



An Integrated Ecosystem for Transforming Medicines Manufacturing

Meeting Summary



CMAC
FUTURE MANUFACTURING
RESEARCH HUB

An Integrated Ecosystem for Transforming Medicines Manufacturing

Meeting Summary

This 2021 symposium was the 5th in a series organised by the International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP). This virtual meeting brought together over 350 pharmaceutical industrialists, regulators, policy makers and academics from more than 22 countries and 142 organisations to inform strategies to grow medicines manufacturing in the UK and internationally through accelerating the adoption of advanced manufacturing and digital technologies. The importance of collaboration across the ecosystem achieved through supporting an integrated, system-wide approach across academia, industry, government and the regulators was strongly emphasised. By harnessing our world leading strengths, along with the combined efforts and innovative ways of working of all stakeholders, the UK can lead the transformation in medicines development and manufacture that will enhance quality, cost, sustainability and security of medicines supply, for the benefit of the economy, manufacturing industry and the environment, in addition to the NHS and crucially, patients.

Meeting Objectives:

- 1 Regulatory:** Protect and improve public health by enabling the earliest access and high-quality supply of safe, effective, and innovative products through proportionate, data-driven decisions on risk and benefits.
- 2 Industry:** Leveraging the combined UK Innovation Ecosystem to deliver a more agile, adaptable and scalable medicine manufacturing supply chain.
- 3 Academia:** Highlight strategic commitment to world class research and innovation in the UK for advanced manufacturing and digital technologies, sustainability and deliver the talent pipeline, developing existing assets.

Key observations from the symposium:

Rapid Innovation in the UK Economy and Learning from the COVID-19 Pandemic:

4 of the world's eight COVID-19 vaccines are manufactured in the UK.

Technology Innovation and Deployment:

We must accelerate the adoption of advanced technologies if we are to retain and increase our medicines manufacturing sector market share.

Continuous Manufacturing is a Key Advanced Manufacturing Technology:

~80% of delegates see CM as very important to the future of medicines manufacturing.

Skills and Collaboration are Vital to the Success of the Sector:

70% of delegates highlighted skills and collaboration as the most important factors in accelerating the adoption of continuous manufacturing.

The UK as a Leading, Innovative Regulator:

Regulators are committed to supporting and accelerating innovation. Industry must engage with them early to expedite new products to market.

Recommendations

The UK already benefits from an excellent research base, investments in innovation centres, leading pharmaceutical manufacturers, dynamic technology and supply chain partners and a leading, independent national regulator, the MHRA. Given the strategic importance and opportunities for growth in the medicines manufacturing sector, a number of recommendations are made to strengthen the UK's position as a leading location to develop, design, manufacture and supply medicines.

Regulatory:

- There is a clear opportunity to adopt new ways of working, with regulators acting as supportive partners to industry on manufacturing innovation. A culture change in industry is needed to engage early and in more open dialogue.
- Industry, academia and regulators must work together to provide guidance and standards for the deployment of continuous platforms.

Industry:

- Investment/incentives are needed to drive the adoption of new, better technologies, which improve supply chain resilience, Net Zero impact and grow the manufacturing sector.
- Collaboration is essential (academia, industry and regulators) to keep the UK at the forefront of medicines manufacturing.
- Investment is needed in skills and innovation in industry.

Academia:

- Targeted and sustained investment is required in training and skills development in advanced pharmaceutical manufacturing at all levels, but in particular, doctoral training to deliver the benefit of a highly trained talent pipeline.
- A strategic approach to supporting the ambitious, multidisciplinary research is required to address industry needs across the full scope of medicines development and manufacture including exposure to regulatory science within university curricula.
- Ensure coordinated mechanisms are in place to support collaborations and connections across the Research and Innovation ecosystem to accelerate the translation and impact of research.

Transforming UK Medicines Manufacture

There are potentially transformative opportunities informed by the combined drivers of the pandemic and supply chain resilience, the urgency for Net Zero and the potential for growing the contribution from manufacturing to the economy across the UK. These could be accelerated through a national project to utilise the integrated UK ecosystem to deliver advanced digital and manufacturing solutions for generics manufacture, second generation medicines, vaccines and emerging advanced therapies.

