Group, University of Strathclyde, United Kingdom

Collaboration as the Best Medicine

abstract

Collaboration can be pivotal in making change happen. So how can new collaborative models be forged in areas where such relationships are not well established, but where change is required?

In UK medicines manufacturing, there is an opportunity and a pressing need for progressive change. But there are also plenty of challenges and obstacles, particularly in a highly competitive and tightly regulated sector. A bold step forward has been taken through a collaborative £23m four-year project, ReMediES, involving 22 industry partners and 2 leading UK Universities.

Dr Jag Srail and Professor Clive Badman, co-Directors of Project ReMediES discuss how the project has forged a model for change through collaboration.

Keywords: Medicines Manufacturing, Pre-competitive Collaboration, Pharmaceutical Supply Chains

Medicines manufacturing is an important part of the UK economy, employing 40,000 people and generating \$33 billion in exports. In many ways, it is productive, strong and successful. However, there is potential for making significant improvements across the medicines manufacturing supply chain.

The pharmaceutical industry's size, scale and complexity, alongside its highly-competitive character, have made change difficult. There is an entrenched pattern of long product development cycles with high attrition rates, 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 commercial supply chain has become cumbersome and inventory-heavy. Furthermore, the sector is highly regulated, which instils caution.

While this status quo may sound problematic and somewhat bleak, in fact it has provided a much-needed stimulus for industry players to seek improvements, and a motivation to reach over those high competitive walls and collaborate for mutual benefit.

REMEDIES FOR CHANGE

Within our advanced manufacturing research programmes we have been working with major players in the pharmaceutical industry for several years on the possibilities that new production and digital technologies can offer to both industry and patients. These can support more responsive inventory-light supply chains, able to deliver medicines more targeted to specific patient groups or even personalised to individuals, with the potential to revolutionise healthcare delivery. However this transformation is too much for a single company, even a multinational, to achieve in isolation. So as a step in the right direction, we developed a vision for a large pre-competitive collaborative project to drive change, with the active participation of the regulator.

In 2014, the ReMediES (Reconfiguring Medicines End-to-End Supply) project was launched, bringing together 22 industrial partners including global pharmaceutical companies GlaxoSmithKline and AstraZeneca, as well as 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.

This broad partnership addressed some of the key challenges facing small molecule medicines manufacturing, with eight workstreams focusing on different aspects of clinical and commercial supply chains.

From a research perspective, across the ReMediES workstreams, we have attempted to tackle some ambitious questions. Could we run our clinical trial production more efficiently 'on-demand', reducing waste, inventory and lead-times? Could we adopt advanced technologies to make both our primary and secondary manufacturing processes right first time, more environmentally sustainable and capable of responding to changing demand? Could we apply science to create more soluble medicines? Could we package medicines in ways that will reduce wastage and help with patient compliance? And could we get better at delivering drugs to the people who need them, when they need them?

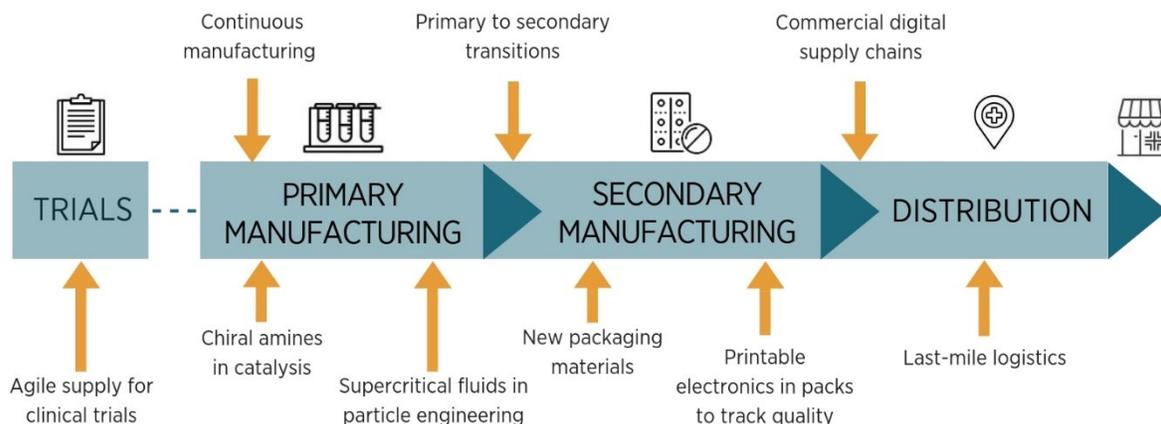
Over its four-year timescale, the ReMediES partners worked to tackle these fundamental, cross-sector, cross-functional challenges. The partners were able to take fundamental and applied research through to prototype or commercialisation.

