EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Exploring Alternative Product-Process Supply Network Models in Pharma

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EPSRC
Engineering and Physical Sciences Research Council

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Industry Team contributors

- AstraZeneca
- Genzyme
- GSK
- Novartis

Project Objectives

- Identify barriers and enablers for Continuous Manufacturing
- Identify the challenges of CM for manufacturing operations and up-stream and down-stream supply chains
  - **WP1:** Architectural differences between current ad future manufacturing operations management and supply chain configurations, structures, processes and systems
  - **WP2:** Analyse key management control challenges and develop appropriate management control processes and capabilities to facilitate effective and efficient management of CM
  - **WP3:** Learning from experiences of other industries that have transformed from batch to flow based continuous production.
- Exploring alternative value chain configuration roadmaps

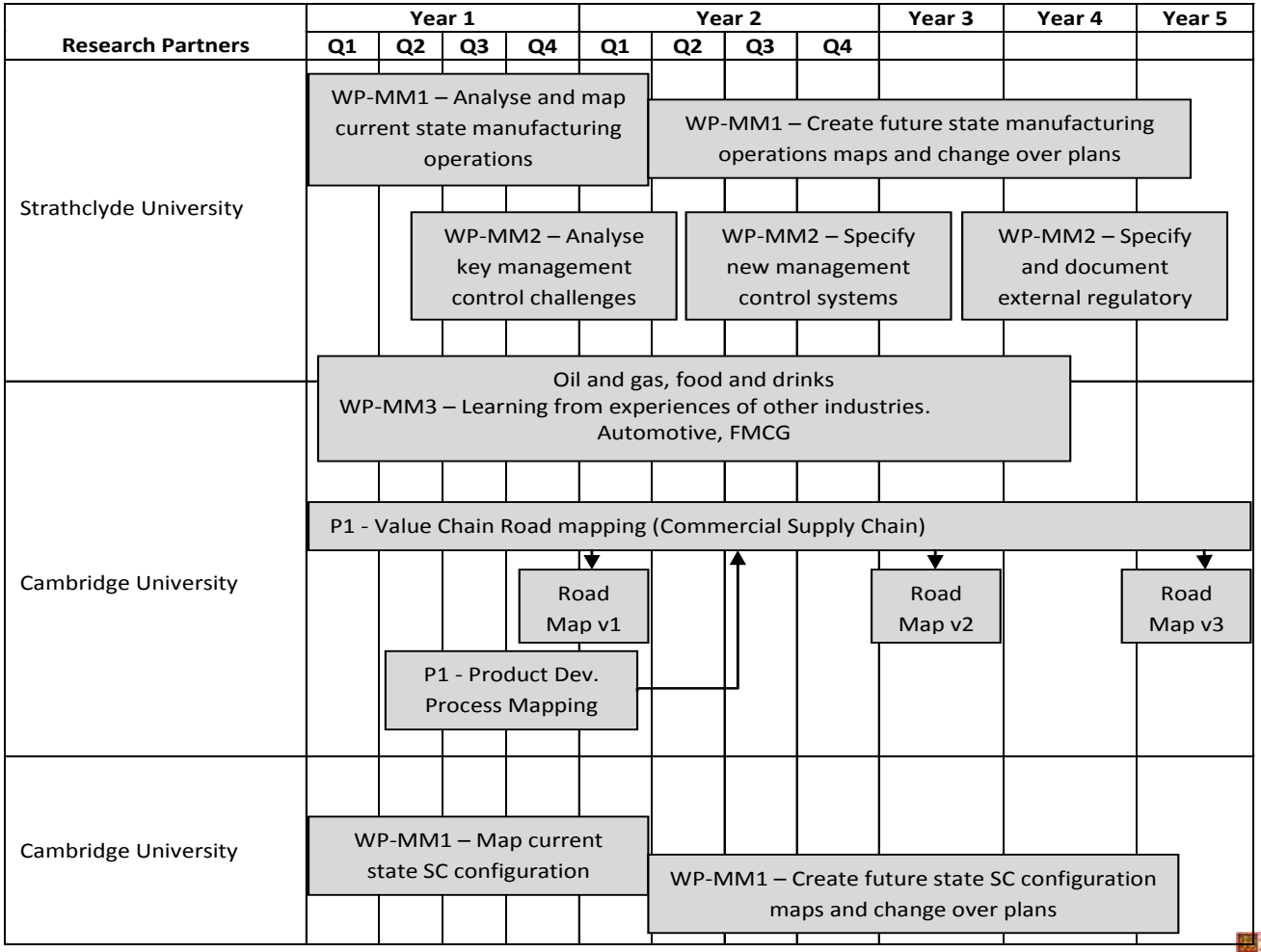
Agenda

- Project Scope
- Evidence from the Literature
- Barriers & Enablers
- Investigative Approach
- Initial Findings
- Opportunities – Pharma feedback
- Opportunities - Other industries
- Next Steps

Project scope

- Not simply about batch to continuous processing?
- More about alternative product-process supply network options and value chain implications?
  - product variety, consistency and functionality
  - energy and resource efficiency
    - capital investment, solvent use, no. of process steps
  - Inventory, minimum ‘lot’ size, customisation options
- Exemplars from other sectors who have reconfigured their manufacturing operations to support more dynamic supply models