UK ISCMP committee members on behalf of ISCMP¹:

- Clive Badman**
(Executive Director at Strathclyde University)
- Alastair Florence**
(Director at CMAC, University of Strathclyde)
- Massimo Bresciani**
(Industry Director at CMAC, University of Strathclyde)
- Martin Wallace**
(Director of Technology at GSK)
- Ian Rees**
(Unit Manager Inspectorate Strategy and Innovation at MHRA)
- Jon-Paul Sherlock**
(Global Technology Strategy Director at AstraZeneca)
- Robert Reid**
(Senior Consultant at Business, Energy and Industrial Strategy)
- Johnathon Marshall**
(Partner at PwC)

Overview

The International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) was established in 2014 and is jointly organised by the UK Continuous Manufacturing and Advanced Crystallisation (CMAC) Hub and US Massachusetts Institute of Technology (MIT). There have been five international meetings to date, with the last two held virtually in response to pandemic restrictions. The 5th virtual and UK-focused meeting took place on 18th February 2021 with more than 350 delegates from around the world, representing over 140 organisations with interests spanning the development, manufacture, supply, regulation and use of medicines.

The meeting started with a UK policy perspective from our first Keynote speaker, Lord Bethell, UK Minister for Innovation at the Department of Health and Social Care. Further sessions allowed delegates to hear about the latest developments from leading academics, industrialists, policy and economics experts, funders, patient advocates as well as presentations on regulation progress from the US Food & Drug Administration (FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA). This document captures the key outcomes of the meeting sessions, highlighting recommendations for action that can accelerate and strengthen advanced medicines manufacturing in the UK.

Rapid Innovation in the UK Economy and Learning from the COVID-19 Pandemic

Four of the world's eight COVID-19 vaccines are manufactured in the UK

As we approach the first anniversary of the COVID-19 pandemic and the new dynamics of the international political landscape post Brexit, the UK economy faces a number of challenges. Medicines manufacturing is already a leading export sector and the meeting heard of the numerous opportunities that exist to build on these strong foundations and contribute to our economic recovery through research, innovation, regulatory leadership, business investment and collaboration. Lord Bethell^(Fig. 1) emphasised the importance around this recovery, as well as highlighting the significant Government investments already committed and expected in the coming year to help achieve this.

The UK has already targeted a number of initiatives for support that include the National Biologics Manufacturing Centre, which received £38 M in Government investment and has been in operation since 2015. In 2018, a £147 M Medicines Manufacturing Challenge Fund was launched which has led to the creation of a number of new innovation centres including the Vaccines Manufacturing Innovation Centre (VMIC) which is currently under construction in Oxfordshire following a £93 M investment. VMIC aims to have capacity to produce enough vaccine doses to serve the entire UK population at scale. An extra £38 M was more recently invested through UK Research and Innovation (UKRI) to establish a rapid deployment facility in the Medicines Manufacturing Innovation Centre (MMIC) in Renfrewshire, Scotland. MMIC will provide transformative solutions in pharmaceutical and fine chemical manufacturing and construction of the £56 M facility began last year. The Manufacturing Challenge Fund also contributed to the expansion of the Cell and Gene Therapy (CGT) Manufacturing Centre, supporting businesses to bring these advanced, life changing therapies to the market. Such investments highlight the Government commitment in working with industry to establish a robust and vibrant manufacturing base for the UK Life Sciences sector. Considering the highest gross value added (GVA) for the UK economy comes from pharmaceuticals, by capitalising on such investments, the UK can not only increase resilience, but also expand on high value jobs into the economy.

