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Reconfiguring global pharmaceutical value networks through targeted technology interventions

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Targeting a series of advanced manufacturing technology (AMT) 'interventions' provides the potential for significant step changes across the pharmaceutical value chain, from early stage 'system discovery' and clinical trials, through to novel service supply models. This research explores future value network configurations which, when aligned with disruptive shifts in technology (process and digital), may enable alternative routes to medicines production and the delivery of additional value to 'end-users', i.e. patients and health care providers. We draw on a categorisation of AMTs that may enable a shift from the traditional 'batch' and centralised manufacturing paradigm of 'make-to-stock', towards more re-distributed 'continuous' manufacturing and 'make-to-order' models. Despite reported benefits in the academic literature (e.g. reduced footprints, improved quality, enhanced flexibility and inventory savings), current adoption rates of continuous technologies in this sector remain low (c. 5%). This paper presents new data sources, in our study of AMT adoption in a global pharmaceutical context – assessing the barriers to implementation, and the pathways to delivering future continuous manufacturing scenarios. Our findings capture the high level of disparity in viewpoints, highlighting the uncertainties and transformational challenges ahead – in terms of opportunity areas, technological readiness and a future vision for the sector, as a whole.

Keywords: continuous manufacturing; technology interventions; pharmaceutical value networks; reconfiguration opportunities; scenario assessment

1. Introduction

The pharmaceutical industry is undergoing a period of great change, reacting to the 'patent cliff', with fewer blockbusters being launched, R&D productivity at record low levels and the requirement for more niche products to serve new markets (Dixon et al. 2010). Many organisations are now actively reviewing their global footprints and legacy supply chains, driven by, for example, growth in emerging markets, and questioning whether they have the optimal architecture for manufacturing in the future (Harrington and Srai 2016). This highlights a particular problem faced by the pharmaceutical sector – the very significant uncertainty around which new molecules and products are selected for development, and around clinical trial outcomes (Shah 2004). While the number of compounds in development has increased by approximately 60% and total R&D expenditures have doubled over the past 10 years, the average number of new drug entities approved each year has declined, with only one in 10 small molecules entering clinical development expected to advance to full FDA approval (Hay et al. 2014). With estimates that average drug development costs are now circa. $2600–2800M (Avorn, 2014) – an increase from averages of $800M in the early 2000s (DiMasi 2002; DiMasi, Hansen, and Grabowski 2003), it is growing more critical to balance risk and potential rewards, promote faster development timelines, and to make better informed and earlier decisions on the pipeline (DiMasi, Grabowski, and Hansen 2016).

The sector has a reputation for being conservative, compared to other related industries that have successfully implemented sophisticated advanced manufacturing technologies (AMTs) that increase both process and product understanding (Saberi and Yusuff 2012; Rantanen and Khinast 2015). While identification, selection, acquisition and implementation issues have been dominant topics to-date in AMT literature (Chan et al. 2001; Goyal and Grover 2012), currents trends across the pharmaceutical industry – in accelerating innovative technology delivery, and establishing new supply chains for medicines – can help address a key research gap of addressing the realities of modern manufacturing environments (Farooq and O'Brien 2012). Here, the sector is looking to reconfigure value networks, moving towards

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smaller and more agile facilities, and associated end-to-end (E2E) supply chains, to support more dispersed and globalised manufacturing models (Srai et al. 2015). However, limited attention has also been paid to the role of the 'industrial system' in 'connecting' technology developments to final products, and how the design of the value network needs to provide a link between the two (Harrington and Srai 2016). In this study, we draw on a categorisation of AMTs (Gunawardana 2006) that may enable the shift from the traditional centralised and batch manufacturing paradigm of 'make-to-stock', towards that of re-distributed 'continuous' manufacturing operations and 'make-to-order' models.

This research forms part of the on-going research agenda at the UK Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation. Research activities are targeting the adoption of continuous processing technologies across the pharmaceutical industry (see Figure 1).

