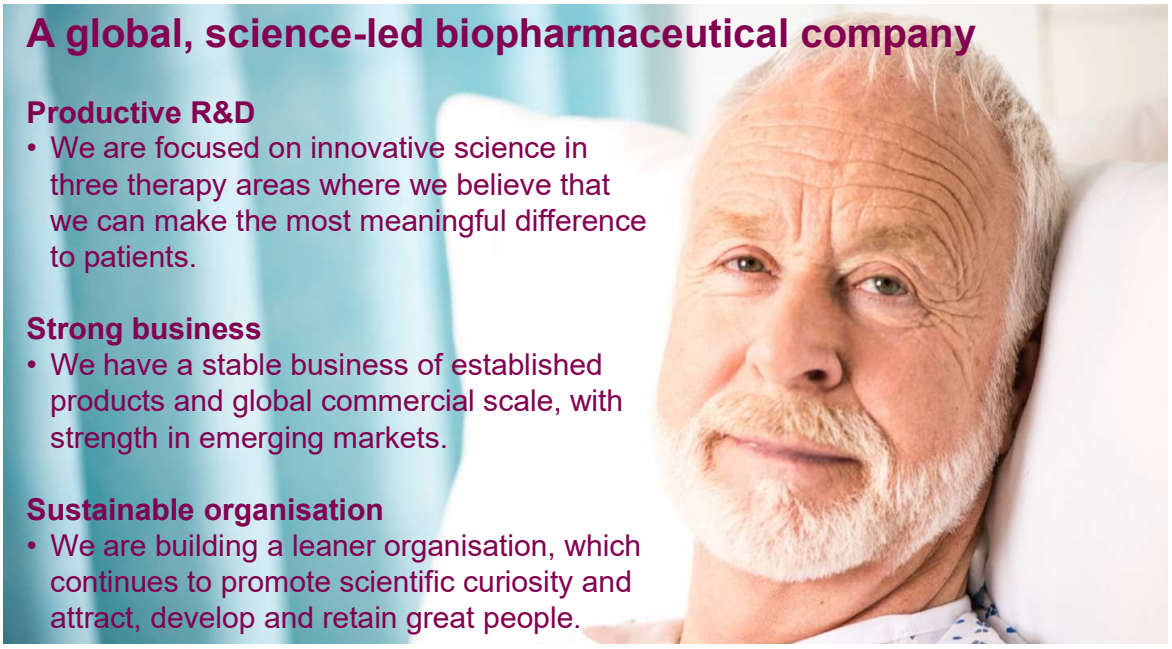
Transforming the development, manufacture and supply of medicines

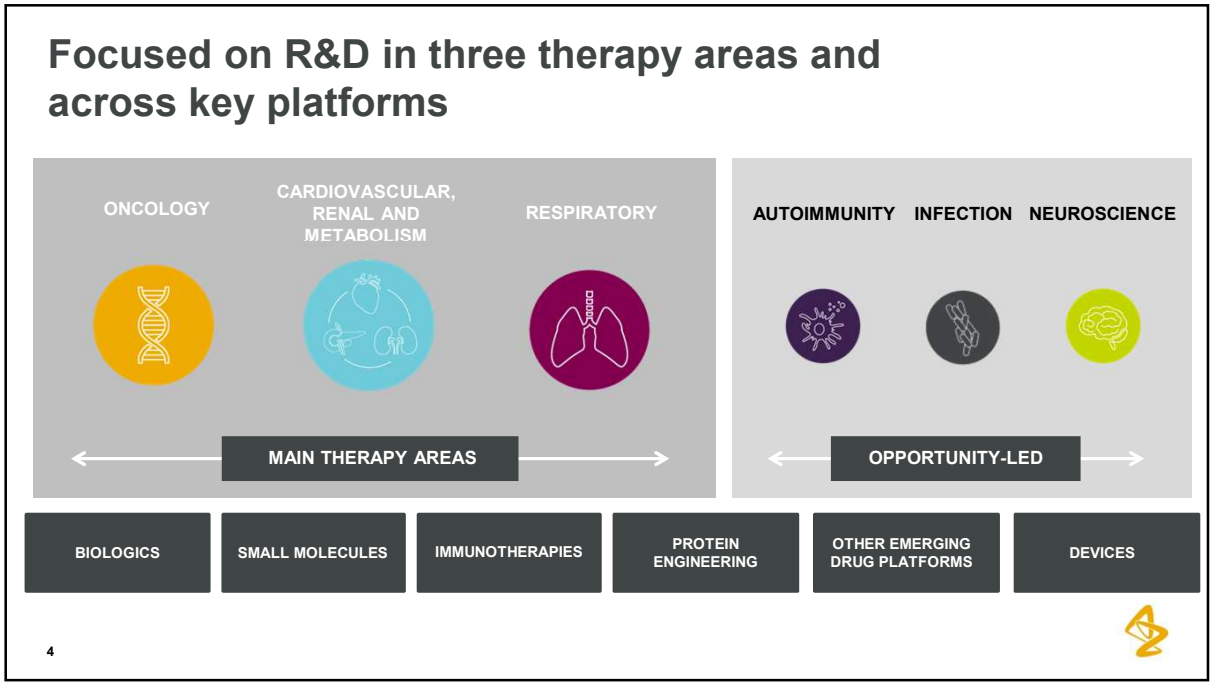
Jon-Paul Sherlock; Global Technology Strategy Director, CMAC Board Chair