High Level Work Plan



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Authors	Drivers of Continuous Manufacturing
[2], [3], [6], [11], [12], [13], [14], [15], [17]*, [18], [19], [20], [21], [22], [24], [25], [26] [2], [3], [4], [5], [6], [12], [14], [15], [18], [19], [21], [22], [24], [26] [2], [5], [10], [12], [17]*, [24], [26]	**Cost** • **Capital investment** Continuous manufacturing allows the use of smaller production facilities with lower capital and operational cost, with a reduced overall plant footprint. • **Operating Costs** Less labour required to operate the processes Continuous process is capable of increasing asset utilisation • **Inventory** Continuous manufacturing has potential for reducing inventory cost (Less WIP inventory, Reduced material handling and transport , Continuous flow of material)
[2], [3], [13], [14], [15], [16], [20], [22], [24]	**Quality** • **Improves process control** CM system is considered to be integration of quality and compliance system. Product yield and quality will be better in CM compared to batch process. – Higher purity • **Less product rejects** The continuous manufacturing enables monitoring of drug quality on a continuous basis rather than through post-production, batch-based testing.
[2], [3], [12], [14], [15], [21], [22], [24], [25], [26]	**Delivery- dependability** Continuous process enhances process reliability
[3], [14], [15], [22], [24], [25]	**Speed** • **Strategic** • Continuous manufacturing accelerates the introduction of new drugs through efficient production processes • Continuous process reduces the time to market • Continuous process is capable of reducing the cycle time • **Operational** • Continuous process is highly capable of minimizing total reaction time through better temperature control compared to batch process. • No Scale-up development is necessary in continuous manufacturing, as the early clinical batches are produced using exactly the same equipment as the large production batches.

Authors	Drivers of Continuous Manufacturing
[2],[5], [8], [10], [11], [15], [20], [22] [11], [19], [22], [24]	**Flexibility** Process flexibility • Different degree of flexibility to change the product mix (product flexibility) • Different degree of flexibility to react to changes in demand (volume flexibility)
[2], [3], [12], [14], [15], [21], [22], [24], [25], [26]	**Sustainability** **Environmental** Continuous manufacturing minimizes waste, energy consumption and raw material use. Solvent can be recycling more effectively in continuous process compared to batch process.

Batch Processing

Advantages:

- Flexible – can use equipment for multiple drugs
- Capacity Management straightforward
- 'Batch' signature for traceability
- Well established process, understood, with installed capacity

Disadvantages:

- Long throughput times, with constrained volume flexibility
- Product-quality testing can be time consuming
- Multi-step batch processing common; waiting times between process steps
- High inventories
- Capital intensive

Drivers of Continuous Manufacturing

Economic Drivers

- Reduce cycle time and footprint
- Less WIP inventories
- Lower CAPEX & Operating Cost
- Integration of quality & compliance
- Increased speed to market
- Better product yield

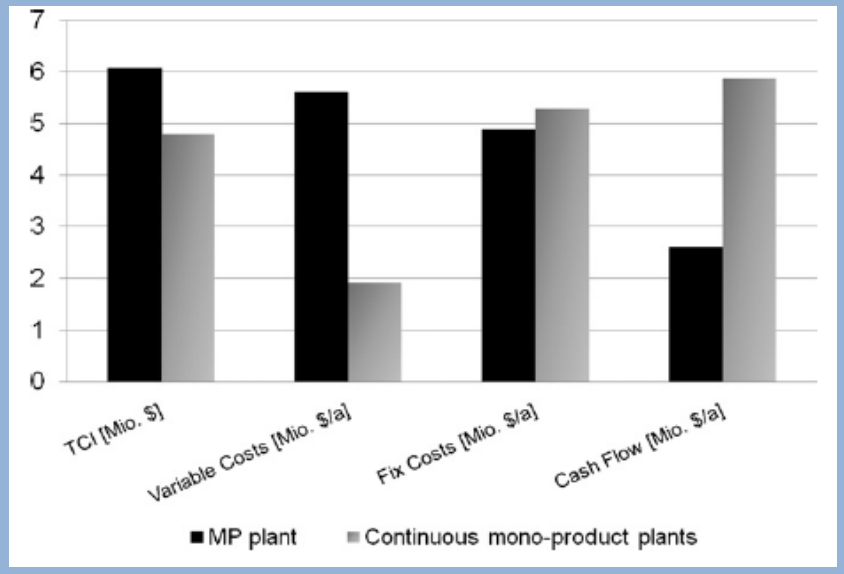
Process Drivers

- Consistency and high quality
- Elimination of scale-up
- Lower catalyst and solvent use
- Less waste through solvent recycling
- Minimize total reaction time through better temperature control
- Effective running and scale-up of exothermic reactions without special equipment/ additional precautions

Case Studies

ECONOMIC

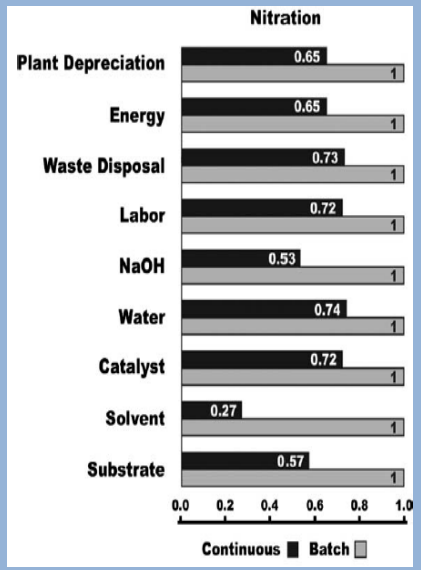
Batch multi-product plant *versus*
Continuous single-product plant
(production of proteins)

