Continuous manufacturing and product-process archetypes: implications for supply network design in Pharma

Tomás Seosamh Harrington (tsh32@cam.ac.uk), Leila Alinaghian and Jagjit Singh Srai
Institute for Manufacturing,
University of Cambridge, UK

Abstract
Continuous Manufacturing has enabled the potential for significant step changes within the Pharmaceutical industry. However, adoption rates remain in the range of 5%. This research examines the challenges and implications of the shift from 'batch' to 'continuous' processing in terms of e.g. product variety and supply network design.

Keywords: Continuous Manufacturing, Supply Networks, Pharmaceutical Industry

Introduction
On-going new technology development in the area of 'Continuous Manufacturing' (CM) has enabled potential for significant step changes within the Pharmaceutical sector e.g. shifting from traditional 'batch' to 'continuous' processing has implications for (a) product variety, consistency and functionality (b) energy and resource efficiency (c) inventory and customization options and (d) overall industry structure. While other industries, such as oil, gas, petrochemicals, polymers, and food currently operate in CM mode; extensive use of CM is still relatively new to the pharmaceutical industry where the current adoption rate of continuous processing is approximately 5 %. Despite the fact that 50% of reactions in pharma could benefit from a continuous process based on e.g. micro-reactor technology, the industry still dominated by batch processes and it is estimated that rejected batches, rework and investigations can equate to as much as 25% of pharmaceutical company revenues (Alinaghian et al. 2012, Arnum and Whitworth, 2011).

The key difference between batch and continuous processing is that in batch mode, the process is in a dynamic state from the beginning of the reaction until the end. Depending on the process the end point is predetermined so that when that point is reached, the process is stopped, and the unit operation is completed. A continuous process, however, must undergo an initial start-up phase before reaching a 'steady state' (Rios 2007). Batch process manufacturing is segmented into many individual steps that are often performed at separate facilities, thereby, requiring frequent interruptions in production activities. In this manufacturing model, specific quantities of a drug are produced to fill an order and quality is assessed through sampling, using analytical test and measurement. If the quality standards are not met, the entire batch is rejected and sent back for reprocessing.

On the other hand, in a continuous manufacturing model, raw materials are put

into the automated system that is capable of carrying out complex chemical tests according to the predetermined quality parameters. These quality checks occur throughout the manufacturing process and most importantly without interruption. Rejected products may be handled through recycling loops, enabling the reuse of some or all component parts (Schaber et al. 2011).

Batch process manufacturing, the current industry standard, offers several benefits and suffers several drawbacks. On the positive side, batch processing assures quality as a batch may be controlled, and thus, accepted or rejected (Leuenberger, 2001). Moreover, when compared with continuous processing, batch process manufacturing provides higher flexibility in producing multiple products in a single plant through the sharing of process equipment (Behr, 2004; Gorsek and Galvic, 1997). On the negative side, batch production presents many disadvantages including long throughput times from start to finish (Calabrese and Pissavini, 2011), large raw material and intermediate inventories (Gorsek and Galvic, 1997; Kim and Lee, 1993), extensive validation and scale-up activities with products often of lower and/or inconsistent quality (batch-to-batch variation). By-products lead to undesirable side effects; products have been rejected at the clinical trials stage because of concerns over purity.

Continuous manufacturing is gaining ever-increasing attention within the pharmaceutical industry because of the expanding profitability gap experienced by most pharmaceutical companies (Gerogiorgis and Barton, 2009). Today, it is becoming more difficult for pharmaceutical companies to meet profit expectation, due to increasing research and development (R&D) operating costs and competition from generic manufactures. A review of the fine and commodity chemical industries has demonstrated that continuous manufacturing could offer both operating expenditure (OpEx) and capital expenditure (CapEx) savings for the pharmaceutical industry. Furthermore, labor for transporting material between batch units, quality assurance/quality control (QA/QC), and in process inventory can all be significantly reduced in continuous manufacturing. According to the Trout research group, the increasing interest in continuous manufacturing can be attributed to a combination of three factors of the beginning of more flexible regulatory approaches, increasing cost pressure and increasing quality and controls specifications of pharmaceuticals (Schaber et al. 2011).

Hence, the pharmaceutical industry and the regulatory bodies are now actively encouraging the development and implementation of innovative pharmaceutical manufacturing systems e.g. a recent study into the future of High Value Manufacturing (HVM) in the UK, commissioned by the Technology Strategy Board, was published in February 2012 (TSB 2012). One of the HVM study recommendations was that particular manufacturing sectors should be explored in greater depth and this report presents the findings from studies of the pharmaceutical and biopharmaceutical sectors. Workshops were held for each sector attended by representatives from industry, government bodies and the research community. The aims were to:

- identify the needs and capability gaps to achieving innovation in manufacturing in each sector through to 2025
- determine priority actions to meet these needs and build capability to enable innovation in manufacturing in each sector over this time scale
- better define the HVM landscape with additional data from the Life Sciences sector.