Cambridge International Manufacturing Symposium September 2018

Outline

- Changing demands on the Pharmaceutical Industry
- Technology trends
- The essential role of collaboration
- Future opportunities


A global, science-led biopharmaceutical company
Productive R&D
• We are focused on innovative science in three therapy areas where we believe that we can make the most meaningful difference to patients.
Strong business
• We have a stable business of established products and global commercial scale, with strength in emerging markets.
Sustainable organisation
• We are building a leaner organisation, which continues to promote scientific curiosity and attract, develop and retain great people.


Focused on R&D in three therapy areas and across key platforms
ONCOLOGY
CARDIOVASCULAR, RENAL AND METABOLISM
RESPIRATORY
AUTOIMMUNITY
INFECTION
NEUROSCIENCE
MAIN THERAPY AREAS
OPPORTUNITY-LED
BIOLOGICS
SMALL MOLECULES
IMMUNOTHERAPIES
PROTEIN ENGINEERING
OTHER EMERGING DRUG PLATFORMS
DEVICES
4

Lifecycle of medicine

We are one of only a handful of companies to span the **entire life-cycle** of a medicine from **research and development** to **manufacturing and supply**, and the **global commercialisation** of primary care and speciality care medicines.

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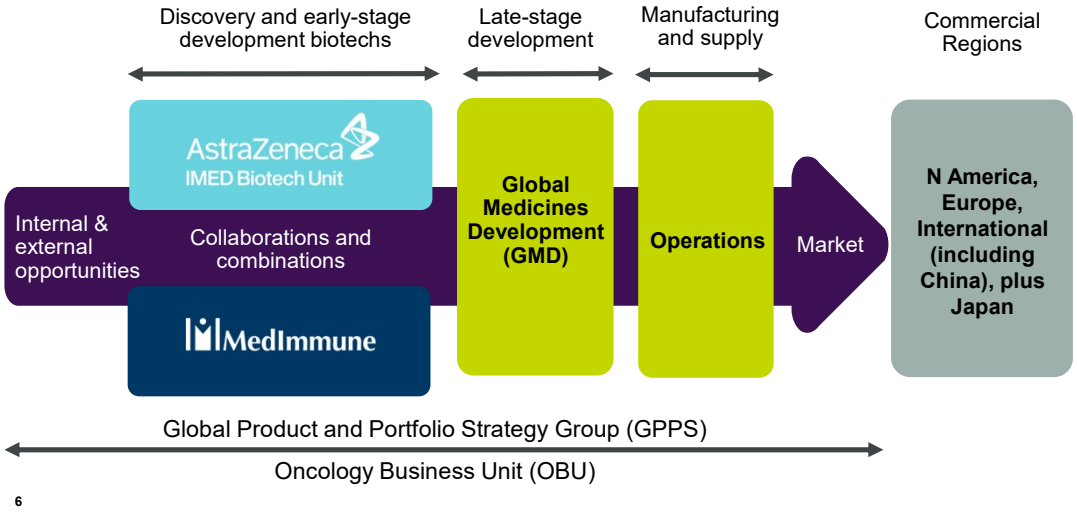
Working collaboratively internally and externally