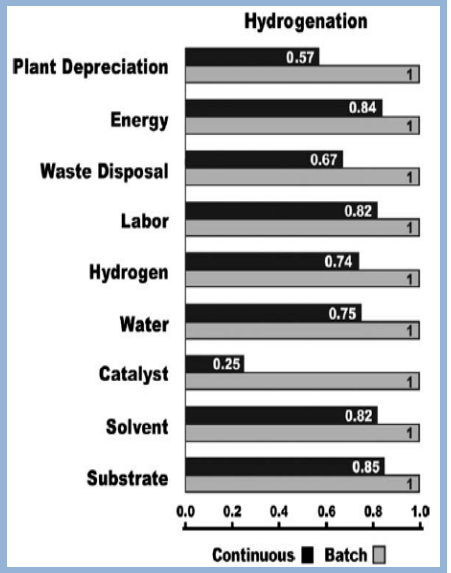


Source: Seifert et al., 2012
(Dortumund University, Germany and Data from Novo Nordisk)

PROCESS

Continuous Flow *versus* **Batch reactor**

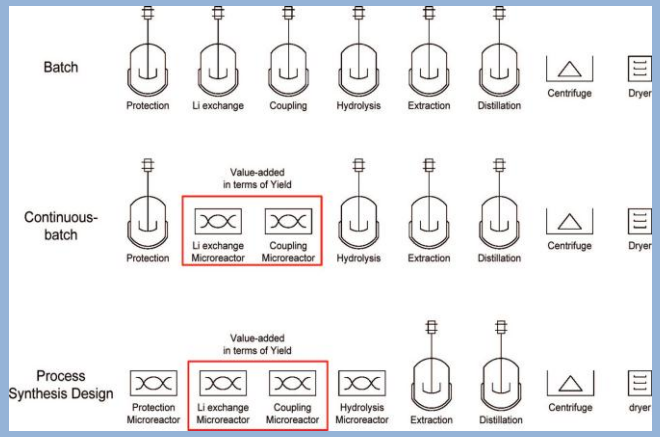




Source: Calabrese et al., 2011
(Corning Incorported Life science)

Case Studies
ECONOMIC EVALUATION

Economic analysis of 3-scenarios from hybrid systems



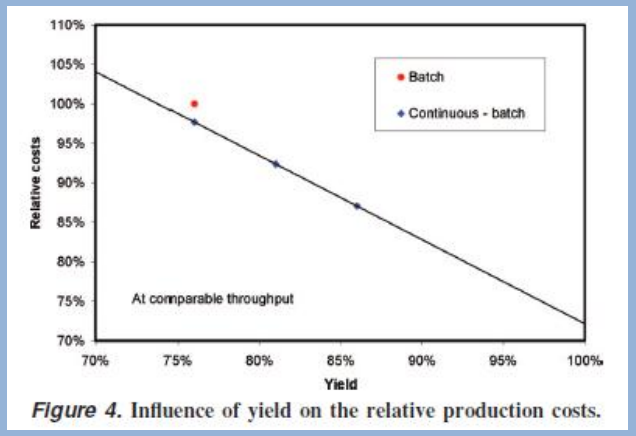


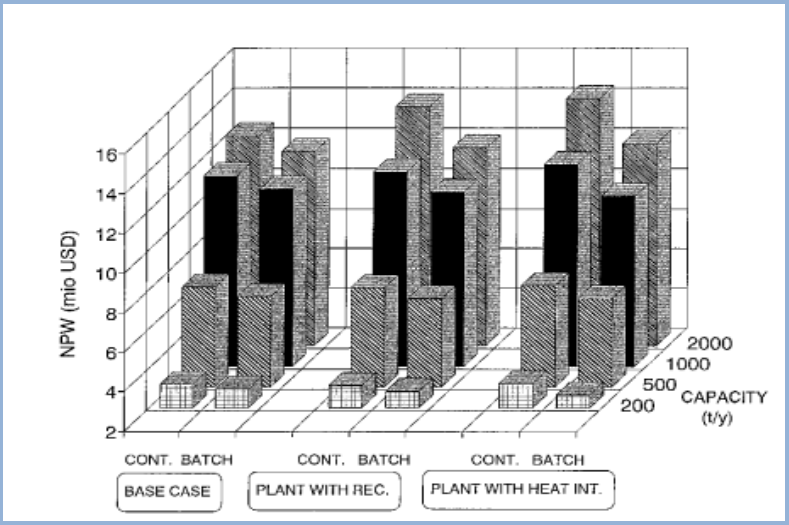
Figure 4. Influence of yield on the relative production costs.

	batch	continuous batch	process synthesis design
campaign size (tons)	5	5	5
batch assets	six 6-m^3 reactors	five 6-m^3 reactors	two 6-m^3 reactors
MR CAPEX[b]	0 Mio $	less than 1 Mio $	more than 1 Mio $
operators	3.5	2.8	2.0
throughput[c] (kg/min)	1.7	2.1	2.1
bottleneck	coupling	distillation	distillation
gain in yield (%)	0	+5	+5
economical gain (%)	**0**	**+10**	**+16**

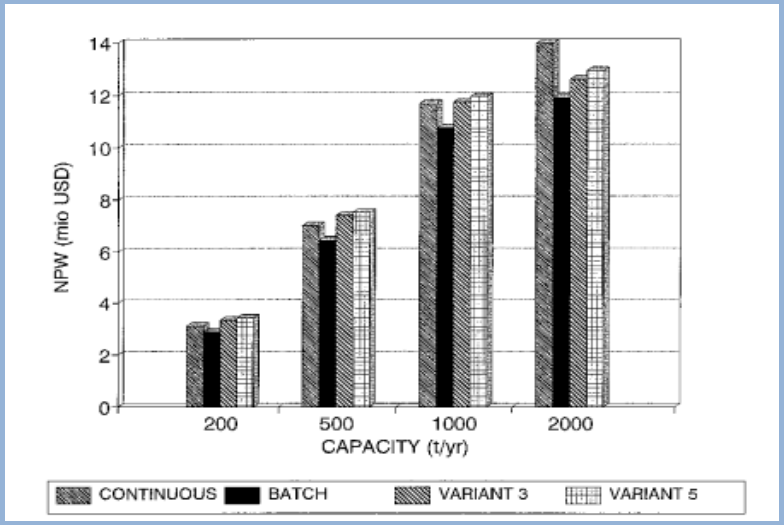
Source: Roberge et al., 2008 (University of Ottawa, Canada and Lonza ltd)