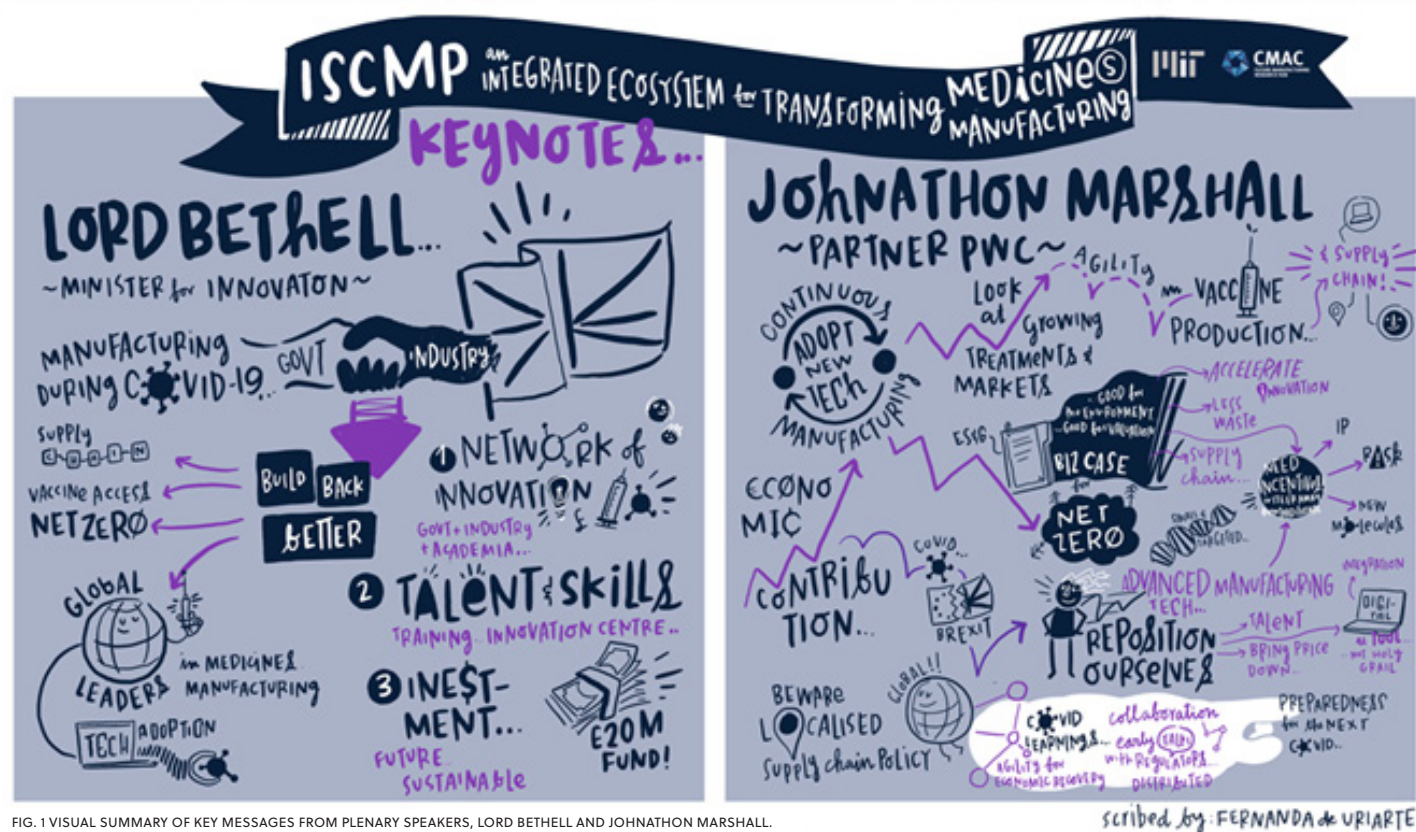


FIG. 1 VISUAL SUMMARY OF KEY MESSAGES FROM PLENARY SPEAKERS, LORD BETHELL AND JOHNATHON MARSHALL.

Of course, with medicines manufacturing representing almost £20 billion per year in exports², the UK is a major provider of medicines to the global population: medicines made in Britain, treating patients all over the world. With an exceptional R&D base and proven track record in innovation, it truly is a vibrant hub for the life sciences sector. It is also a testament to the potential of the UK's R&D, manufacturing and regulatory systems that four of the world's eight COVID-19 vaccines are being manufactured in the UK. However, there is more that needs to be done to consolidate and grow our position, building on these strong foundations. With notable developments in the US and also throughout Europe in accelerating advanced medicine manufacturing research and innovation, the UK is in real danger of being left behind. Now is the time to restore the message that as a global leader in medicines manufacturing, there are few locations better placed than the UK to develop, adopt and implement innovative approaches in the manufacturing of existing, second generation and innovative medicines and therapies.

As with other parts of the world, the UK has in the last few decades outsourced significant amounts of medicines manufacture, mainly due to the struggle to compete on cost alone with low wage economies overseas. However, the pandemic, and Brexit to some extent, has highlighted the importance of reshoring production to ensure resilient and secure access to all medicines and in particular, generics. Lord

Bethell also expressed the importance of rebuilding the UK's domestic manufacturing capacity to rebalance the country's economy. In the second Keynote, Jonathon Marshall, Partner at PwC, emphasised that reshoring should be driven by logistical reasons and with a refreshed, patient-centric approach. The case was made that Government financial incentives are also crucial, in order to support the transformation in manufacturing which is urgently needed if we are to secure the full benefits from innovation.