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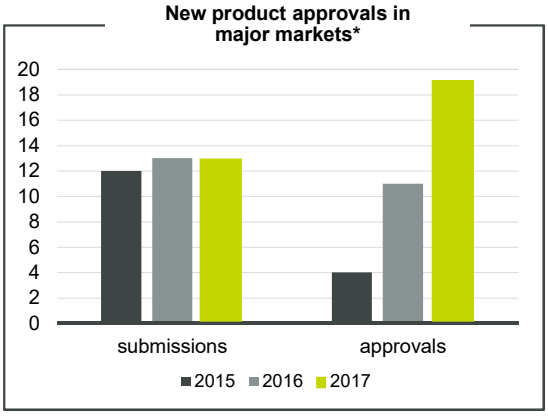
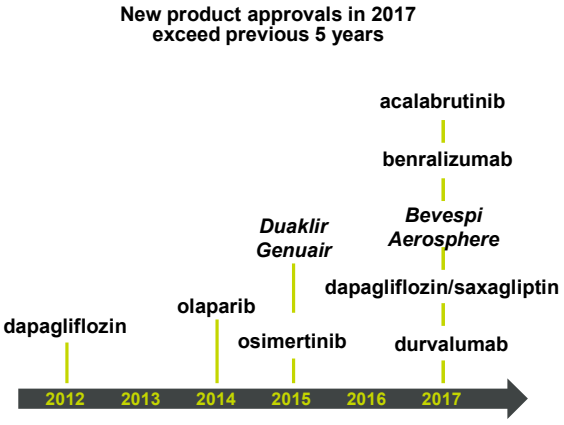
Pushing the boundaries of science and delivering for patients





* US, Europe, China, Japan

The Pharmaceutical industry's previous strategy is not fit for the future

Placing big bets on a few molecules and growing them into blockbusters worked well but R&D productivity dropped the environment is changing.

Innovative medicines become generic and raise expectations for future medicines

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Major trends for the pharmaceutical industry

1. Aging population
2. Increasing cost of healthcare
3. Outcomes based pricing
4. Clinical advances; fatal to chronic to cured
5. Growth in emerging markets
6. Regulators cautious
7. Patient centricity

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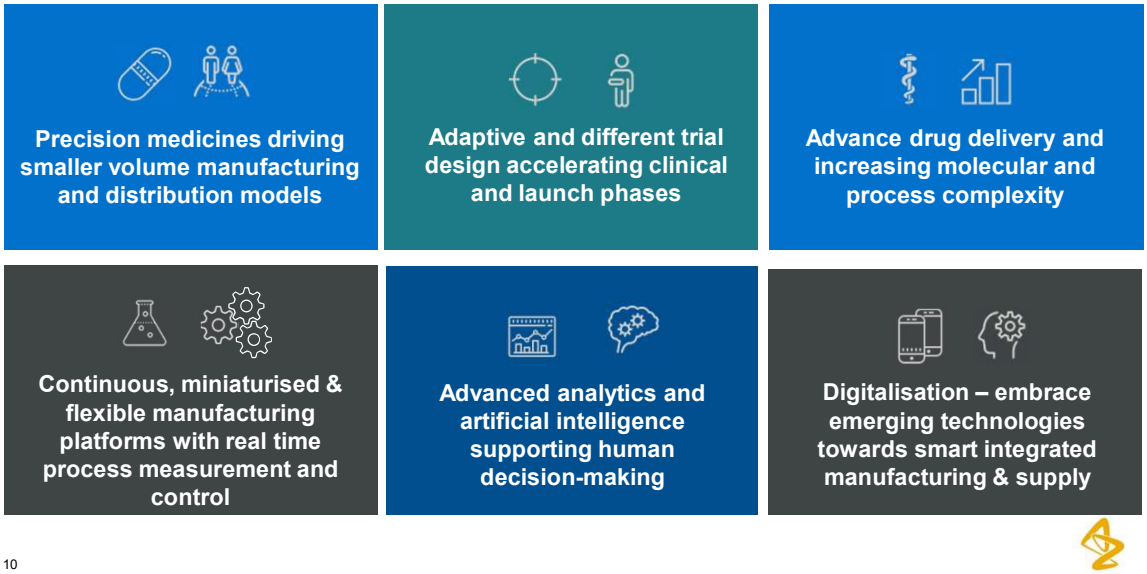
Trends & Drivers influencing manufacturing



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"To unlock innovation, pharma needs to be honest about failure"

June 5, 2018

Many successful leaders agree that a company's willingness to embrace and learn from failure can unlock innovation – and it's a lesson the pharmaceutical industry would do well to learn.

Take Jeff Bezos, for example. As the CEO of Amazon, he encourages designing bold experiments that may lead to failure. After Amazon acquired Whole Foods, he explained: "***If you're going to take bold bets, they're going to be experiments. And if they're experiments, you don't know ahead of time if they're going to work***."

