Exploring Implications of Continuous Manufacturing within the Pharmaceutical Sector through Industrial Landscape Mapping and Cross-Sector Analysis

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Abstract

On-going new technology development in Continuous Manufacturing (CM) has enabled potential for significant step changes within the Pharmaceutical sector e.g. shifting from '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. However, current adoption rates of CM remain in the range of 5%. This research looks to explore and address the operations and supply chain management challenges associated with CM, specifically through learning from other industrial systems.

Research question(s): Emerging research questions include (a) what are the architectural differences between current (batch) and future (continuous) manufacturing operations and (b) associated implications for up-stream and down-stream supply chain configurations, structures, processes and systems.

Methods: An Industrial landscape mapping methodology was developed (integrating value chain analysis with supply network configuration mapping) that is applicable to a broader industrial systems context. The pharmaceutical sector was mapped to provide the basis for (a) exploring alternative product-process supply network options and value chain implications of a shift to CM and (b) cross-sector analysis involving six previous case studies (i.e. six industrial systems that have exhibited different types of disruptive innovation).

Key findings: This research provides a basis for understanding (a) current and future supply network configurations (b) critical interconnections between industry actors and (c) the overall industry structure. Preliminary cross-case analysis suggests several generic aspects to supply networks, including the blurring of industry boundaries, and the critical requirement to manage uncertainty in selective elements of the value chain.

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).

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 manufacturers. 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 (see figure 1) were used to help participants explore the pharmaceutical 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).

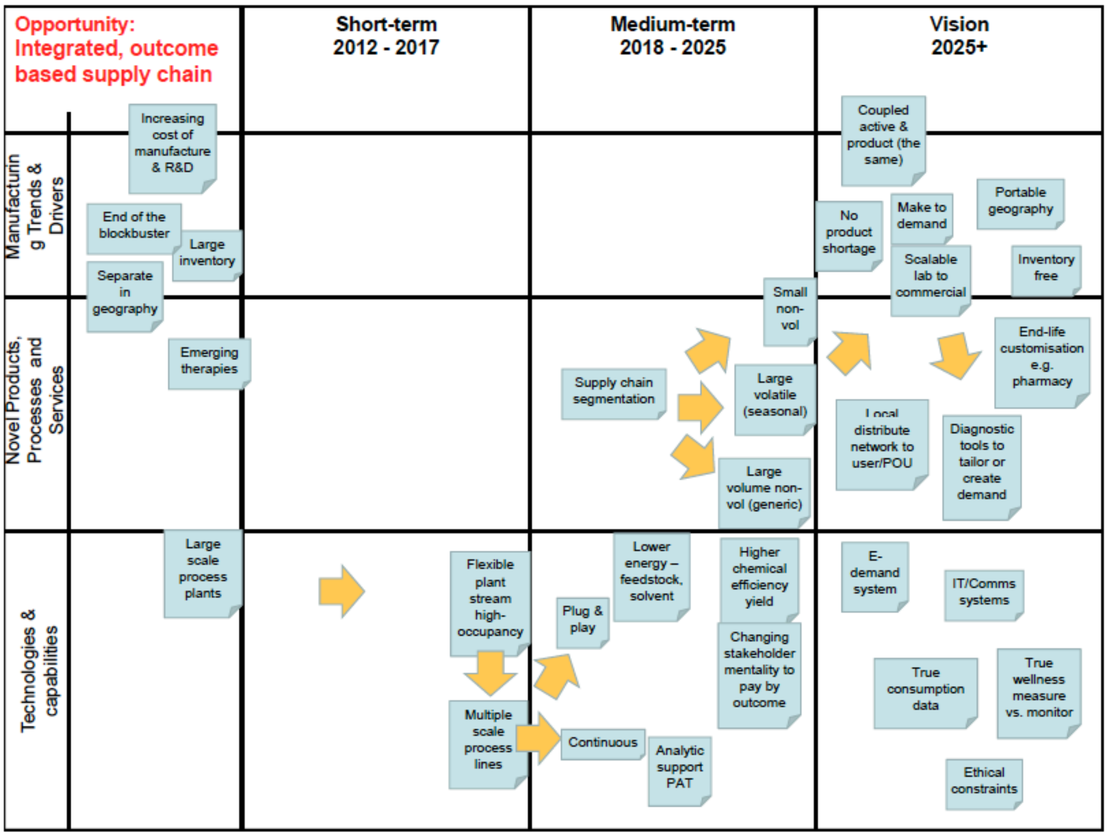

Figure 1. Opportunities for the Pharmaceutical sector in terms of integrated, outcome-based based supply chains - one of seven priority topics (TSB, 2012)

Research Approach

This specific research paper looks to initially explore research questions include (a) what are the architectural differences between current (batch) and future (continuous) manufacturing operations and (b) associated implications for up-stream and down-stream supply chain configurations, structures, processes and systems through e.g.