Specifically, this study focuses on AMTs, in the area of continuous crystallisation (CC), which is a critical unit operation in influencing the pharmacological properties and therapeutic efficacy of a final drug product (specifically respiratory and solid oral doses, which remain the prevalent dose forms today). Through design and control of this purification process, the aim is to promote improved crystal quality, in terms of targeted crystal size distribution, shape, polymorphic form and purity, which is critical for the efficiency of downstream processes from the crystallisation step (filtration and drying) (Laird 2013). Such characteristics have a strong effect on the properties of the final drug product, in terms of dissolution, bioavailability, quality and shelf life (Variankaval, Cote, and Doherty 2008). We extend an analytical framework – previously developed from a *supply network* perspective (Srai et al. 2015), using key literature and a series of case examples to develop assessments involving a series of technology interventions. In the context of this paper, we define 'technology interventions' as those which enable a significant breakthrough in one or more research areas involving continuous crystallisation-based AMTs (Brown et al. 2014; Callahan and Ni 2014; McGlone et al. 2015), and process analytical techniques (Powell et al. 2015, 2016). A series of workshop engagements involving industry and academic experts were used to then test, refine and validate the assessment framework and outputs.

The paper is structured as follows: first we review the key literature on industrial system evolution, value networks and reconfiguration concepts, and perspectives on technology interventions, which inform our framework extension. Section 3 summarises the investigative phase in developing a framework to assess technology interventions, involving a combination of literature synthesis, case histories and secondary data, and an outline of framework testing/refinement using expert panels. Next, the methodology section outlines the research strategy and process/methods of data collection and analysis. Section 5 demonstrates application of the four-step assessment framework, and criteria, in a pharmaceutical context. Section 6 presents new sources, of AMT adoption in a global context, assessing the barriers to implementation, and the pathways for delivering future continuous manufacturing scenarios. Finally, Section 7 presents conclusions, study limitations and future research activities.

2. Literature review

This section is organised around the following themes relevant to the extension of a prototype framework, which have emerged from literature on emerging technologies and industries, e.g.
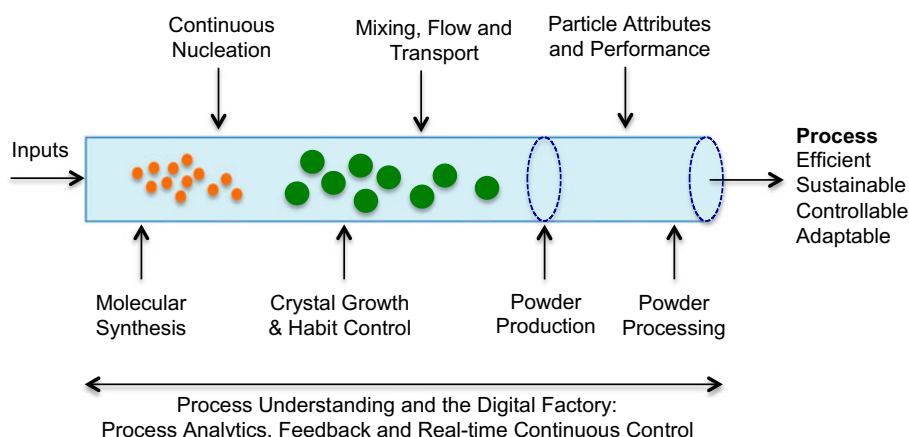

Figure 1. Continuous processing in the manufacture of pharmaceuticals – 10 focus areas targeting the adoption of AMTs (adapted from CMAC 2014).

- Industrial system evolution
- Value networks – reconfiguration concepts
- Perspectives on technology interventions

Key insights, from this review, are then integrated to inform the development of a assessment framework to better evaluate 'technology interventions' – from a value network perspective, in Section 3.

2.1 *Industrial system evolution*

Value networks and industrial systems continue to evolve, enabled by innovative manufacturing processes, and the emergence of new technologies (Royal Academy of Engineering (RAE) 2012). Traditional approaches, to the study of industrial systems in management literature, have often been developed on the assumption of 'stable' environments, which do not adequately provide theoretical or practical guidance on how to effectively capture new and emerging market opportunities (Zhang and Gregory 2011; Harrington and Srai 2012). Hence, a better understanding of the industrial system in which a network operates (capturing context, resources, activities, processes, actors and interdependencies) and an assessment of reconfiguration opportunities, which may result from an AMT intervention, provide valuable insights for both research and practice (Saberi and Yusuff 2012).