Netflix provides another notable example of this mindset. As of the first quarter of 2018, Netflix had 125 million subscribers with a revenue of over $11 billion. Yet, when Netflix CEO Reed Hastings spoke at a technology conference, he said: "***Our hit ratio is too high right now. We have to take more risk," implying that the company needs to take more chances and, hence, fail more.***

But in pharma a fear of failure too often kills creativity and prevents researchers from taking chances. Instead of regarding failure as the worst possible outcome, researchers need to give themselves permission to fail and to share their failures with others – as long as they are able to extract valuable lessons to learn from the experience.

https://pharmaphorum.com/views-and-analysis/unlock-innovation-pharma-honest-failure/

The Pharma Industry does innovate however, manufacturing innovation is challenging

Core business is to discover, develop and commercialise new medicines

Attrition: *Will technology be used?*

Large margins: *Will technology create value?*

Flexible manufacturing processes: *Will current assets be sufficient*

Collaboration is critical

- Share risk
- Innovate at interfaces
- Build on frontiers of science and engineering
- Leverage investment
- Accelerate adoption of new technology
- Greater influence of regulatory and research directions
- Demonstrate the business case

Why would you want to do this on your own?
Control
Simple

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Experience has demonstrated the value of a collaborative. leveraged approach

- **ReMediES**
  - Innovative programme brought together 23 industrial and academic partners with regulators and healthcare professionals.
  - **£1.3M in-kind funding from AZ geared to £23M**
  - Innovations delivered include;
    - augmented reality training
    - new forming material, reduced the overall footprint of the blister
    - printed electronic labels
    - breakthroughs with immobilized enzymes for biotransformations
    - JIT Clinical Pharmacy concept

ReMediES
RE-configuring MEDIcines End-to-end Supply

- **CMAC** (Continuous Manufacturing and Crystallisation)
  - **£2M from AZ geared to £150M** (2011 to 2023) funding over 75 researchers and ISPE FOYA winning facilities.
  - Influential network of 8 major pharma peers sharing experience
  - Created a talent pipeline and critical to AZ capability build in continuous manufacturing
  - Underpinned development of an API reprocessing method for 10 batches

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FUTURE MANUFACTURING RESEARCH HUB

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Introducing continuous manufacturing technologies (CMAC & Remedies)

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Why is continuous manufacturing of such interest?

- Batch Manufacturing
  - Quality
    - End product testing
    - Control through fixed process parameters
  - Flexibility
    - Campaign delivery
    - Multipurpose
  - Development
    - Well understood
    - Scale up, material intensive
  - Digitalisation
    - Models (complex multiscale)
- Continuous manufacturing
  - Quality
    - Real time process measurement
    - Flexible parameters to maintain controlled state
  - Flexibility
    - Miniaturised
    - Modular
  - Development
    - New capability required
  - Digitalisation
    - Automation
    - Real time decision making

Is the balance shifting?

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Addressing the blockers to implementation

Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance May 20–21, 2014 Continuous Manufacturing Symposium

IAN R. BAXENDALE,[1] RICHARD D. BRAATZ,[2] BENJAMIN K. HODNETT,[3] KLAVS F. JENSEN,[2] MARTIN D. JOHNSON,[4] PAUL SHARRATT,[5] JON-PAUL SHERLOCK,[6] ALASTAIR J. FLORENCE[7]

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[5]Institute of Chemical & Engineering Sciences, A*STAR, Singapore 627833, Singapore
[6]Global Medicines Development, AstraZeneca, Macclesfield, SK10 2NA, UK
[7]EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation, University of Strathclyde, Glasgow G1 0RE, UK

Consensus on Need to Develop:

- Flow chemistry toolbox with selectivity
- Modular equipment (lab-scale / standardization)
- Modelling & control methods across operations
- Integrated E2E approaches
- Means to manage change (catalyst / fouling)
- Workflows for process design
- Culture: inputs from across organisation; multidisciplinarity
- Skills development
- Disseminate examples of CM
- Engage with regulators
- Economic case for CM
- Bridge primary to secondary

J. Pharm Sci. 104(3), 781–791, 2015

PROGRESS & BARRIERS (API)

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
pubs.acs.org/OPRD

The Evolving State of Continuous Processing in Pharmaceutical API Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations

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[∥]Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, Indiana 46285, United States
[⊥]API Chemistry, GSK, 709 Swedeland Road, UW2810, P.O. Box 1539, King of Prussia, Pennsylvania 19406, United States