Batch *versus* Continuous

Batch single-purpose equipment
Versus Continuous plant



Batch multi-purpose equipment
Versus Continuous plant



Source: Gorsec and Glavic, 2000
(University of Maribor, Slovenia)

Case Studies

ECONOMIC EVALUATION

Summary of cost differences for all process options (relative to batch case)

	API mass loading = 10%			API mass loading = 50%		
cost of KI :	$100/kg	$500/kg	$3000/kg	$100/kg	$500/kg	$3000/kg
batch (basis for differences)	[$1515M]	[$2337M]	[$7472M]	[$5117M]	[$9225M]	[$34902M]
CM1R with direct tablet formation	−32%	−22%	−9%	−40%	−24%	−9%
CM1 with direct tablet formation	−21%	−10%	4%	−24%	−9%	5%
CM1R with roller compaction	−30%	−21%	−9%	−40%	−23%	−9%
CM1 with roller compaction	−20%	−9%	4%	−23%	−8%	5%

Source: Schaber et al., 2011 (Novartis with MIT)

References

- Comparisons of single step processes
- Limited real-life examples to draw generalisations
- Impact not generally assessed beyond single process or site

Gaps:

- Lack of end-to-end supply chain assessments
- Potential for reconfiguring the value chain

1	Ahmad	Refining the product-process matrix	2002
2	Behr	New Developments in Chemical Engineering for the Production of Drug Substances	2004
3	Calabrese	From Batch to Continuous Flow Processing in Chemicals Manufacturing	2011
4	Collins	Feature-Based Investment Cost Estimation Based on Modular Design of a Continuous Pharmaceutical Manufacturing System	2011
5	Gorsek	Design of batch vs. continuous processes. Part I	1997
6	Gorsek	Design of batch vs. continuous processes. Part II	1997
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8	Hayes	Link manufacturing process and product life cycles	1979
9	Jodlbauer	Range, work in progress and utilization	2005
10	Kim	Manufacturing strategy and production systems: An integrated framework	1993
11	Konstantinov	Continous bioprocessing: an interview with Konstantin Konstantinov from Genzyme	2011
12	Lawton	Continuous Crystallization of Pharmaceuticals Using a Continuous Oscillatory Baffled Crystallizer	2009
13	McKenzie	Can Pharmaceutical Process Development Become High Tech?	2006
14	Pieters	The Impact of Microtechnologies on Chemical and Pharmaceutical Production Processes	2007
15	Plumb	Continuous processing in the pharmaceutical industry: Changing the mind set	2005
16	Safizadeh	Empirical Analysis of the Matrix Product-Process	1996
17	Safizadeh	Linking performance drivers in production planning and inventory control to process choice	1997
18	Schaber	Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study	2011
19	Schoeters	Overcoming the Misconceptions of Continuous Processing	2011
20	Schwalbe	Novel Innovation Systems for a Cellular Approach to Continuous Process Chemistry from Discovery to Market	2004
21	Seifert	Small scale, modular and continuous: A new approach in plant design	2012
22	Trout	Next-wave model	2009
23	Trout	Continuous Manufacturing of Small Molecule Pharmaceuticals: The Ultra Lean Way of Manufacturing	2009
24	Vervaet	Continuous granulation in the pharmaceutical industry	2005
25	Werani	Semicontinuous granulation—the process of choice for the production of pharmaceutical granules?	2004
26	Wilburn	The Business Case for Continuous Manufacturing of Pharmaceuticals (Thesis)	2010

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Barriers to Continuous Manufacturing

Regulatory	Social	Process	Technology	Economic
• PAT and QbD requirements • FDA/ Regulatory approval • Quality validation • Harder traceability • Sterility issue as contaminants and by-products build up within the system	• Market acceptance Varying customer demands in a global, agile market • Perception of 'only suitable for large volume' • Lack of experience and fear of unknown	• Process control and safety • Lack of process understanding • Supply chain effect • Uncertainty in time-to-market • Process design and development • Process is not flexible • Change in already validated process • Process mgmt. and execution system	• Cont. isolation and drying technology • Long reaction times of solids • Start up and shut down issues • Smaller scale, multi-purpose line production tech. • Cont. crystallisation tech. • Out of spec material handling (OOS)	• Resource availability at start-up • Equipment cost • Investment risks • Capital requirement to switch to continuous mode • Specialised personnel required