Within industrial systems, established firms are constantly reviewing and looking to reconfigure their legacy networks, leveraging existing capabilities where possible and creating advantages in terms of quality, flexibility and lead time, to support the emergence of new technologies and new operating or business models (Adner and Kapoor 2010). However, optimising the configuration of these fragmented networks is particularly challenging especially when there are 'multiple tiers' of partner firms within an industrial system, spanning component and intermediate goods supply, presenting a plethora of options on location and partnering models (Srai and Gregory 2008).

With the focus of this paper on reconfiguring value networks driven by AMTs, two common 'enablers' were identified that support the successful emergence of a new market, based on a radical technological intervention, and the 'process' of commercialising a new technology. Firstly, the successful emergence of any new market depends largely on the parallel development of a *new* supply or value chain to support commercialisation activities (Jacobides 2005; Sebastiao and Golicic 2008; Harrington and Srai 2016). Secondly, 'new market creation' has been considered as the overall process involving the coming together of a new *network* of stakeholders for the commercialisation of a new technology (Zahra and Nielsen 2002; Voelpel, Leibold, and Tekie 2004; Sarasvathy and Dew 2005). Hence, a key criterion in analysing technology interventions and the subsequent effect on emerging and evolving industrial systems is the role that the network of key institutional, industrial and supply network actors may play in the development of alternative business models, effective supply network strategies and viable products and services.

2.2 *Value networks – reconfiguration concepts*

For many decades, the drug product manufacturing model has been controlled by a regulatory framework – safeguarding the quality of the final product, by stringent process monitoring, testing of raw material, in-process material and end-product characteristics – using batch-based operations (Rantanen and Khinast 2015; Srai et al. 2015). However, the sector needs to become more responsive to a changing environment, to devise new ways of providing patients with improved health 'outcomes', at a fraction of today's cost (Erhard et al. 2013).

In studies of the pharmaceutical sector, 'value network' terminology has often been more applicable, given the complex interaction of clinical trials supply, primary (API) and secondary (drug product) manufacturing, and post-dosage activities being increasingly spread across networks of specialised firms, who may also be geographically dispersed and operating in mature and emerging economies (Edwards 2009). In terms of pharmaceutical value networks, new innovative manufacturing processes (such as 'continuous'), the emergence of specialist CMOs in 'continuous', new supply chain partners (in distribution, logistics and the provision of digital technologies) are contributing to the need to reconfigure the pharmaceutical landscape (Srai et al. 2015). One of the key drivers of 'high value' manufacturing is targeting AMT solutions that present both tangible and intangible benefits (Ariss, Raghunathan, and Kunnathar 2002). Previous studies have shown that many enterprises commonly focus on too narrow a segment of the value network, to an extent that the requirements of the ultimate 'end-user' (as opposed to the immediate customer for the product or technology) are often not adequately recognised (Harrington and Srai 2016). Hence, critical linkages, between continuous crystallisation-based processing and other continuous technologies both upstream and downstream, and any associated implications for patients and government health providers should be considered. There may be unseen benefits in a number of areas; product variety, consistency and functionality, energy and resource efficiency, inventory and customisation

options, that may well contribute to a move towards more 'continuous' or 'hybrid' modes of processing becoming the norm and not the exception.