COVID-19 has given the world a wake-up call in many regards, but the supply and manufacture of medicines has understandably been at the forefront. Scientists have been challenged around responding rapidly and speed to market and it's evident that we need to move away from out-dated, inefficient and unresponsive supply chains. With new variants of the virus already spreading, it cannot be a case of going back to normal, but instead a refreshed approach must be adopted around research and manufacturing mobilisation to achieve the agility and resilience that will be essential. The Oxford-AstraZeneca and Pfizer-BioNTech partnerships have been fantastic examples of collaboration, but more of this is needed. Once the COVID-19 pandemic is brought under control, the spotlight will return to oncology, HIV, diabetes and the array of other essential and emerging treatments at the heart of modern healthcare: obsolete, slow, costly approaches to R&D will not be well received by the patient.

² <http://www.worldstopexports.com/drugs-medicine-exports-country>

³ <https://www.madesmarter.uk>

Technology Innovation and Deployment

We must accelerate the adoption of advanced technologies if we are to retain and increase our medicines manufacturing market share

Advanced technologies and smarter approaches to manufacturing must continue to be adopted if the UK is to succeed in restoring a robust economy around pharmaceutical research and supply. Digital solutions and automation (Industry 4.0)³ should be embraced, whilst also recognising the need for harmonising equipment and control systems across the sector. Larry Lee, Deputy Director of Science, Office of Pharmaceutical Quality at the FDA, highlighted the benefits of specific advancements in real-time release testing and process analytical technology (PAT)/control with high frequency measurements of critical quality attributes (CQAs). The increased importance of modelling, chemometrics and multivariate analysis in the manufacture, control and release of medicines was also cited. Other areas of interest include 3D printing, which is now a technology used for multiple licenced products on the market and continues to show further promise, particularly for oral dosage forms.

In terms of innovation, Dave Tudor, Managing Director of MMIC, discussed the importance of ensuring new technology solutions meet an industry need. There are many innovative technological approaches that are and have been demonstrated, but the challenge is to bring these into mainstream use and convert their potential into real world value. Translating academic, proof of concepts and solutions at technology readiness scale (TRL) 1-4 into pilot and manufacturing at TRL 5-9 can often prove to be a significant hurdle, if not impossible, where collaboration has not been made early on. The importance of successful collaboration between organisations was exemplified through MMIC's grand challenge programme, the first being focussed on a

partnership to provide solutions to enable and de-risk continuous direct compression (CDC) that will benefit manufacturers by removing significant inefficiencies in current tablet production. Dave Tudor also discussed the need for innovative approaches to shorten lead times between packaging and patient supply, suggesting a turnaround of less than 4 weeks is achievable.

Ian Shott, Managing Partner of Shott Trinova, highlighted innovative approaches to develop and invest in their infrastructure to better support advanced manufacturing. He discussed the importance of the logistics of research and development as well as manufacturing facilities and how their plans were pushing the boundaries of current practice where it is uncommon for drug substance, drug product and testing equipment to be located on one site. This naturally brings challenges in tech transfer, such as scale up/out or the incorporation of analytical methods, but by working with academia and project partners, these modernised approaches to the facilities to support flexible, small scale, integrated manufacturing can be achieved. Sir Jim MacDonald, Principal at University of Strathclyde & President of the Royal Academy of Engineering, encouraged the use of cross-sectoral collaborations to maximise technology advancements, citing the unconventional support in ventilator production during the current pandemic as a real highlight of how this can be successfully mobilised to great effect when the need is identified. This can be done more, but requires a joined up, systemic approach involving all partners in the research, innovation and manufacturing ecosystem to work together on well defined, common goals, building a common understanding of the challenges and risks faced.

The UK Government is also committed to investing in new technology. Lord Bethell indicated that through the Manufacturing Made Smarter Challenge, £147 M backed by a further £153 M from industry, is being put forward to support businesses in boosting their manufacturing productivity, in addition to creating thousands of highly skilled jobs. Furthermore, at the end of last year, the Prime Minister announced a £20 M Medicines and Diagnostics Manufacturing Transformation fund, which will offer capital grants to businesses, incentivising them to place internationally mobile, high value manufacturing investments in the UK.