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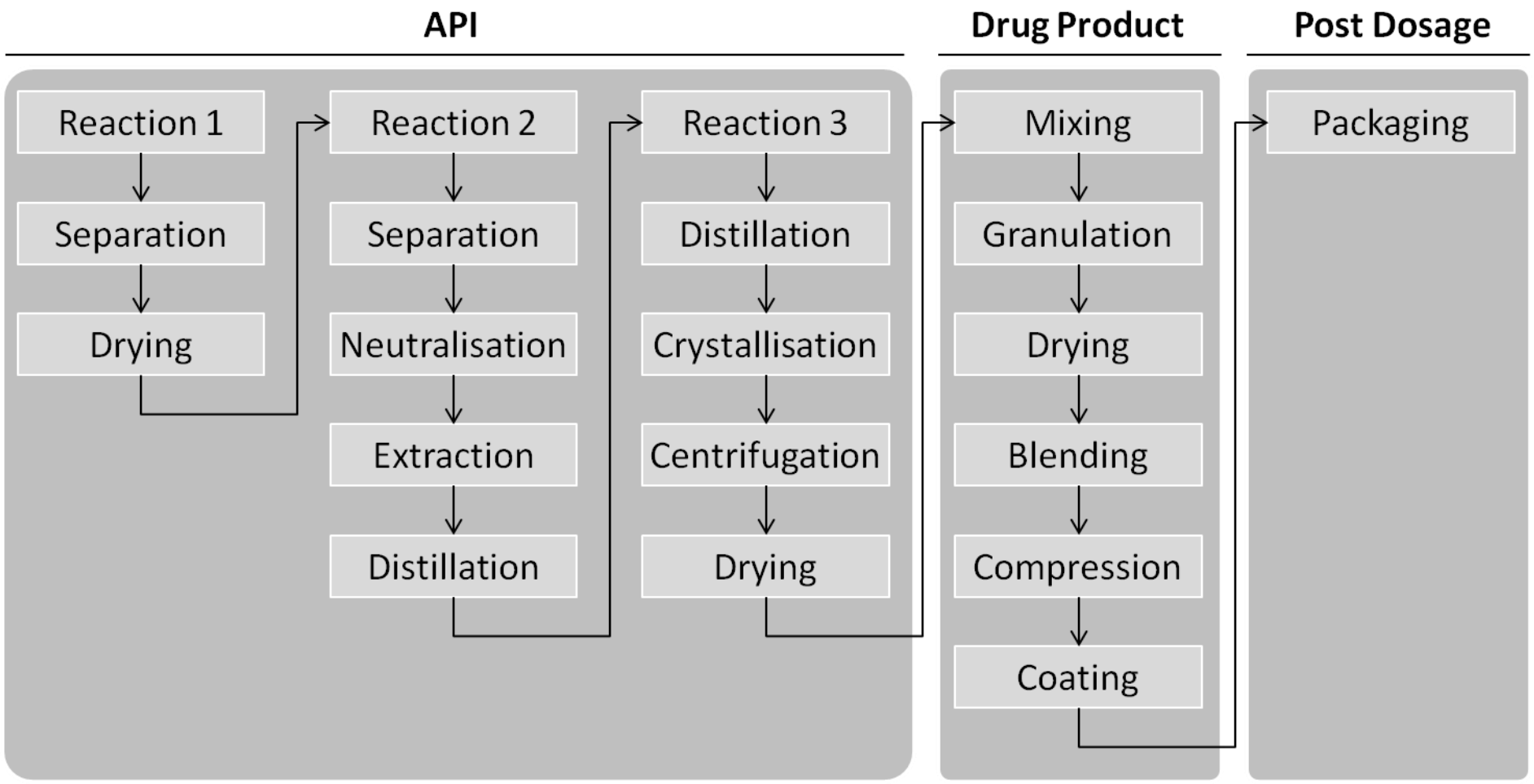
What are likely process archetypes (and their likely supply chain implications) ?



Typologies of change identified as suitable basis for exploration

- What do continuous manufacturing technologies *enable* pharma companies to do? – and what might be the implications?

Typology	Level	Category	Description
1A	Single Plant[1]	Process rationalisation	Simplification of individual process steps
1B			Stringing process steps together
2A	Manufacturing Network[2]	Plant configuration	Fewer plants (joining processes in same location)
2B			Many smaller plants (more dispersed)

[1] Manufacturing facility including all processes in that location
[2] Network comprised of a number of manufacturing facilities, e.g. primary and secondary processing

Value-chain implications [WIP]

Typ.	Description	R&D	Supply	Production	Distribution	In Use & Service
1A	Simplification of individual process steps	•Flexibility and expertise concerning production •Organisational barriers	•Lean supply chains •Supply order automation •Material specifications	•Quality •Manpower •Waste •Scalability •PLC (IP) •On-demand production	•Lead time •Meeting pull from market / end user •Inventories / Warehousing	
1B	Stringing process steps together					
2A	Fewer plants (joining processes in same location)	•Up-front cost and effort for risk mitigation •R&D lead time	•Impact on process side (1A/1B) •Level of integration	•Footprint and CapEx •Economies of scale •Waiting time •Maintaining reliability	•Complexity and cost •Distance	•Lead time to patient
2B	Many smaller plants (more dispersed)		•Fluctuation & complexity •Economies of scale	•Manpower •Quality in various markets	•Distribution frequency and volume •Distance	•Local market access •Pricing & reimbursement •Cross-border trade

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Process Archetypes

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	1	2	3	4	5	Comments
PROCESS ARCHETYPES						
Volume (process capacity)	ml/min		lt/min		t/day	Small, medium and high volume with single and multi product - continuous manufacturing is favourable.
Variety (multi or single)	single	2 or 3	4 to 7	8 to 15	more than 15	Multipurpose plant with small volume - batch plant is favotable.
Use	Discovery	Development	Semi-tech	Pilot	Production	
Stage	API		Drug products		Post dosage	More challenges in API manufacturing compare to drug product formulation.
GSK Pilot Plant						
Volume (process capacity)	ml/min		lt/min		t/day	
Variety (multi or single)	single	2 or 3	4 to 7	8 to 15	more than 15	
Use	Discovery	Development	Semi-tech	Pilot	Production	
Stage	API		Drug products		Post dosage	
Genzyme Plant						
Volume (process capacity)	ml/min		lt/min		t/day	
Variety (multi or single)	single	2 or 3	4 to 7	8 to 15	more than 15	
Use	Discovery	Development	Semi-tech	Pilot	Production	
Stage	API		Drug products		Post dosage	
Lupin Limited (Cefpodoxime)						
Volume (process capacity)	ml/min		lt/min		t/day	Capacity - 3 to 4 t/day - All Products
Variety (multi or single)	single	2 or 3	4 to 7	8 to 15	more than 15	Multi product plant (3 products)
Use	Discovery	Development	Semi-tech	Pilot	Production	
Stage	API		Drug products		Post dosage	All products are API.