- Exploration of the barriers and enablers for CM adoption within the pharmaceutical industry (Harrington *et al*, 2013)

- An Industrial landscape mapping methodology previously developed (Srai et al, 2013) integrating value chain analysis with supply network configuration mapping) was used to map the pharmaceutical sector to provide the basis for exploring alternative product-process supply network options and value chain implications of a shift to CM.

- Cross-sector analysis involving six previous case studies (i.e. six industrial systems that have exhibited different types of disruptive innovation) e.g.
    - Defence Aerospace (Service)
    - Maritime
    - Built-Environment
    - Industrial Biotechnology (IB)
    - Photovoltaic (PV)
    - Last Mile (LM) Logistics

Industrial Landscape Mapping

The industrial system mapping approach builds on techniques developed in mapping SN configurations (Srai and Gregory, 2008), across the manufacturing value chain (Srai and Shi, 2008). 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". Within this definition the four elements, which constitute the foundation of the configuration mapping approach, are:

- 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

Extension to the industrial system level was a key requirement for effective industrial system and cross-case analysis. Hence, these mapping approaches were developed further in order to capture industry system level actors (institutional, industrial support as well as product supply chain actors) and explore linkages between them (Srai et al, 2013) e.g.

- **Identification of sector institutional players and secondary stakeholders** e.g. research, industry development, specialist firms etc
- **Development of a Value Chain Process Map** e.g. production processes and unit operations etc
- **Identification of the industry actors** e.g. supply chain actors, organisational types, linkages between organisations, material, potential information and value flows etc
- **Technology process and product types** e.g. Identification of substrates, process technologies etc

Cross-sector analysis

The integration of the methods outlined above, resulted in an industrial system-level mapping framework, which served as a consistent method of analysis to enable cross-sector comparison.
The industrial systems mapping framework was then used to inform e.g.

- Capture of industry structure at a broad industrial systems level
- Capture of alternative supply network configurations within the industrial system

Industrial system context and structure mapping, involved focal firm case-study investigations with actors from each of the main product categories, with focal-firm case-selection based upon their central role in the value chain. Respondents from focal firms informed the identification of various actors (Institutional, Industrial and SN) and to generate an understanding of key enablers of high value and emergence of each industrial system studied.

Tables 1-5 summarise the key points for five of the industrial systems e.g. aerospace service, maritime, built environment, industrial biotechnology and last mile logistics.

Table 1. Observations from Industrial Landscape Mapping - Aerospace (Service)

Trends & Drivers	Emergence
• Industrial Integration and leadership to deliver outcome-based contract management • Unique customized services • Contracting and sub-contracting mechanisms and protocols (formal/informal ConOps) e.g. engines, manpower, systems support, spare parts • Integrating Design and Build know how with Maintenance and Repairs • The ability to configure and reconfigure resources to provide capability to achieve desired effects • At an operational level, to achieve effective network integration across partners • Home market critical for historical sector evolution • Adaptability (Network design and operation) vital to meet adjacent and new markets (products and regions)	• New Outcome based Service Models involving multiple partners • Emerging markets requiring more dispersed network capability • Through-life contracting models that are increasingly industrially dominated; industry penetrating into all elements of service delivery • Failure mode analysis driven by through-life costs as well as functional integrity • Unmanned aircraft demanding real-time information systems, remote trace and control • Blurring of sector boundaries: defence, Intelligence and information driven security systems (defensive and offensive)

Table 2. Observations from Industrial Landscape Mapping - Maritime Sector

Trends & Drivers	Emergence
• Design and Equipment Manufacturers enjoy high margin; assembly/shipyards do not • Highly customized niche products • High barrier to entry • In-house production provides capability to execute on novel designs • Direct customer interaction enabled through 'own production'; end-client conversation currently with ship-yards • No desire to compete in high volume commodity markets • Home market critical for cluster scale and consequent capability development • Adaptability (Network design and operation) vital to meet adjacent and new markets (products and regions)	• Designers talking direct to end clients • Industry structure moving from many national players to International networks requiring firms with global scale • Blurring of sector boundaries: maritime, off-shore wind, energy • Radical reconfiguration paths to meet new market sectors, new regions

Table 3. Observations from Industrial Landscape Mapping - Built Environment Sector

Trends & Drivers	Emergence
• Rapid commercialization of new energy efficient technologies • Retro-fit installation capability • Urban environment requires tailored delivery models e.g. consolidation centres, local government support, community engagement • New concepts of value including carbon credits etc.	• Regulation driving new business models • Regulatory uncertainty and ability to deliver, a barrier to industry growth • New ecosystem lacks natural leaders and champions • Demand requires step change in industry scale but no obvious migration paths • Fragmented network structure frustrates rapid evolution • Blurring of boundaries: construction, environment, energy; interface between government, industry and academia.