² <http://www.worldstopexports.com/drugs-medicine-exports-country>

³ <https://www.madesmarter.uk>

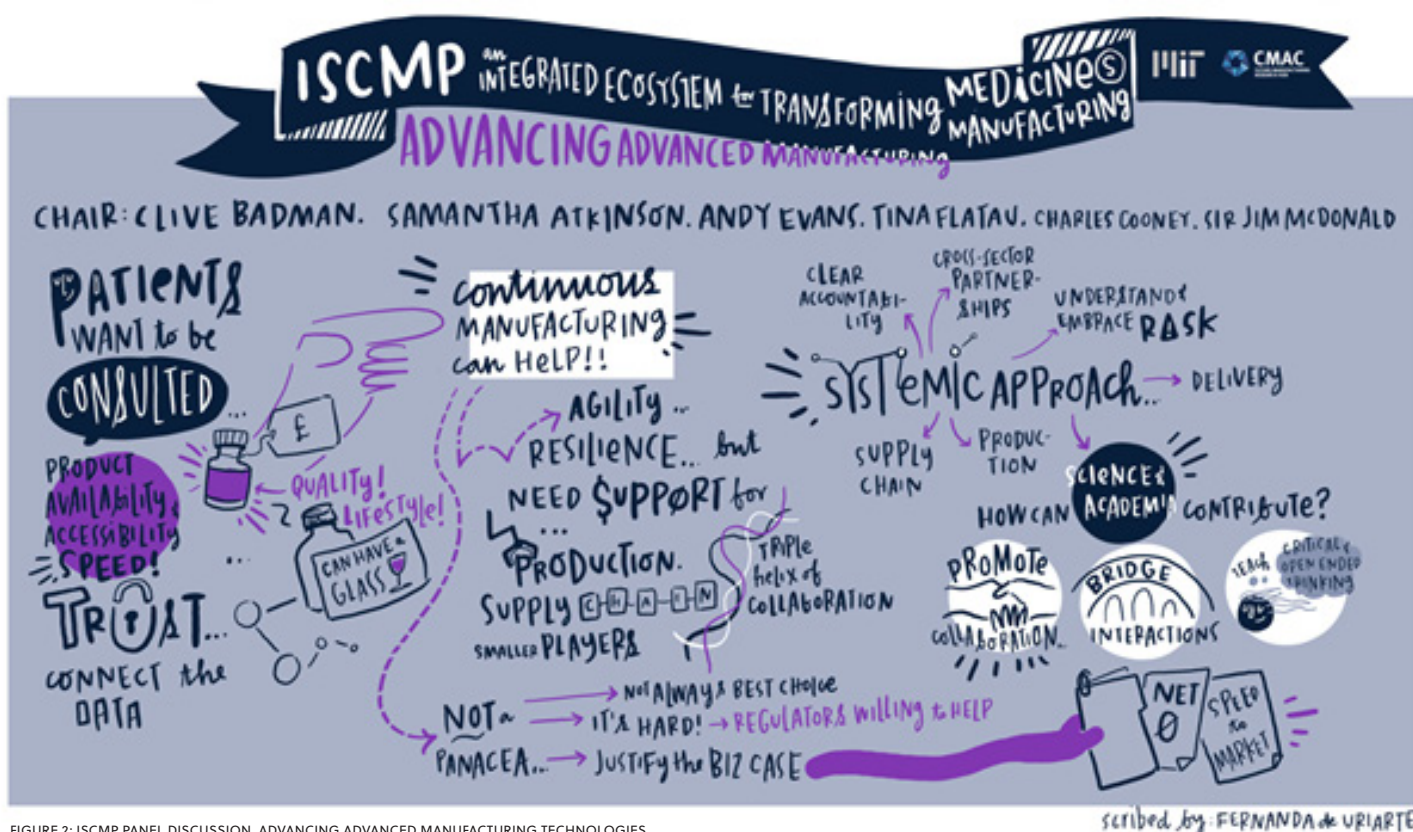


FIGURE 2: ISCMP PANEL DISCUSSION, ADVANCING ADVANCED MANUFACTURING TECHNOLOGIES

Continuous Manufacturing is a Key Advanced Manufacturing Technology

ca. 80% of delegates see CM as very important to the future of medicines manufacturing

A core focus for ISCMP is around Continuous Manufacturing (CM) which, although has started to see adoption in the production of a growing number of new medicines, still shows slower progress than may be expected, given the potential benefits that can be realised. To date, only 7 products featuring a continuous aspect to their manufacture have been approved by the FDA. Many organisations are actively exploring and developing their internal capabilities⁵ or engaging in collaborations as a means to build knowledge and increase the rate of progress, yet more needs to be done.