2.3 *Perspectives on technology interventions*

Recent advances in novel technologies (in areas such as 'continuous' processing, printing, sensing and diagnostics) are now creating the potential for significant step changes across the health care sector, with opportunities ranging from clinical trials, right through to the 'end-user' (Srai and Alinaghian 2013). In a recent review paper, examining the research and manufacturing potential of inkjet '2-D' printing, for the development of pharmaceutical drug products (Daly et al. 2015), six 'entry points' and opportunity areas, in terms of research and specific technology 'intervention', were identified (see Appendix 1). These 'interventions' included the potential of the AMT in enabling breakthroughs in rapid prototyping for early stage 'system' discovery and clinical trials, instant and rapid changeovers within secondary processing, late customisation – leading to increased flexibility and service in terms of packaging/distribution, and the provision of personalised 'dial-a-dose' drug delivery to the patient. However, current adoption rates of continuous technologies within the pharmaceutical sector remain low, with industrial exemplars of 'continuous' manufacturing only operating at pilot and/or R&D lab scale capacities in many cases (Srai et al. 2015). While evidence exists that continuous processing delivers financial benefits (mainly for single-purpose plants), studies and modelling have largely been focused at production and plant levels, with the business case, in each case, lacking any formal E2E network assessment (Srai et al. 2015).

Implementing such innovations require organisations, and their extended global networks, to proactively adapt their strategies to ensure an optimal fit between changing competitive priorities and the development of critical support structures (Nair and Boulton 2008). To illustrate these opportunities, examples of radical value network reconfiguration from other sectors, as a result of the emergence of a new technology are briefly outlined here:

- In vitro diagnostics (IVDs): here, new industrial actors have emerged such as IVD companies, specialist clinics and laboratory equipment manufacturers to support the emergence of a technology. Subsequent disaggregation of the value network has led to the reconfiguration of information, material, and revenue flows between industrial actors, resulting in radically different patient-centric supply chain models, and the potential for novel business models (Srai and Alinaghian 2013).
- Digital inkjet decoration and the industrial ceramics sector: a current drive to explore inkjet printing in many sectors is largely due its very successful implementation as part of late-stage customisation tactics, involving variant production at scale, in order to satisfy proliferation demands. Emergence has led to a revitalised industrial ceramics sector in Europe, characterised by vastly reduced inventory levels, yet with enhanced flexibility with respect to near-market supply (Daly et al. 2015).
- The Internet, digitisation and the recorded music sector: historically dominated by five major record labels, a series of innovations including the emergence of file compression techniques and the establishment of peer-to-peer (P2P) networks have radically transformed value networks within the recorded music sector. Furthermore, e-business models in this space, continue to open up opportunities for novel digital distribution channels involving music and film (Leyshon 2001).

In the context of the pharmaceutical sector, equivalent disruptions on a par with these three examples could enable the adoption of technologies compatible with (i) the rapid scale-up of new niche drug products in smaller volumes, (ii) novel delivery formats, with the option of late-stage personalisation and customisation and (iii) agile supply chains designed to manage the potential of significantly increased stock-keeping-units (SKUs).

The next section presents the development of an assessment framework to explore current and future configurations, which when aligned with disruptive shifts in technology, may enable alternative routes to drug product production.

3. Literature synthesis – framework extension

An analytical framework – developed from a *supply network* perspective (Srai et al. 2015), was refined using key literature across a series of research domains (see Figure 2). It is argued that it is critical to assess technology interventions in terms of the E2E supply chain benefits that breakthroughs may enable (e.g. time-to-patient; quality; inventory; enhanced volume flexibility and customisation; financial impact; return on investment). In summary, this synthesis phase examined:

- literature on emerging industry systems, in addition to eight technology-driven adoption/evolution case studies e.g. product-service systems in Defence Aerospace; niche high-specification production in Maritime; technologies for
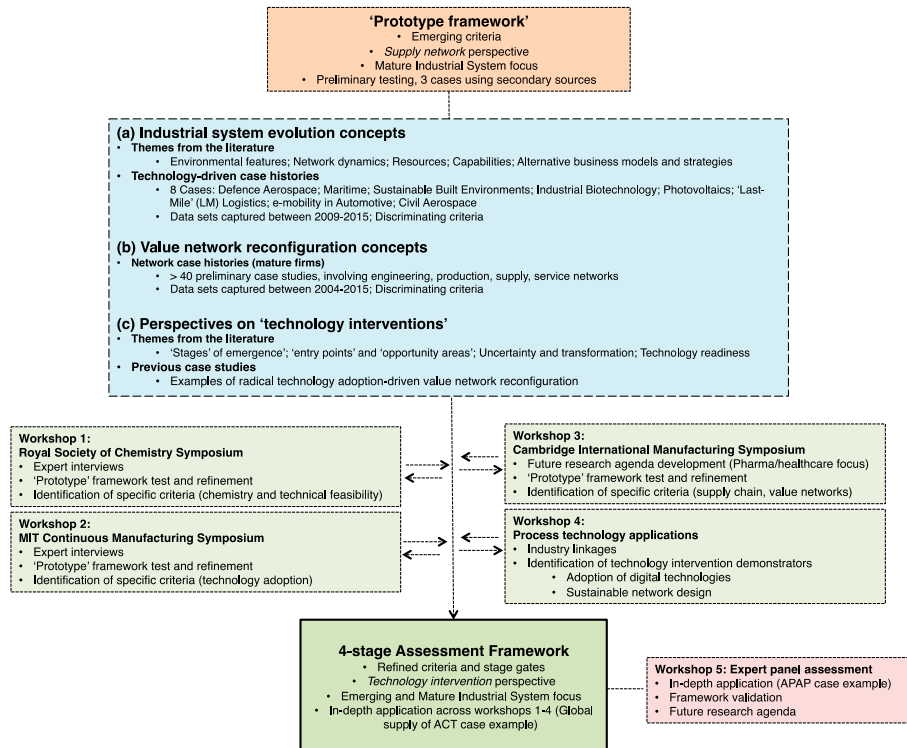
Figure 2.   Literature synthesis, expert workshops and development of assessment framework.

sustainable built environments; technology platform development in Industrial Biotechnology; next-generation technologies in Photovoltaics; e-Commerce driven 'Last-Mile' Logistics; e-mobility in Automotive, composite materials in Civil Aerospace (Harrington and Srai 2012, 2016; Harrington et al. 2016). These were selected in order to provide insights and inform the dimensions of analysis to consider in terms of technology adoption.

- literature on supply chain and value networks (configuration concepts, 'states', 'archetypes') supported by in excess of 40 network case studies and secondary data from the literature reflecting a number of diverse network forms (data-sets capturing engineering, production, supply and service networks) was used to explore dimensions of analysis as a basis to understanding the linkages between supply networks and technology interventions in a Pharmaceutical context (Srai et al. 2015).
- Perspectives on 'technology interventions', examining previous studies on radical value network reconfigurations in other sectors, and themes from the literature which included 'stages' of emergence, maturity descriptors, entry points, opportunity areas and technology readiness (Daly et al. 2015; Harrington and Srai 2016).

The prototype framework was then tested and refined through a series of workshops – capturing rich insights and evidence from a variety of industrial practitioners on their specific AMT adoption and investment decisions, across a range of pharmaceutical drug products. Outputs from the case study interviews, in combination with case-specific secondary data, were then used to refine and finalise the assessment framework.

4. Methodology

This section presents an overview of the methodological approach used in his research paper. A mixed methodology was employed, involving expert group input, followed by a multiple case study method. This multiple case study strategy we adopt is in line with Yin's definition (2009) of it being an empirical inquiry that investigates a contemporary phenomenon both in-depth and within its real-life context. The approach is particularly appropriate here as this study seeks to explore both practice-based (where the insights of key industrial stakeholders are critical) and emerging phenomena when research and theory may be at an exploratory or formative stage (Eisenhardt and Graebner 2007; Yin 2009). The next section provides both details on the data collection process and methods, including information regarding the qualitative investigation and case studies development (interviewees and timescales) to inform the development of the technology intervention assessment framework.

4.1 *Data collection and analysis – process*

This process involved a series of workshop-type engagements, targeting specific outputs (see Figure 2). Appendix 2 sets outs the 58 expert informants, by role, contribution, and workshop linkages where applicable. The expert engagements are summarised as follows:

(1) Royal Society of Chemistry workshop, on 'redefining the twenty-first Century E2E pharmaceutical supply chain through enhanced manufacturing flexibility' (Cambridge, March 2014). This initial stage involved 15 experts across industry and academia, active in the area of continuous AMTs in pharma, sharing insights from specific cases. Questionnaire outputs and a group discussion were then used to formulate a specific case review structure, to identify synergies across cases, with focus centred on assessment of the barriers to future continuous manufacturing scenarios.