Table 14. Barriers to Implementing CPs (IQ and CMO groups)

IQ Group	CMO Group
• Compelling business case and internal sponsorship, especially when existing batch capacity is available	• Existing batch capacity weakens business case, less compelling if only a small portion of the process is continuous
• Cost of equipment and training	• Cost of equipment and training
• Time to make the transition from batch to continuous	• Lab development tools are lacking
• Cultural - scientists have batch design mindset, continuous perceived as higher risk	• Risk averse nature of pharmaceutical companies
• Higher initial costs to outsource - vendors charge additional development costs	• Requires additional time to develop, not widely accepted by Pharma customers
• Alignment with Quality function	

ReMediES
RE-configuring MEDicines End-to-end Supply

INNOVATION IN CONTINUOUS MANUFACTURING

Our Objectives

- The development of mobile continuous process equipment capable of a range of chemistries with open access.
- Identifying and exploiting suitable technologies for continuous processing for specific applications.
- Creating an asset network for use by CMOs and primes.

The Result

- A series of continuous process solutions – demonstrated, evaluated & scaled:

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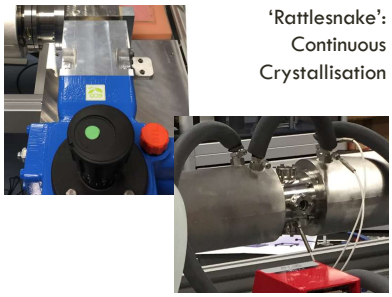
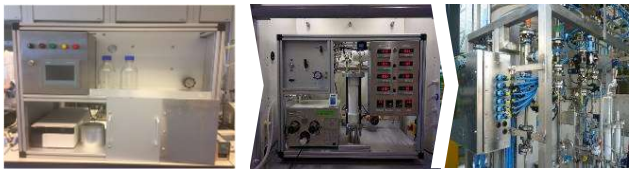
BLACKTRACE
'Titan' Continuous Processing (including reaction, separation and particle formation

CAMBRIDGE REACTOR DESIGN
'Rattlesnake': Continuous Crystallisation



INTENSICHEM
Continuous Hydrogenation Platform



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CHANGE IS ALREADY HAPPENING

FDA Approves Tablet Production on Janssen Continuous Manufacturing Line

FDA approved an update in the manufacturing of Prezista (darunavir) using a continuous manufacturing line at Janssen Supply Chain's facility in Puerto Rico.

Apr 12, 2016 By Pharmaceutical Technology Editors

With the April 8, 2016 FDA approval of an update in the manufacturing of PREZISTA (darunavir) 600 mg tablets, Janssen Supply Chain (JSC) can now produce tablets on a continuous manufacturing production line at its manufacturing facility in Gurabo, Puerto Rico. The use of continuous manufacturing to replace the existing batch manufacturing process is a result of a five-year partnership with Rutgers University and the University of Puerto Rico to develop a process that integrates all manufacturing steps (weighing, milling, blending, compression, and coating) into one single line.

"….reduce manufacturing and testing cycle time….
reduce waste and environmental impact….
lower process risk….
maintaining quality…
reduced a two-week production timeline to a one-day….
allows continuous monitoring of quality"

Development and TT Benefits

De Belder, ISCMP, Boston, 2014

Development Benefit	Watchout
Speed to Market	New technology: risk for delays
Less effort	PAT will add effort
Less API	No parallel development Batch/CM
More robust	More API needed
More formulations in DC	More API needed

Tech Transfer Benefit	Watchout
Less effort, Less API	Often still small differences – verification will be needed, unless launch from the same line.

janssen

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Early Choices to be made

- Product versus Platform
- Preblend – in line feeding
- Coating or not
- Which technologies
- Collaboration partners
- Level of PAT
- Use of Modeling
- RTR plan
- Sampling plan
- Control Strategy
- When to start communicating with HA

janssen

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SYSTEMS TO SUPPORT CONTINUOUS CHEMISTRY

Continuous drug substance filtration : designing equipment for continuous filtration of drug substance with the ability to reduce processing time, improving linkage to continuous drying and to deliver enhanced control over particle properties rendering the material more compatible with downstream drug product processes.

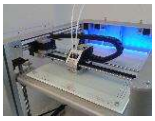
- Demonstrating benefits via exemplary case studies.

Continuous direct compression : defining a design space for the implementation of continuous blending and direct compression in terms of critical material attributes and critical process parameters.