Strategic road mapping techniques were used to help participants explore the pharma sector's key trends and drivers; the novel products, processes and services which could be developed in the future; any technologies and capabilities required to support these opportunities; and the enabling factors that would help the sector respond successfully. The list of potential new products, processes and services was prioritized to identify key areas where it was thought the most valuable opportunities for innovation exist. A 'case for action' was developed to justify further work in each area, outlining the potential benefits, critical gaps and steps required (TSB 2012).

Research Approach

This specific research paper looks to initially explore and address (a) the operations and supply chain management challenges associated with CM and (b) relevant findings from the TSB report, through the following approaches:

- Exploration of the barriers and enablers for CM adoption within pharma
- Developing an emerging Value Chain Road mapping approach: exploring product-process archetypes and the implications new product and technology roadmaps, within CM and Pharma, may have on the future value chain
- Development of an emerging analysis framework; to enable end-to-end supply chain assessment and support overall business impact analysis in making a shift to CM where applicable (currently at conceptual level).

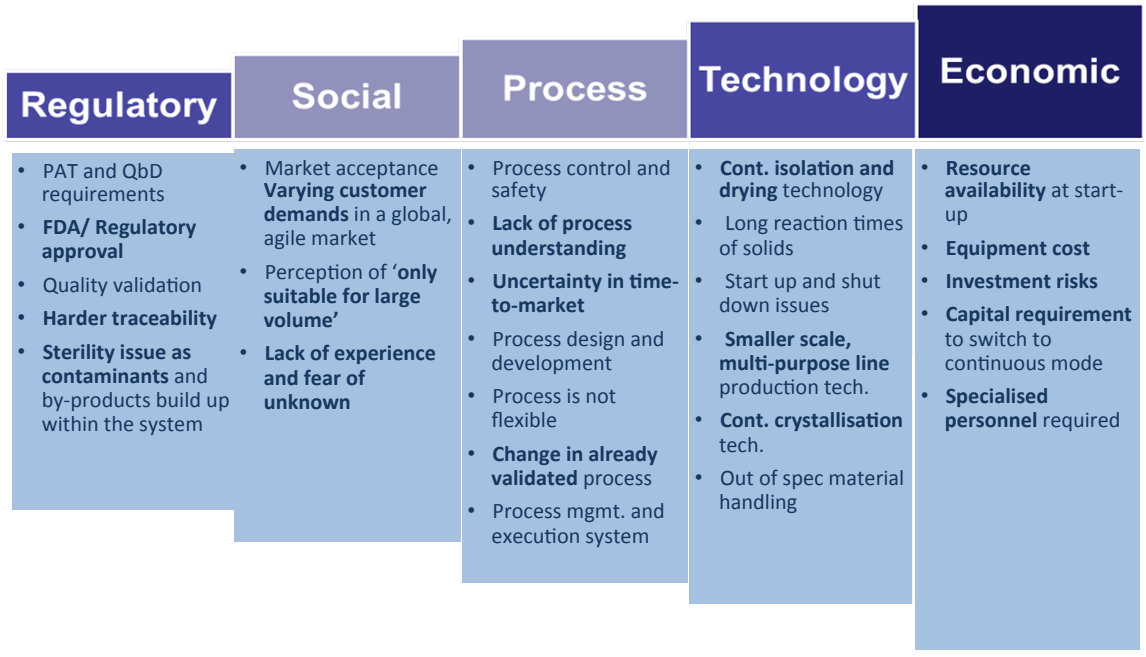

Figure 1. Barriers to CM adoption in Pharma (adapted from Alinaghian et al. 2012)

CM: Barriers and Enablers

Previous work has summarized the existing barriers and enablers to the adoption of the continuous manufacturing model within the Pharma industry (Alinaghian et al. 2012), which benefited from collective discussions and one-to-one interviews with the organizations currently going through the transition from batch to CM and encountering such challenges. The key findings are summarized in figures 1 and 2.

This exploratory qualitative research included two main phases of systematic literature review and exploratory case studies comprising of semi-structured interviews, theory building and concept development workshops involving industry practitioners, technologists and process engineers. The study revealed that despite recent efforts to quantify economic benefits of continuous manufacturing, the overall business impact of continuous manufacturing lacks an end-to-end supply chain assessment (Alinaghian et al. 2012).