A key question posed at the symposium is how to accelerate adoption of CM (see Figure 3). Andy Evans, VP of Clinical Manufacturing and Supply at AstraZeneca and Chair of the Medicines Manufacturing Industry Partnership (MMIP), indicated that one of the reasons for the slow uptake is that continuous operations are inherently more complex than batch, in particular regarding control systems. Some organisations cannot afford to take risks with high value materials, new chemical entities in particular, and will generally revert to traditional batch methods as a consequence. The fact that a significant amount of the UK manufacturing infrastructure consists of batch reactors cannot be ignored, however there is a risk this will always remain the default approach unless further effort and support is provided. Without this, the benefits of CM and opportunities for enhanced integration, intensification and interrogation to deliver cost, speed, quality, agility, sustainability and security will not be realised by UK industry.

Of course the environmental benefits of CM remain clear; reduction in carbon emissions (PwC have indicated up to 80%), energy, solvent and water savings and smaller physical footprint. Lord Bethell reinforced that the UK Government is extremely committed to the Net Zero initiative and is actively looking to support innovative research approaches. The Government plans to invest £12 billion to create and support up to 250,000 highly-skilled, 'green' jobs in the UK. Andy Evans indicated that the financial case for CM is often unclear for businesses, but

environmental impacts may be the best angle to encourage further investment and the structural and cultural shifts required to make the change.⁶

The technical benefits of CM also continue to be demonstrated; improvements in process consistency, control and understanding, better management of challenging chemistry, reductions in waste and easier scale-up being the most commonly cited. Gavin Halbert, Director of The Cancer Research UK Formulation Unit & Professor at University of Strathclyde, discussed how scale-up is a common challenge with academic developments and delivering promising treatments to patients can often suffer as a result. Notably, Vertex's first Cystic Fibrosis drug would not have made it to market without the efficiencies afforded by a CM approach, highlighting that the relevance of the technology.

Andy Evans also discussed how CM will bring benefits in drug development processes as well as commercial supply. It should not just be associated with high volume/high tonnage supply,

but also with high potent drugs and lower manufacturing volume. Incorporating smaller footprint and end-to-end 'MicroFactories' will allow manufacturing to be brought closer to the patient and create impact, as well as stepping away from complex supply chains. Integrated designs and flexible switching between processes smoothly and quickly will also create opportunities to meet an uncertain and changing patient demand. An interesting approach could be to lower manufacturing costs for existing medicines to free up funding for innovative treatments, but there must be clear incentives for stepping away from traditional manufacturing and encourage working in this way. Of course, CM will not be suitable for every process or product scenario and hybrid batch/continuous processing may be likely elements of pharmaceutical manufacturing. CM offers considerable opportunity for efficient, cost effective, sustainable and productive supply of high quality medicines and is a critical element of a future, advanced manufacturing strategy for the UK.