- Demonstrating potential for the wider application of continuous blending and direct compression and the subsequent benefits for clinical and commercial supply chain.

Hot melt extrusion : demonstrating the ability of hot melt extrusion technology to produce oral solid dosage forms in one continuous process.

- Demonstrating potential for the wider application of hot melt extrusion and the subsequent benefits for clinical and commercial supply.



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CONNECTING TECHNOLOGY PLATFORMS FOR AGILE SCS

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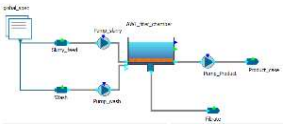
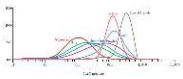
Continuous drug substance filtration

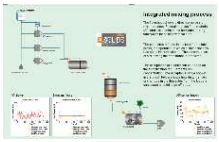
- AWL lab scale prototype
- Continuous washing, filtration and drying



Continuous direct compression

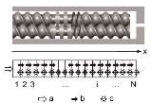
- GEA CDC50 test rig, PAT enabled
- Continuous feeding, blending and compression

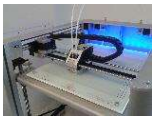




Hot melt extrusion/3D printing

- 16mm twin screw extruder at Univ of Strathclyde, PAT enabled
- Potential to direct couple HME and 3DP





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Innovating across the supply chain

USING ANALYTICAL TOOLS TO MAP & MANAGE COMPLEXITY

First visualisation of complete GSK Manufacturing & distribution network
(836 global locations)

distribution centres
manufacturing sites
multi-market hubs

Flow arcs shaded by quantity

- Managing Complexity not just SKUs but managing multiple connections for supply planning
- 2,744 point-to-point network connections

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MAKING THE BUSINESS CASE

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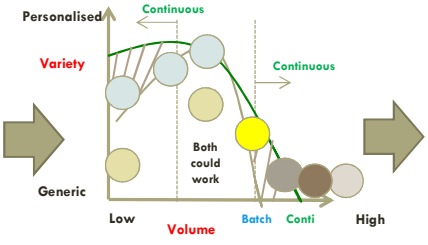
Conceptual analysis: identifying opportunities and challenges of batch to continuous

- **Patient centric supply, less managerial oversight and regulatory sanction**
- **Responsive production & distribution models, digitally enabled patient engagement**
- **Reduced capex and operating costs with Volume flexibility, more distributed mfg**
- **Process-control based quality and regulatory assurance**
- **Smaller patient groups, dynamic closed loop control, based on downstream**

Future supply chains enabled by continuous processing –opportunities and challenges. 2014 MIT Symposium, Journal of Pharmaceutical Sciences,

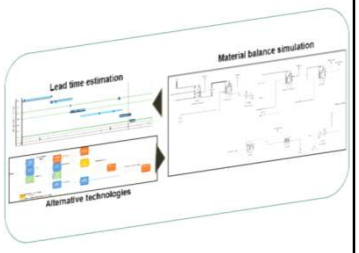
Srai, J. S., Badman, C., Krumme, M., Futran, M., & Johnston, C. **2015**. 104(3), 840–849.

Strategic targets identified through product category analysis and patient populations



Evaluating the potential for the continuous processing of pharmaceutical products – a supply network perspective.
Srai, J. S., Harrington, T.S., Alinaghian, L.S., Phillips, M.A. **2018**,
Chemical Engineering and Processing, 97, 248–258

Operational business case for specific products; quantification through supply chain analysis



Towards a new approach to modelling pharmaceutical supply chains in a changing technological landscape.
Settani, E., and Srai J.S., **2018**,
Pharma Horizon, 2(1)

BUSINESS CASE ANALYSIS THROUGH DIGITAL TOOLS

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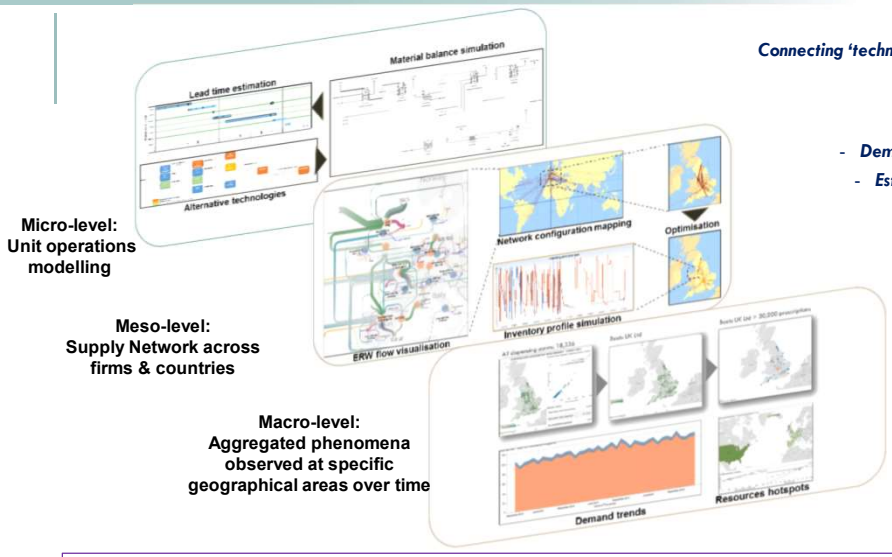