Cost	• **Capital investment**
	  • Continuous manufacturing allows the use of smaller production facilities with lower capital cost, with a reduced overall plant footprint.
	• **Operating Costs**
	  • **Less labour** required to operate the processes
	  • Continuous process is capable of **increasing asset utilisation**
	  • Lower **catalyst and solvent use**
	  • Minimize **total reaction time** through better temperature control
	  • Effective running and scale-up of exothermic reactions without special equipment/ additional precautions
	• **Inventory**
	  • Continuous manufacturing has potential for **reducing inventory cost** (**Less WIP inventory, Reduced material handling and transport , Continuous flow of material**)

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 reject**
	  • The continuous manufacturing enables monitoring of drug quality on a continuous basis rather than through post-production, batch-based testing.

Delivery	• Continuous process enhances **process reliability**

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.

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)

Sustainability	• Continuous manufacturing minimizes waste, energy consumption and raw material use. • Solvent can be recycling more effectively in continuous process compared to batch process.

Figure 2. Enablers of CM (adapted from Alinaghian et al. 2012)

Some high level findings from this literature review show that evidence exists for:

- CM delivering financial benefits (mainly for single-purpose plant).
- A need to better quantify the economic benefits of CM (given that the overall business impact lacks an end-to-end supply chain assessment)
- While most opportunities lie in supply chain design and configuration, existing studies are largely focused on production and plant level.

Emerging Value Chain road mapping approach

Outputs from previous work (Alinaghian et al. 2012) also suggests that many of the critical issues are not simply about a 'batch to continuous shift' but more about the alternative product-process supply network options and value chain implications of e.g.

- Product variety, consistency and functionality
- Energy and resource efficiency (e.g. capital investment, solvent use, number of process steps)
- Inventory, minimum 'lot' size, customisation options etc.

To this effect, this research is currently exploring the viability of attractive product-process archetypes which may exist at required scale [CM-batch mix, intermediates (e.g. batch unstable), substance dose form), plug-and-play instant/rapid changeover process technologies, viable product-process network configurations which may exist that meet product portfolios].

To support capture of the associated alternative product-process supply network options and value chain implications for such 'attractive product-process archetypes', an emerging value chain road mapping approach has been developed which builds on techniques in mapping supply chain configurations (Srai and Gregory, 2008) across the manufacturing value chain. In these studies, the supply network configuration has been defined as "that particular arrangement or permutation, of the supply network's key elements including, the "network structure" of the various operations within the supply network and their integrating mechanisms, the flow of materials and information between and within key "unit operations" the "role, inter-relationships, and governance" between key network partners, and the "value structure" of the product or service delivered". In summary, the four elements include:

- Supply network structure

  Network tier structure and shape, composition, ownership, levels of vertical and horizontal integration, location, co-ordination, manufacturing processes, optimum sequence, complexity, flexibility, etc.

- Material and Information Flow

  Both intra- and inter-key unit operations; value and non- value adding activities, process steps, optimum sequence, levels of flexibility, network dynamics (e.g. replenishment modes), infrastructure, and enabling IT systems

• Relationships and Governance

The role, inter-relationships, and governance between key network partners; the nature of these interactions or transactions, number, complexity, partner roles, governance and trust

• Product/Service value-structure

Product composition and structure (including components, sub-assembly, platforms, modularity), product replenishment mode (e.g. is the product make-to-stock, make-to-order, configure-to-order), SKUs, products as spares, and through-life support and services

Exemplars from other sectors (non-Pharma) who have reconfigured manufacturing operations to support more dynamic supply models are currently being investigated using this approach (Harrington et al. 2013, Srai and Harrington 2013). In addition, this research approach may also be used to describe the linkage between technology platforms and final product innovations (limited attention is currently paid to the industrial system that 'connects' technology developments to final products e.g. changing industrial system with a shift from batch to CM).

Figure 3 summarizes the industrial value chain road mapping approach, and how it may be reconfigured to provide a linkage between technologies and technology options to product iterations. It runs orthogonal to standard technology or product roadmaps and may identify the industrial challenges in reconfiguring the industrial chain to new and emerging industries e.g. (a) Mapping the Industrial Value Chain i.e. Pharma sector or for a specific organization/network (b) Current state Supply Network Configuration Analysis and (c) Re-Configuration Process (i.e. supporting 'evolving' Future state Value Chain, 'V1' to 'V2' and 'T1 Batch' to 'T2 CM' implications).