Product Archetype

PRODUCT ARCHETYPES	1	2	3	4	5	Comments
Purity	93-95%		96-97%		98-100%	Higher quality compare to batch process.
Consistency	low		medium		high	Higher consistency in quality will be achieved in continuous processes due to steady state process
API Type	Chemical				Bio	In API manufacturing continuous Crystallisation,isolation and drying is a major challenge
Processing routes (chemical, physical)	Chemical				Physical	Reactions which takes very long time and highly exothermic can be succesfully performed in microreactor in significant time.
Cost of KI (key ingredient)	100/kg	500/kg	1000/kg	2000/kg	3000/kg	As Price of KI increases percentage of overall profit decreases due to start up and shut down losses.
Final form of product	tablets	capsules	creams	liquids	steriles	
Volume (Quantity)	low		medium		high	
Manufacturing Strategy	make-to-stock				make-to-order	
Patent protection						

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Continuous Manufacturing transformations.....many industrial examples to draw from

- Unit Operation level: Fast Moving Consumer Goods
  - Massive reduction in WIP inventory by moving from full batch to Common-Base manufacturing and post-dosing technologies
  - Supply chain impact on inventory, flexibility and product variety

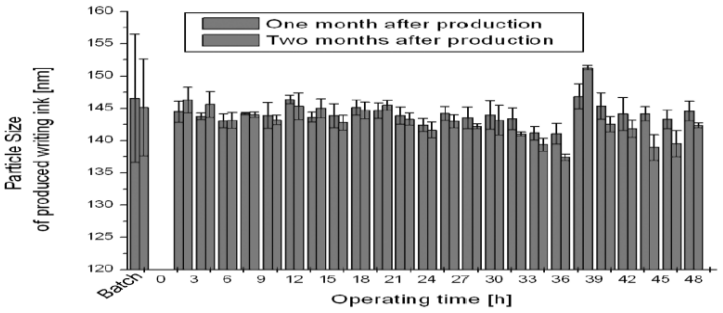
- Process Change: Introduction of Print-head technology in Ceramic tile decoration
  - Continuous ink-flow print heads driving industry resurgence of fast declining European ceramics industry; a new application
  - Transformation from long campaigns to 'on-demand' production

- Production System level; Pulse-line Production/Service Systems in Auto/Aero
  - Introducing a 'continuous' rhythm in traditional job-shop manufacturing
  - Data complicated in Aero by changes on who does what but dramatic changes in productivity/control

Cross-sector Case Studies

CM of Ink products

- Total reaction time was reduced by 95%
- Sample produced in continuous run shows very high and constant product quality compared to batch.



- Waste water production found to be reduced by factor of 1000 through micro-continuous manufacturing.

Source: Grundemann et al., 2009
Technische University and Pelikan PBS & Co.

CM of ADL (Antiseptic Disinfect Liquid)

- By application of lean manufacturing techniques: following benefits are observed:
  - NVA (Non-Value Added) time has been decreased from 1,170 to 420 minutes.
  - TCT (Total Cycle Time) has been reduced from 28 to 10 minutes.
  - Workforce has been reduced from 6 to 3 (50%).
  - Reduction in WIP inventory from 6,092 to 864 units.
  - Reduction in floor space (38 %) has been achieved.

Source: Chowdary and George, 2012
University of West Indies and Genethics Pharmaceutical Limited

Cross-sector Case Studies

CM of oral care products (A leading multi-national co.)

- Reduction in materials flow by 65%.
- Increase in labour productivity by 33.5%.
- Increase in throughput by 25% (through higher Capacity utilization)
- Reduction in lead times from 3-4 days to 24h.
- Reduction in WIP.
- Achieving `zero defects'.

Source: Mukhopadhyay and Nandi, 2000

(NITIE, Mumbai and leading multi-national toothbrush mfg company)

Application of JIT principles in CM supply chain system

- DOW Company and it's channel partners were able to improve demand forecast accuracy by 25% and decrease the lead time by 50%.

Source: Cook and Rogowski, 1996
(Central Michigan University and Dow chemical company)

Key conclusions

Pharma implications

Industry views

"It's kind of like what happened with the first iPad. When it became successful, everybody else started making tablet computers…I think the benefits are so huge, companies are almost going to have to try to do it." ***Tom Van Laar, Head of Global Technical Operations for Novartis.***

Academic

Many 'specific' examples that encourage further investigations as to when it makes sense and when it does not!