Micro-level:
Unit operations modelling

Meso-level:
Supply Network across firms & countries

Macro-level:
Aggregated phenomena observed at specific geographical areas over time

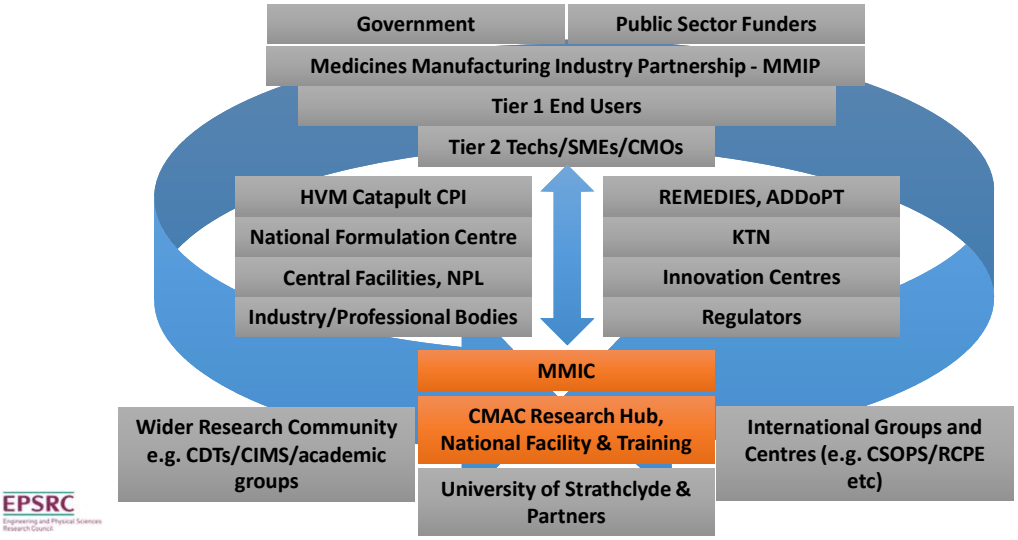
Connecting 'technology silos' to drive an end-to-end supply chain perspective

- ***Establishing the opportunity***
- ***Demonstrating a systems approach***
- ***Establishing a modelling platform***

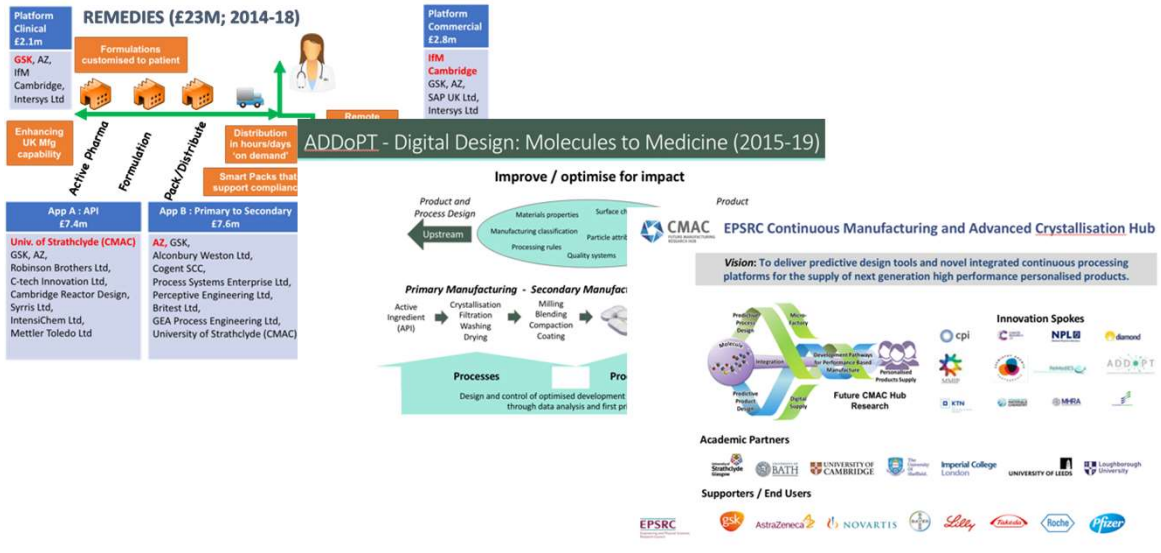
- Srai J.S., Christodoulou P., Settanni E., (2017) Next generation supply chains: making the right decisions about digitalisation. University of Cambridge Institute for Manufacturing, Cambridge, UK
- Settanni E, Srai JS. (2018) Towards a new approach to modelling pharmaceutical supply chains in a changing technological landscape. Pharma Horizon 2018;2(1):26–8.