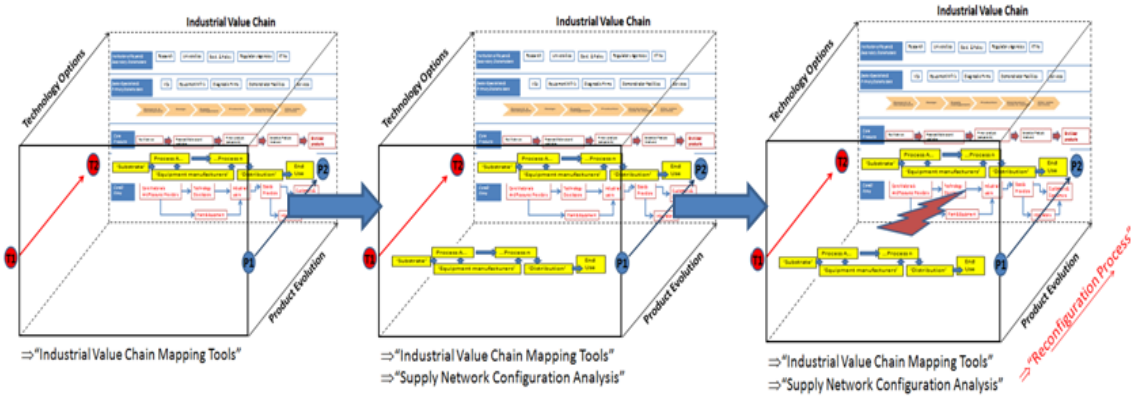

Figure 3. An Emerging Value Chain road mapping approach: Conceptual Framework linking technology evolution, network configuration and product evolution

Development of an emerging analysis framework

Figure 4 presents a conceptualization of the Volume-Variety matrix as a means of representing potential areas (e.g. low volume for niche products, high volumes) where the benefits of CM may out-weight those of batch processing e.g. in terms of cost, providing beyond-OTIF profitably, reliably and sustainably.

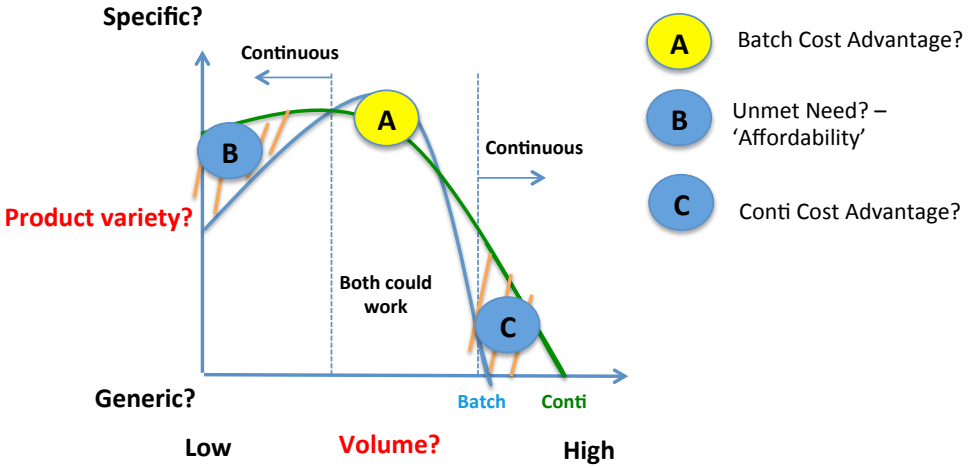

Figure 4. Conceptualization of a Volume-Variety matrix: Batch v. CM

In the development of an analysis framework (currently at the conceptual stage), it is proposed to identify potential 'sub-systems' in order to examine different and competing opportunities to influence/add value, e.g.

- Therapy or Disease v Patient population?
- Clinical trials: £ v. t
- Primary/Secondary Processing: Quality/Yield v. Inventory?
- Packaging: Volume v. Variety?
- E2E: Inventory vs. Service?

- Examine unit level critical features, critical operational metrics that may be targeted
- Examine the linkages between the identified sub-systems
- Explore the opportunities for disruptive supply chain models

Conclusions

On-going new technology development in the area of 'Continuous Manufacturing' (CM) has enabled potential for significant step changes within the Pharmaceutical sector e.g. shifting from traditional 'batch' to 'continuous' processing has implications for (a) product variety, consistency and functionality (b) energy and resource efficiency (c) inventory and customization options and (d) overall industry structure. This specific research paper looks to explore and address the operations and supply chain management challenges associated with CM through the development of the following approaches:

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Exemplars from other sectors (non-Pharma) who have reconfigured manufacturing operations to support more dynamic supply models are currently being investigated using emerging Value Chain Road mapping approach. These studies will look to feed into development of an emerging analysis framework for Pharma (currently at the conceptual level); to enable end-to-end supply chain assessment and support overall impact analysis in making the business case for CM.

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