Scope is complicated as benefits at multiple units of analysis and major benefit is probably at the systems level challenging perhaps how things are done altogether in both the innovation chain and supply chain

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1. Product-Process Archetype development

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Use	Discovery	Development	Semi-tech	Pilot	Production
Stage	API		Drug products		Post dosage
Primary	Reaction	Extraction	Crystallisation	Filtration	Drying
Secondary	Milling	Blending	Granulation	Compression	Coating

	1	2	3	4	5
PRODUCT ARCHETYPES					
Purity	93-95%		96-97%		98-100%
Consistency	low		medium		high
API Type	Chemical				Bio
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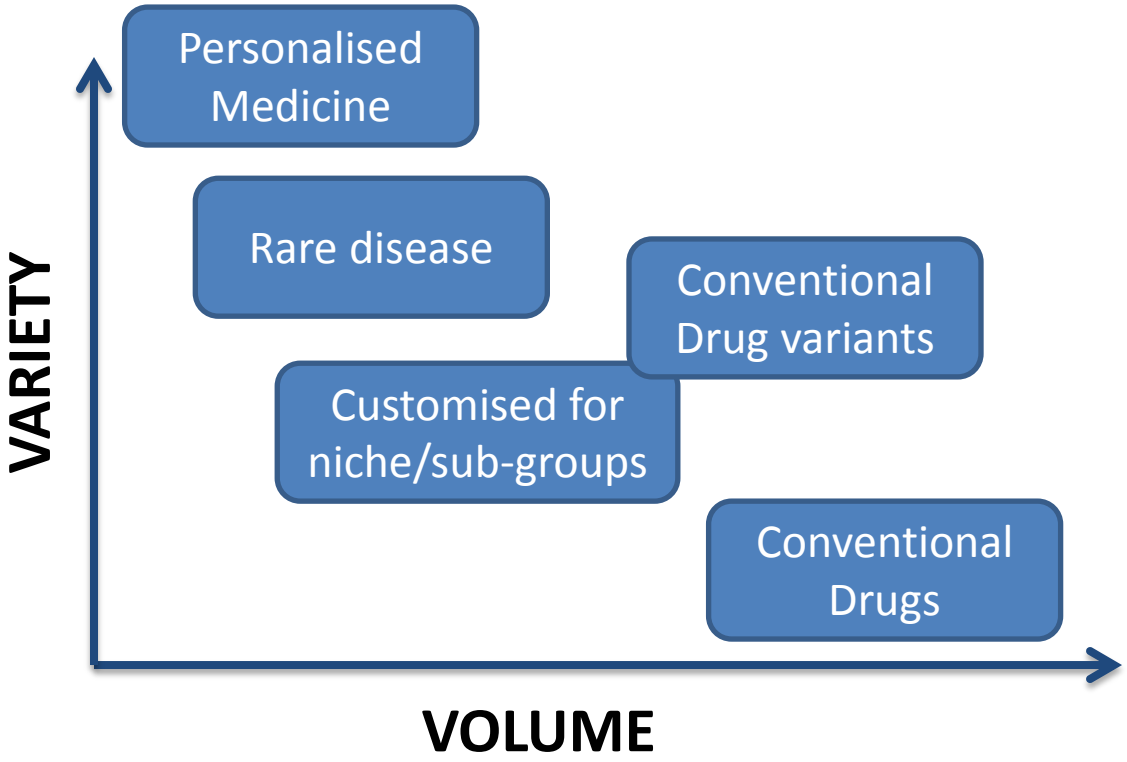
Cost of KI (key ingredient)	100/kg	500/kg	1000/kg	2000/kg	3000/kg
Final form of product	tablets	capsules	creams	liquids	steriles
Volume (Quantity)	low		medium		high
Manufacturing Strategy	make-to-stock				make-to-order