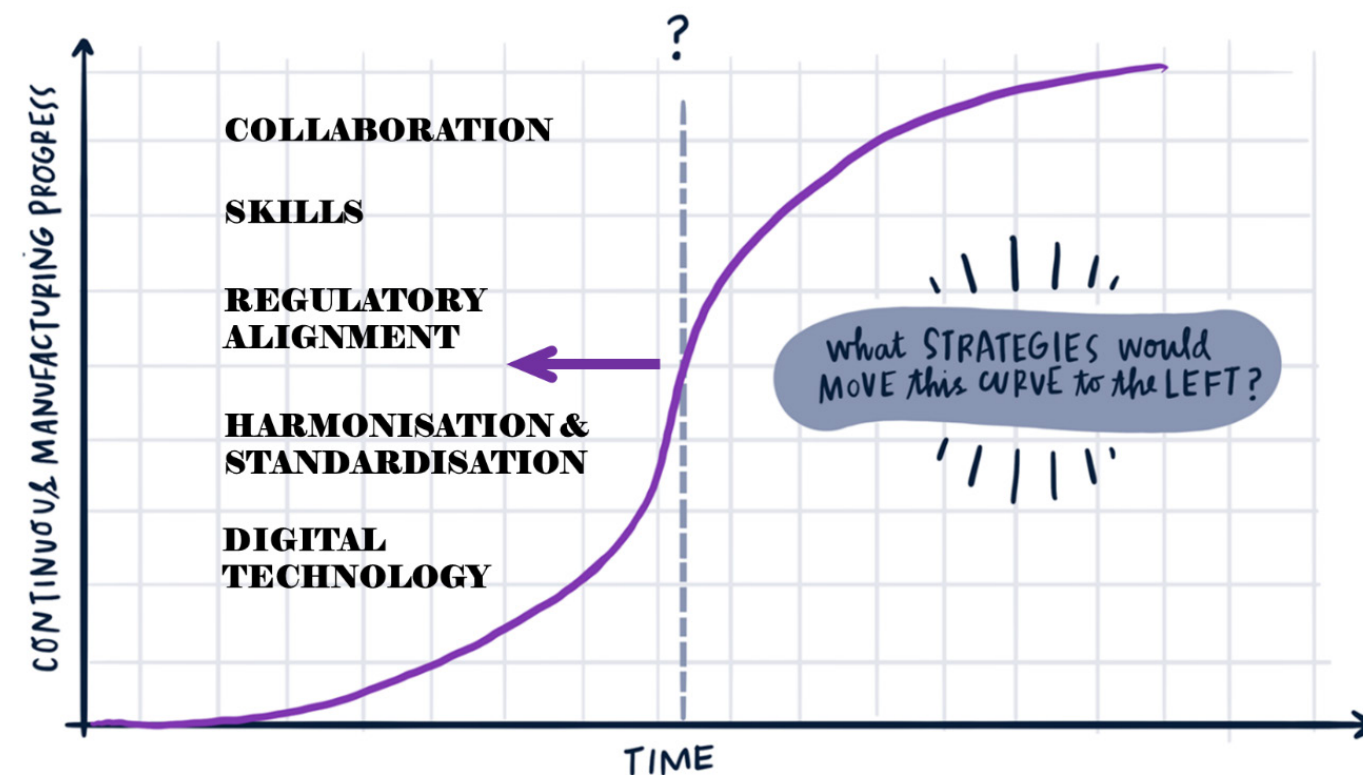


FIGURE 3: 'S-CURVE' HIGHLIGHTING CM PROGRESS VS. TIME

⁴https://www.cmac.ac.uk/Business_Case_Insights_for_CM.pdf

⁵Hayek, M. (2017). Continuous Manufacturing: Is Pharma Ready? | Accenture. [online] Accenture.com. Available at: <https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready>

Skills and collaboration are Vital to the Success of the Sector

70% of delegates highlighted skills and collaboration as the most important factors in accelerating the adoption of continuous manufacturing

Lord Bethell described three core strengths that the UK offers international investors concerning medicines manufacturing. The first is a unique network of research and innovation centres, largely highlighted by the overview of Government investments above. The second is a strong culture of collaboration between academia, industry and Government, often referred to as the triple helix model, seen to excellent effect in the COVID vaccines response. The third is long-term Government investment in talent and skills across all levels. The EPSRC Future Manufacturing Hubs (CMAC being one example) have already proven valuable assets.⁷

42% of delegates indicated that skills are the most important factor in accelerating CM. Of course, the challenges around this are two-fold: upskilling the existing workforce and attracting new talent. Considering medicines in general, the

level of interest has never been higher due to the pandemic, meaning now is an unprecedented time to nurture the latter. Charles Cooney, Emeritus Professor of Biomedical Engineering at MIT, discussed how students need to be taught how to deal with open-ended challenges, in addition to providing the fundamentals. This better equips them for future research and industry challenges, to solve problems, be innovative and develop solutions. The UK has also seen significant success in Doctoral Training Centres for PhD students which provide focussed approaches towards specific industry challenges. Lord Bethell highlighted the importance of apprenticeship schemes and the Government's commitment to attracting the best talent to the UK, particularly post-Brexit.

The power of collaboration remains clear and global consideration must be taken into account. The triple helix model, (Figure 4), must also be extended to regulators and policy makers to establish the culture and connections that will allow all stakeholders to work together in an informed and aligned manner. Andy Evans of MMIP discussed how precompetitive collaboration is an effective way to 'share the risk' when it comes to investing in new technologies. 27% of delegates responding to a live poll also indicated that the sharing of experiences would make the biggest difference in accelerating CM. In reference to the first of Lord Bethell's summary of relevant core UK strengths, effective collaboration must continue to be embraced by enabling easy access to technical expertise and working with businesses to develop step-change technologies for enhancing productivity.