From an industry perspective, we had observed that many of the firms have experimented with some of the technologies we are talking about in ReMediES but have not had the scale and the expertise that the ReMediES consortium offers to take things forward.

HIGHLIGHTS OF THE PROJECT

So what were the positive outputs from this collaborative approach? As the project reaches the end of its funding, partners have been reflecting and reporting on some of its key achievements, including in the following areas...

ReMediES explored and delivered innovations across the supply chain, including in...



Clinical Supply Chains – ‘Just in Time’

Clinical trials are a critical part of pharmaceutical R&D, but are 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.

In the current system, it typically costs in excess of £75 million to run a clinical trial for a new drug; a significant cost considering only 25% of drugs trialed 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 have to decide doses and quantities of a trial drug 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 randomization strategies.

The ReMediES clinical trials workstream looked at how this could be improved, with the ambitious aim to cut supply time from 4-6 months to less than a week, and develop the ability to be agile to changing trial needs.

As commented by the Project Lead for Clinical Trial Supply Chains, Andrew Dwyer from GSK,

“We prototyped a new ‘Just-in-Time’ clinical pharmacy that can provide drugs to support complex drug trials, reducing costs, increasing responsiveness and enabling a more flexible and exploratory approach to clinical research.

“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.”

Primary Manufacturing – from batch to ‘continuous processing’

The challenges at the primary manufacturing stage are similar to those facing the clinical supply chain: a reliance on the overproduction of stock to mitigate a lack of agility in the supply chain, creating a high level of wastage. 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 is constantly monitored and adjusted to ensure quality.

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 biocatalysis and the use of enzymes in flow.



BlackTrace is one of the continuous manufacturing technology platforms developed within Remedies. It provides a complete continuous processing scale-up including reaction, separation and particle formation, and will be commercially available from 2019.

Secondary Manufacturing

A major three-part project in secondary manufacturing has piloted new equipment for capabilities that enable shorter production cycles and volume flexibility.

Liz Meehan, responsible for Pharmaceutical Technology and Development at AstraZeneca, and project leader for the Secondary Processing workstream in ReMediES, comments:

“A more flexible and agile medicines supply chain will be enabled by wider implementation of advanced (continuous or additive) manufacturing processes for both drug substance and drug product.”

The ReMediES project included user trials and case studies for some strategic technology platforms including continuous drug substance isolation, continuous direct compression, hot melt extrusion and 3D printing. As Liz Meehan explains:

“By taking a multidisciplinary approach, ReMediES has shown how these advanced manufacturing processes can be deployed and accelerated to meet the challenges of future clinical and commercial supply chains.”

Substantial reductions in the cost of production will result, estimated in one company alone at £10m per year once fully implemented.

Smarter Packaging

The ReMediES packaging workstream, in which AstraZeneca and GSK have collaborated closely, looked at using new materials and processing techniques to improve blister pack moisture barrier properties whilst at the same time reducing their size leading to significant cost-savings and reductions in environmental impact.

This production process is going to full trial suggesting a 10 fold improvement in moisture barrier compared with other similar cost materials. For one company alone it could mean, based on an application on a leading product:

- A reduction in CO₂ emissions of 700 tonnes annually.
- Savings of around £380k for materials and £1.5million on distribution.
- A material productivity increase of 25%.

The ReMediES team, led by Centre for Process Innovation (CPI) also developed smart labels for use on medicines packaging using printed electronics which enable product tracking, monitoring and could be used to support patient engagement. Successful demonstration is leading to commercialisation opportunities that are being pursued with leading packaging manufacturers.

Digitalisation of Commercial Supply Chains

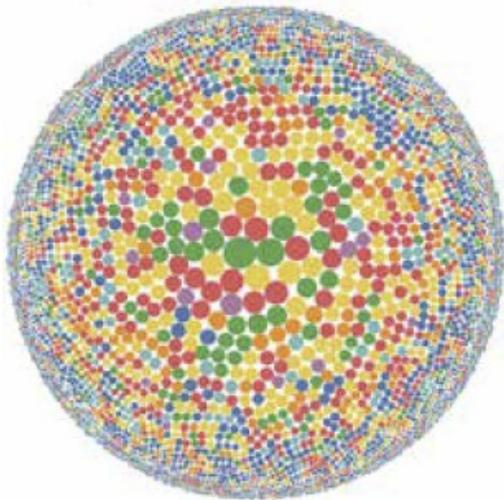
Several projects have underpinned the development of future supply chain models led by the team at IfM Cambridge.

