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Evaluating the potential for the continuous processing of pharmaceutical products—a supply network perspective

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ABSTRACT

This paper presents an approach to evaluating the potential supply chain benefits of adopting continuous processing technologies for a diverse set of pharmaceutical products. The approach integrates upstream 'continuous' processing considerations for the production of active ingredients and final product formulation, with the downstream implications for packing and distribution. Currently, these upstream and downstream operations largely operate as decoupled operations with independent coordination and governance mechanisms, and the approach presented in this paper identifies opportunities for more case-specific integrated end-to-end supply chains enabled by continuous flow technologies. Three specific product (and corresponding processing technology) case studies are used to demonstrate the utility of the approach in assessing the supply network and system integration opportunities that emerge from the continuous processing of pharmaceutical products.

1. Introduction

In many industries, supply chains have become 'disaggregated', with activities spread across multiple firms and locations, with individual manufacturing sites increasingly geographically distributed. In pharmaceuticals, this specialisation has been heavily influenced by the separation of unit operations between the discrete steps of active pharmaceutical ingredient (API), primary product formulation, secondary pack processing, and distribution activities. Indeed within each of these manufacturing supply chain stages, the predominance of batch processing models has meant that existing pharmaceutical supply chains operate in a high inventory, slow response environment. Traditionally, manufacturing supply network design has involved integrating these discrete manufacturing activities but has been constrained by the fact key unit operations are run in batch processing modes. However, continuous flow technologies, present new opportunities to the network designer as radically reconfigured supply networks, with genuine flow-through capabilities through to the end-user, become genuine possibilities [1]. In this paper, we develop an approach to assessing the potential for the continuous processing of pharmaceutical products, including specific implications of defined technology developments for three case studies. Thus, potential users of the methodology will include supply chain designers, future product process-engineering developers and those involved in new product business appraisal. The technology focus of each of the case studies is in:

- Case 1—anti-retrovirals (ARVs): firstly, on particle size control and continuous crystallisations to enable better API quality control (especially for high drug loading products). In addition, continuous formulation advances are used to manage the high complexity of product variants, which is a defining characteristic of the product group. The case, therefore, also incorporates considerations on supply models, as case 1-type drug products often tend to be 'made-to-order'. This has lead to longer lead times and an inability to meet emergency orders when minimum batch size requirement (5000 packs) have resulted in 8 month delays between initial orders and initial production for low volume, niche derivatives [2].
- Case 2—anti-malarial artemisinin combination therapies (ACTs): continuous synthesis to reduce solvent use (which is a major issue in the current, low yield batch extraction process), reduce lead times and lower production costs. Here, continuous technology 'interventions', from synthesis right through to packaging and labelling, have been considered in developing and assessing a series of alternative supply models [3].
- Case 3—diabetes drug, such as metformin: addressing the need for significant additional capacity, based on future trends, where volume projections suggest a doubling of demand by 2035. Here, utilising continuous granulation, and moving towards significantly smaller plant footprints with associated capital cost reductions are commercially attractive [1].

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Research on the disaggregation of value chains has tended to consider 'industry sectors' as their unit of analysis where changes to industry structure in for example, computing [4] and financial services [5] has been driven by trends in outsourcing and off-shoring which continue to shape modern manufacturing networks.

Within this industry focus, different patterns of specialisation have been identified as firms seek to integrate new external capabilities and capture location benefits [6–8]. Mudambi and Venzin [9] introduce technology as a key analytical approach to how networks evolve. Within healthcare, and specifically in-vitro diagnostics, the disaggregation of value networks has been analysed from an emerging technology context [10]; the healthcare context providing radically different patient-centric supply chain models and potentially novel business models.

From a theoretical perspective, supply chain analysis and design requires a focal firm perspective of an extended network of firms across a defined product category. However, the optimum configuration of these increasingly complex and fragmented networks is particularly challenging where there are 'multiple tiers' of partner firms, spanning component and intermediate goods supply, presenting a multitude of options on location and partnering models [11,2]. These supply networks comprise of semi-independent sub-systems that have then become part-disconnected with independent governance mechanisms. These sub-systems can, over time frustrate the operation of integrated outcome based supply chains. For these complex multi-tier supply networks, the more holistic approach presented here considers the industrial system design activity as an integrating process that spans the discrete sub-systems that make up the end-to-end supply chain.