FIGURE 4: TRIPLE HELIX MODEL OF GOVERNMENT, ACADEMIC AND INDUSTRY COLLABORATION

The UK as a Leading, Innovative Regulator

Regulators are committed to supporting and accelerating innovation and industry must engage with them early to expedite new products to market

Whilst assuring patient safety remains the top priority for regulators, the COVID-19 pandemic has undoubtedly reinforced the message that traditional timescales for new treatment approvals need to change. 47% of delegates who responded to a live poll indicated that they still see the regulatory bodies as a barrier which is an interesting statistic, given the consistent messages from regulators at previous ISCMP meetings that they are fully supportive. The time is right to learn from the innovative approaches to review and approve medicines during the pandemic and develop these into standard practices for agile approval. With an open and willing

regulatory agencies, industry must work together to break down perceived barriers to encourage CM adoption, engage early and often with regulators to get support for regulatory filings, removing the perception of risk that can be associated and difficult to justify trying to combine innovative medicines introduction with innovative manufacturing technology introduction. Here too, the role of the wider ecosystem and sharing experience and case studies can be highly influential.

Indeed, both the MHRA and FDA provided a clear and unified message at this meeting: to come and speak to them early around new and innovative approaches in medicines manufacturing. Samantha Atkinson, Chief Quality & Access Officer at MHRA, described a refreshed process with a strengthened evidence base and regulatory simplification, in addition to a new innovation licencing pathway launched in January this year, aiming to reduce time to market for innovative medicines. The FDA are also expecting to publish their guidance on harmonising global regulations for CM (ICH Q13) in June. Larry Lee of the FDA discussed a renewed vision of high quality drugs without extensive regulatory oversight, reinforcing the message that regulators are more open to innovation than they may have been previously.



FIGURE 5: VISUAL GRAPHIC OF KEY MESSAGES FROM SPEAKERS IN THE ISCMP REGULATORY AND POLICY SESSION

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⁴How Development and Manufacturing Will Need to Be Structured—Heads of Development/Manufacturing, May 20–21, 2014 Continuous Manufacturing Symposium. Kevin Nepveux, Jon Paul Sherlock, Mauricio Futran, Michael Thien, Markus Krumme. <https://doi.org/10.1002/jps.24286>

⁷<https://epsrc.ukri.org/research/centres/manufacturinghubs>

¹Regulatory and Quality Considerations for Continuous Manufacturing, May 20–21, 2014 Continuous Manufacturing Symposium, Gretchen Allison, Yanxi Tan, Cain, Charles Cooney, Tom Garcia, Tara Goonen Bizjak, Oyvind Holte, Nirdosh Jagota, Bekki Komar, Evdokia Korakianiti, Dora Kourti, Rapti Madurawe, Elaine Morefield, Frank Montgomery, Moheb Nasr, William Randolph, Jean Louis Robert, Dave Rudd, Diane Zezza. <https://doi.org/10.1002/jps.24324>

Conclusions

The 5th ISCMP meeting set out three main objectives:

Regulatory

Protect and improve public health by enabling the earliest access and high-quality supply of safe, effective, and innovative products through proportionate, data-driven decisions on risk and benefits.

In **regulatory**, both the MHRA and FDA provided positive messaging around the need for flexibility where appropriate and a refreshed approach towards the time scales for novel medicine approvals. With around one third of new drugs currently coming from emerging companies, now is the right time to be doing this. It's clear however, that work is still needed in linking research and manufacturing with the regulator, particularly in early development stages (47% of respondents felt regulatory was a barrier). Industry and regulators need to work together to provide guidance and standards for the deployment of continuous platforms and other advanced technologies.

Industry

Leveraging the combined UK Innovation Ecosystem to deliver a more agile, adaptable and scalable medicine manufacturing supply chain.

In **industry**, there is greater need for agility in manufacturing and adopting a patient-centric approach. Beyond the pandemic, ageing populations and increasingly complicated health problems are re-emphasising the need for more personalised treatments. More than 60% of new drugs may be still small molecule, but significant growth is expected in biologics and gene therapies, monoclonal antibodies and recombinant vaccines. Investment/incentives are needed to drive the adoption of innovative technologies which improve supply chain resilience and Net Zero impact. Investment in skills is also critical.

Academia

Highlight strategic commitment to world class research and innovation in the UK for advanced manufacturing and digital technologies, sustainability and deliver the talent pipeline, developing existing assets.

In **academia**, the need for targeted and sustained investment is clear, and the UK Government has already taken significant steps in the right direction. However, further support is still needed in order to keep our community on the leading edge of the different areas of medicines development and manufacturing research and maintain our status as a global champion. The academic community must continue to explore advanced technologies, such as CM, and have a pivotal role in training and nurturing the talent pipeline. The correct mechanisms must be in place to support collaborations and accelerate translation connecting the rich landscape of assets that are emerging and realising the full potential of the UK triple helix and the power of precompetitive collaboration.



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