2. Key Network Design variables: e.g. Variety-Volume Matrix

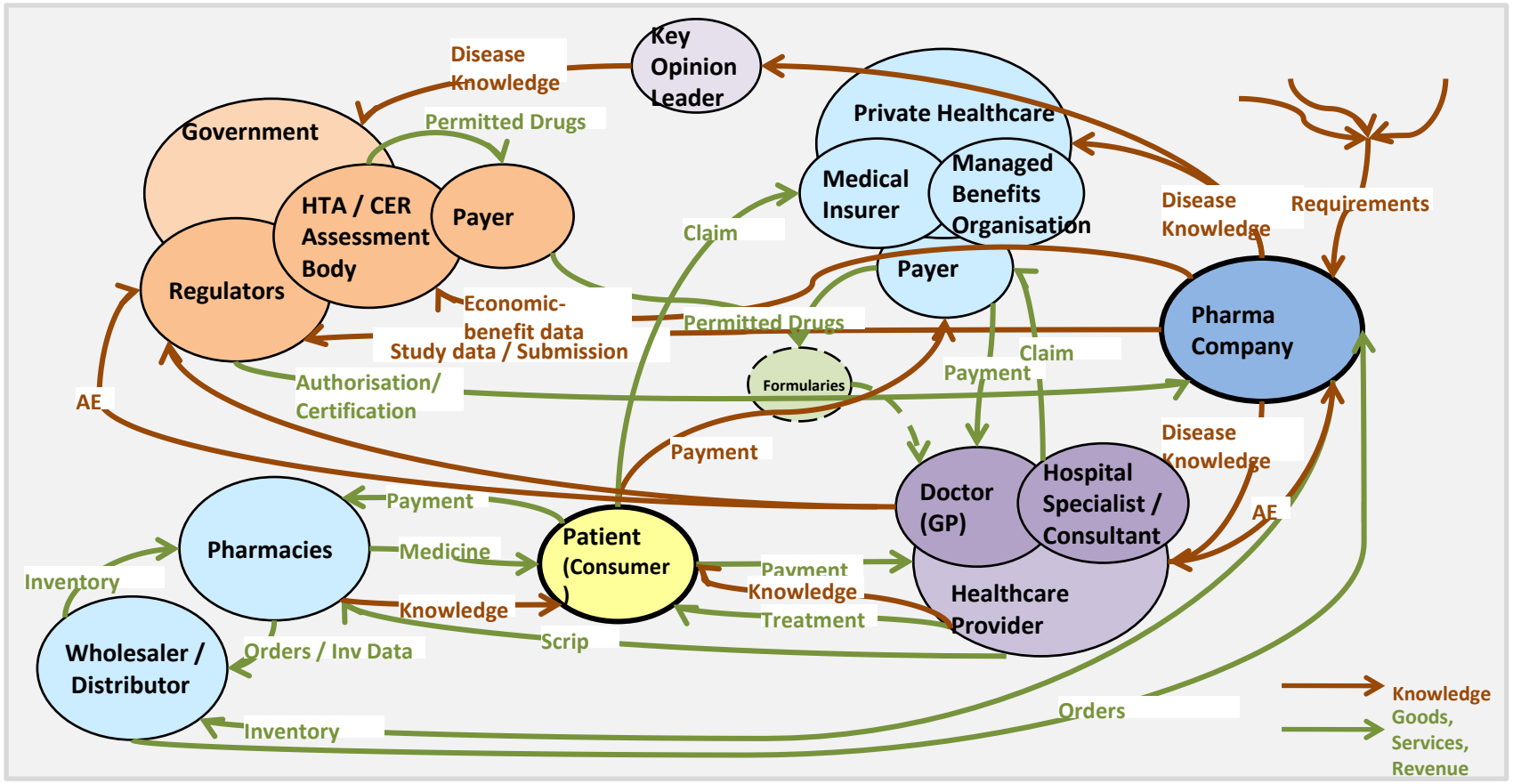


- Focus on 2-4 extremes
- Cover the landscape
- Select some representative products

3. Mapping the Current State Value Chain and Supply Network

- Value Chain Analysis
- Supply network structure map
- Production: Unit operation map
- Capture performance data and compare with other industries

Pharma Value Chain Actors, and Information, Material & Revenue Flows – New Value Propositions?

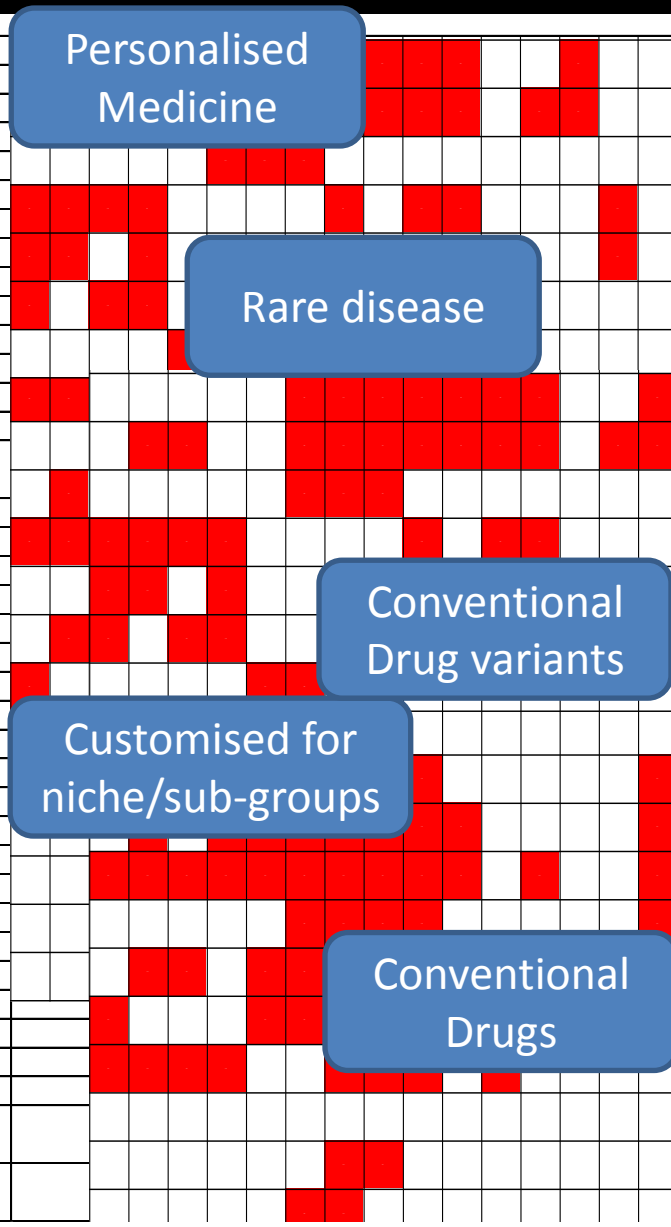


Expected Outcomes

Identify attractive product-process supply network configurations

Identify attractive product-process technology challenges

Outcomes
Greater responsiveness (Speed and Agility)
Minimising Working Capital
Ability to ramp up and down production rates
Shorter Change over
More Flexible factory
Patent Extention
Lower Processing cost (energy consumption)
Fiscal benefits
Lower Fixed costs
Improved Cash Flow
Higher Purity
Higher Consistency
Better Yield
Less Environmental Impact (solvent removal/ reduction)
Less WIP Inventory
Reduces the Time to Market
Higher Transferability/ portable
Reduce Footprint
Lower CAPEX
Lower operating cost
Lower Variable Cost
Less labour required
Increased asset utilisation
Reduced material handling and transport
Improved flow of material
Improved process control
Less product rejects
Lower cost of quality
Better process reliability
Reduced cycle time
Accelerated new product development rate
Minimising total reaction time
Better temperature control
Greater control over product quality
More predictable scale-up
Sustainability (less waste, greener chemistry, lower CO2 footprint)
Enabling the manufacture of more complex products and processes with safety issues



4. Future State Scenarios

Will be developed based on ….

- Continuous Manufacturing Impact Matrix
  - opportunity identification based on scenario development
- Innovative business models and Supply Chain models
  - feasibility
- Alternative Product-Process technology roadmaps
  - feasibility
- Learning from other industries
  - best practice and knowledge transfer