2. Network systems analysis and integration of sub-systems

The methodology that is presented here builds on cross-sector observations of complex multi-tier supply networks where sub-systems have evolved as discrete entities [12], and an underlying premise that a whole systems perspective can support a re-examination of end-to-end network design. A re-configuration of the network requires identification of the drivers of, and interactions between, the main sub-systems in these complex, multi-tier supply networks. The attractiveness of applying the sub-systems integration approach will arise in multi-tier supply networks where the production of intermediate goods, as discrete sub-systems, has emerged as a mechanism for the effective organisation of the current industrial system. In consumer electronics for example, global scale contract manufacturers now dominate the sector, supplying key components and/or providing final assembly operations. In Aerospace, major component supply chains have emerged that operate as discrete entities; the UK for example is no. 2 globally in aerospace manufacture without major final assembly. Intermediate goods supply chains are also prevalent in the textile sector where opportunities for supply network development involve re-integration of discrete operations, with some manufactures considering closed loop supply chains to optimise resource re-use. These reconfiguration options are invariably driven by technology changes.

However, in most sectors sub-systems operate as independent units targeting internal efficiencies, functioning as silos of activity, mirroring the functional units seen in large organisations. This internal sub-system focus can work to the detriment of the end-to-end supply network. In highly regulated environments, regulation can inadvertently 'lock-in' this structural development and frustrate end-to-end supply chain optimisation. In Pharmaceuticals, the sub-system of clinical supply often imposes production process and consequent regulatory constraints for the commercial supply chain.

The reconnecting of semi-isolated sub-systems presents opportunities for an end-to-end supply network perspective, connecting upstream and downstream elements. This approach to supply network integration and optimisation can inform the product-process technology agenda. Alternative production processing models would target system outcomes that aim to address sub-system constraints, redefining supply network drivers of network performance. Examples of alternative processing models that might support more 'flow-through' end-to-end operations include continuous-processing and crystallisation in previously batch-process-oriented Pharma, additive manufacturing in engineering component manufacture that replaces traditional subtractive processes (e.g. aero-engine casings are now manufactured at the point of final assembly rather than being produced in three separate locations before being shipped to the assembly site), and late product post-dosing finishing models that enable more near-market supply (e.g. in FMCG post dosing used for variant production with reduced lead times; industrial ceramics continuous inkjet variant production in Europe to satisfy SKU proliferation demands [1]). Each of these alternative supply chain models have required significant technology breakthroughs to enable a broader industrial systems optimisation agenda, enabling radically different product quality and/or flexibility (volume, variety) opportunities, potentially enabling previously elusive markets to be served economically.

In this research, we develop an approach to evaluate the system level business opportunities that arise from the continuous processing of pharmaceutical products. To demonstrate the utility of the approach, the three different cases are considered to evaluate the relative benefits of continuous processing.

3. Methodology development—pharma context

While evidence exists for continuous processing delivering financial benefits (mainly for single-purpose plants), these studies

Table 1
Summary of companies with significant investments in continuous processing.

Company	Summary of Industrial and/or R&D continuous processing applications
Eli Lilly	Significant R&D lab capability (Indianapolis, US); activities involve the design and scale up of fully continuous processes including reaction, workup, and isolation; typical research scale throughputs are 1–10 g/h and pilot scale throughputs are 5–15 kg/day [18]
GSK	R&D pilot facility (Stevenage, UK); investing $50 million to install and validate commercial-scale continuous processing equipment in Singapore [19]
Lonza	Developed micro and mini reactors; Integrated continuous process steps into the manufacture of more than 43 drug products. New construction of a multi-million euro facility for continuous flow and microreaction technology (Visp, Switzerland) [20]
Novartis	Primary and secondary pilot plant in progress (Basel, Switerland) [19]; 10-year research collaboration being driven by the Novartis-MIT Center for Continuous Manufacturing (Boston, MA) [21]
Pfizer	R&D facility (Groton, US); in 2007, further €11M investment in continuous kilo lab facilities (Cork, Ireland) [22]
Sanofi-Genzyme	Patent protected continuous API manufacturing facility in operation (Haverhill, UK) [23]
Sigma–Aldrich	Multi-purpose, medium scale continuous flow plant in operation (Buchs, Switzerland) [24]; estimated that >70 products are manufactured continuously at very low volume