Drawing data from 138 companies and 34 research organisations an asset library for use across the industry was developed in the form of a ‘capability matrix’ setting out what asset capabilities exist across extended supply chain. This was then extended using extensive data-mining of commercial databases, to identify collaborative relationships in key capability areas. An interactive digital platform tool was created for use by Remedies partners to interrogate the current collaborative network across the UK pharmaceutical landscape for specific asset capabilities, and to foster future collaboration.

A number of projects were conducted in the use of specific digital technologies across the end-to-end supply chain. These include an electronic patient-information leaflet, to co-exist or potentially replacing the paper version used in medicine packs, developed in consultation with the regulator, with a prototype mobile phone app providing patients electronic access. The hope is that such innovations can increase patient compliance and reduce waste.

An end-to-end supply network design, analysis and modelling platform has also been developed to help manufacturers understand the opportunities available to reduce inventory and increase speed-to-market. The multi-layer modelling platform allows organisations to evaluate new production processes, how these might influence production location and scale, inventory requirements of segmented product portfolios and market service levels. As Dr Srini commented on the work in his Centre being led by Dr Ettore Settanni, *'We can slice and dice a range of data to observe the interplay between cost, service and environmental resource efficiency in an integrated way: from a unit operations production processes perspective, a manufacturing footprint analysis and the final distribution of medicines to patients - rather than the functional 'silos' in which new technologies are often assessed'*

The workstream also analysed 'last-mile' logistics, with global pharmacy Alliance Healthcare, and life sciences division of the logistics specialist, DHL, as part of the ReMediES project. Adopting approaches used by the IfM researchers in FMCG and retail distribution logistics, the team modelled direct supply to patients to evaluate feasibility in terms of cost and service levels.



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

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

It has not all been hard work and no play – the team have for example used gamification to develop a mobile app helping industry experts and multiple supply chain stakeholders within the Remedies program evaluate otherwise complex risk interdependencies across the extended supply chain. This work links well with a broader disruption risk assessment tool available from SME Remedies partner Intersys (<http://intersys.co.uk>), now marketed commercially.

WHAT NEXT?

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.

FORGING A MODEL FOR COLLABORATION

Whilst new technologies are offering major opportunities to patients, healthcare providers and manufacturers, they require new collaborative platforms to address the complex technical and regulatory challenges that are involved. It's too big to do alone.

However, the concept of pre-competitive collaboration is relatively new in the medicines manufacturing arena, and many companies are concerned about becoming engaged from a cost and IP perspective. ReMediES addresses this concern in part by providing an exemplar collaboration model where innovations emerging from fundamental and applied research can be taken to prototype or commercialisation. The platform has enabled multi-stakeholder perspectives to be considered drawing in expertise from technology providers, regulators, academia and industry. Individual firms have been able to leverage their resources, upwards of 50% on direct activity, and by greater than 300% at a programme level.

Dr Will Barton, Chairman of the Advisory Board of the EPSRC Centre of Innovative Manufacturing in Additive Manufacturing, was the independent advisor to the ReMediES Project. He comments:

“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.

“ReMediES was a well-run project that will deliver some early wins for the SMEs and longer-term impacts across the board. It was really exciting seeing teams deliver great results. Things happened that nobody would have believed possible at the start.”

REFERENCES AND NOTES

This Article first appeared in the IfM Review, published by The Institute for Manufacturing, Department of Engineering, University of Cambridge, December 2018.

<https://www.ifm.eng.cam.ac.uk/insights/global-supply-chains/remedies-collaboration-as-the-best-medicine/>

A full report on the project outcomes is also available on: <https://remediesproject.com/wp-content/uploads/2018/11/ReMediES-Collaborative-Research-in-Action.pdf>

Dr Jagjit Singh Srani is Head of the Centre for International Manufacturing, Institute for Manufacturing, University of Cambridge. He has Director/Investigator roles across several major multi-disciplinary research projects, bringing an engineering and strategic operations management perspective to the design, analysis and operation of international supply chains. Research projects explore the disruptive impacts of new production and digital technologies on supply chains, markets and regulation, and involve close collaborations with industry, academia, and public bodies.

Clive Badman took on a role in the Business Engagement Group at Strathclyde University, in October 2013, where he is a Professor of Practice. Concurrent to this role he was VP Pre-Competitive Activities, R&D, GSK where he worked for 40 years before retiring in July 2018.

Clive was Industrial Chair for Continuous Manufacturing and Crystallisation (CMAC), an award winning academic/industry collaboration from 2011-2018 and he led the Remedies project from 2014-2018 representing 2 institutions and 22 industrial companies.