Table 4. Observations from Industrial Landscape Mapping - Industrial Biotechnology

Trends & Drivers	Emergence
• Platform technology serves multiple end-user markets • Upstream R&D, process technology and substrate developers introducing innovation • Downstream biochemical and industrial users of global scale – opportunities and barriers (sunk costs) • Feedstock growth and degradation determines upstream location, with complex intermediate biochemical processing and storing options • Relatively benign operating conditions, low CAPEX, lower minimum economies of scale, higher volume flexibility • Higher R&D costs and more complex process control • Close partnership between universities, demonstrator facilities, VCs and new players	• Great uncertainty on adoption rates of new technology • Upstream players are small, recently formed and financially constrained with high attrition rates • Lack of connectedness and visibility between upstream emerging firms and downstream established actors; pairings between SMEs and MNCs emerging • Regulation can drive/hinder development • End-user market proliferation likely

Table 5. Observations from Industrial Landscape Mapping - Last Mile Logistics

Trends & Drivers	**Emergence**
• Value generated by waste reduction and demand creation through new routes to market (more flexible, dependable, resource efficient) • Providing consumer choice; options on delivery mechanism, time, location and format • Mass and late customization enabled through customer-friendly information exchanges e.g. Apps, portals etc. • E-commerce and IT enabled elasticity of demand • Eliminating waste through consolidation (minimising missed deliveries, JIS, efficient forward/reverse logistics) • Consolidation centre enables value to be added at the local level (engaging new actors) whilst providing simplicity for remote suppliers and potential multi-modal connections.	• New 'route to customer' models emerging o B2C e.g. Packages o B2B e.g. Construction, Retail logistics • Interface between regulators, local government, industry and end-users, and academia • Network Integration between governance bodies, industrial actors and end-users • Real-time information networks are key enablers • Blurring of industry boundaries: multi-modal solutions, IT and transport, product and service, retail/industry and logistics.

In the context of this research, outputs from previous work (Alinaghian et al. 2012) 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.

Table 6 presents the key trends, drivers and emerging factors for the pharmaceutical sector. Based on initial interviews with respondents, the following key questions were also identified e.g.

- Pharma supply chain genuinely customer/consumer/patient driven? Intent? Know-how?
- Are business needs compelling for new supply chain models (vision, tangible)?
- What products, diseases areas, therapy areas, patient populations should be targeted?
- Industrial and technical feedback often contradicting; clarity on problem?
- Consider radical change – incorporate potential supply chain disruptive influences
- Realistic timeframes, investments/resources, delivery models, risks

Table 6. Preliminary Observations from Industrial Landscape Mapping – Pharmaceutical Sector

Trends & Drivers	Emergence
• Smaller lot size, Personalization, Convergence with Diagnostics and Stratified Medicine • Cost of development • Complexity of supply chain, Changing Manufacturing locations • Collaboration, partnership and open innovation • Responsive regulation, Quality by design • Complex therapies and formulations • Price and cost pressures	Key novel products, services and processes emerging: • Flexible, Distributed Factories • Integrated Design and Manufacture • Diagnostics and Pharma Personalization (Product) • Holistic Integrated Healthcare and Treatment (Patient Service) • Made to Order • Improved Formulation and Platforms • Future Therapies and Unmet Needs Solutions • Drug Delivery • Smart Packaging • Data and Customer Understanding

Discussion/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 industrial landscape mapping (integrating value chain analysis with supply network configuration mapping) that is applicable to a broader industrial systems context. The pharmaceutical sector was mapped to provide the basis for (a) exploring alternative product-process supply network options and value chain implications of a shift to CM and (b) cross-sector analysis involving six previous case studies (i.e. six industrial systems that have exhibited different types of disruptive innovation). Initial observations involving exemplars from non-Pharma sectors (who have reconfigured manufacturing operations to support more dynamic supply) include the following:

- Blurring of industry boundaries in almost all cases with ‘connections’ beyond the traditional ‘sector’ boundary
- Platform technologies that support multiple product categories ‘disconnected’ from end-user markets requiring institutional support
- New SN actors providing ‘network integration’ and supply/demand balancing capabilities to actively support major supply and demand-side uncertainties
- ‘Open’ but selective nature of supply networks with models observed that

demonstrate open-upstream models (biotechnology), open-downstream models (service, last mile), as well as single-product category clusters (maritime) with uncertainty/asset pooling coping methodologies selectively deployed to manage both technology and market uncertainty

- Co-existence of 'product generations' with particular evolution paths for SNs that use distinctly different new assets and diversifying where sunk costs can frustrate or significantly constrain development, and
- Fabless models that draw resources from the wider industrial system

These studies will look to inform 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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