What Does The Future Hold?

Pharmaceutical Manufacturing Innovation System Landscape:



Build on existing capabilities



Future opportunities to collaborate, de-risk and accelerate delivery

TRL 1-3	TRL 4-7	TRL 8	TRL 9
Fundamental research	Technology development	Technology exemplification	Full commercial deployment
ACADEMIA	**MMIC**		INDUSTRY

UK based, leveraging UK Government funding and established
Globally recognised centres of manufacturing research

INDUSTRIAL STRATEGY

MADE SMARTER. REVIEW 2017

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JIT AUTOMATED CLINICAL PHARMACY

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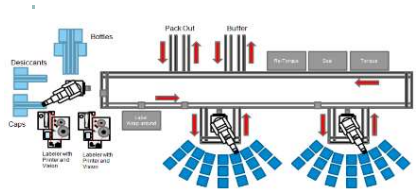
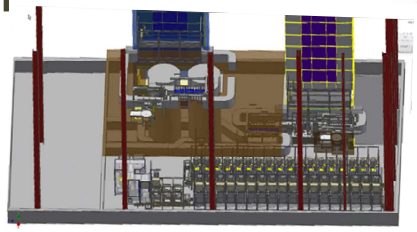
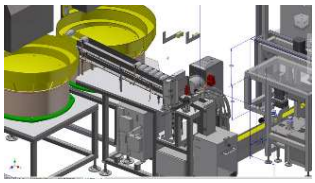
gsk



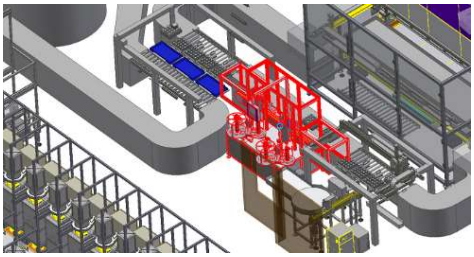
Facility overview





Bottle singulation

Bottle filling unit 1



Printing station

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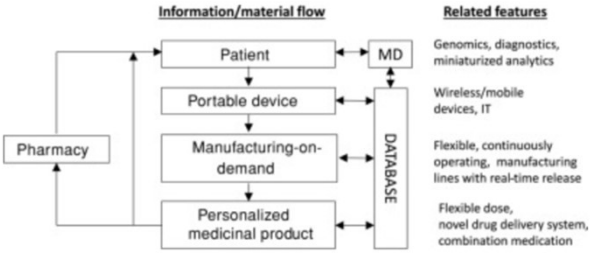
Could this enable a more radical future?

e.g. Enable future business models?



Transforming the development, manufacture and supply of medicines

- Healthcare systems, clinical advances and manufacturing innovation driving demand for change
- Collaboration is critical to overcome barriers to delivery
- CMAC and Remedies have helped shape a collaborative UK landscape and delivered transformative insight and technologies
- The emergence of MMIP, MMIC, ISCF will present exciting opportunities to shape and develop future manufacturing and supply technologies

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Cambridge University Professor, Andy Neely:

Clearly the future in health is around digital technologies and the way that digital technologies will shape the way that we deliver services to patients... I think one of the really interesting things about this collaboration with AstraZeneca and Wuxi is the fact that Wuxi's been investing in digital technologies for quite a while, so there are some really interesting lessons that the UK can learn from China and hopefully some interesting lessons that China can learn from the UK

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Acknowledgements

- Prof Jag Srai; Remedies
- Prof Alastair Florence; CMAC

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