(2) Workshop on 'Reconfiguring pharmaceutical supply networks E2E through continuous manufacturing', MIT Continuous Manufacturing Symposium (Boston, May 2014). This stage involved eight experts, active in the area of continuous AMTs, who shared insights on specific adoption and investment decisions, in assessing a series of future continuous manufacturing scenarios for the global supply of Artemisinin-based Combination Therapies (ACTs) – see Appendix 3.

(3) Workshop on 'Pharmaceutical supply chains – setting the future research agenda', Cambridge International Manufacturing Symposium (Cambridge, September 2015). This stage involved 12 academics – specialising in supply chain and global manufacturing domains – assessing a series of future continuous manufacturing scenarios, involving novel technologies (in areas such as 'continuous' processing, printing, sensing and diagnosing).

(4) Leveraging access to 24 industrial partners, aligned with the Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), and project 'ReMediES' (Re-configuring Medicines E2E Supply), this workshop explored (a) what firms are using to select continuous manufacturing technologies to meet specific E2E supply chain objectives and (b) linkages between in practice criteria and those derived from the literature (Glasgow, March 2016).

(5) The final validation workshop (Glasgow, June 2016) involved 12 experts, active in the area of continuous AMTs in pharma, who shared insights on the technology assessment process for a specific in-depth application e.g. CMAC continuous demonstrator, involving the manufacture of Paracetamol (APAP).

5. Assessment framework application

One of the main aims of this research is to highlight the management of AMTs in an increasingly globalised world. The case studies (outlined in Section 3) informing framework extension, suggest significantly enhanced product variety and/ or flexibility to be key criteria in any future industry development. This together with the observed trend in the cases to locate production closer to the end-user suggest future manufacturing will support small-scale distributed operations where speed, and product/product-service customised solutions are more attractive value propositions, enabled by technology developments that provide these viable options.

In this section, the assessment framework is applied to demonstrate how one (or a combination of) continuous AMT 'interventions' may enable (a) reduced investment costs, through smaller production facilities with lower capital cost, reduced overall plant footprint; (b) operating costs through lower catalyst and solvent use, and by minimising total reaction times and (c) reducing inventory cost (less WIP inventory, with reduced material handling and transport).

A set of pre-screening criteria is first used to identify the barriers to adopting alternative product-process technologies and business models. Using *basic operational* and *societal data* inputs to explore future trends (where implementation of 'continuous' may have a cost advantage or increase speed to market for an entity) and market requirements (in terms of *volume* and *product variety*, *affordability* and *unmet needs*) the pre-screening stage facilitates the rapid analysis ('go' vs. 'no-go') of whether an existing drug product or new molecule may be a viable candidate to investigate further in terms of business case evaluation and AMT implementation. As outlined in Appendix 3, criteria should include:

• *Therapy or disease area; patient population; treatment profile; volumes (current, projected); basic financials (price, cost, revenues, margin); SKU mix; inventory; CapEx* and *quality/waste.*

• In addition, to inform workflow development for rapid product assessment and continuous process selection, 10 critical 'attributes' – in terms of technology feasibility and chemistry that may also be assessed at this pre-screening stage – were identified. Focus here looks at complexity and area(s) of opportunity (in the context of 'continuous' processing) with respect to *molecule; polymorph; chirality; number of process steps; particle engineering; kinetics; stability; bioavailability; final dosage form* and *ease of scale-up/scale-out.*

The next phase (stage 2) involves mapping the 'current state', in terms of technologies, unit operations and the supply network. This leads to the identification of critical 'sub-systems' (e.g. *clinical trials, primary manufacturing, secondary processing, packaging and distribution*, and *E2E supply*) that may be affected by a shift to a future, more continuous operating model. The first current state mapping exercise identifies those unit operations where an existing batch production process may be 'pre-disposed' to a series of continuous technologies (in terms of current state and future potential), namely, in *synthesis; purification; isolation; formulation* and *packaging*. Here, the specific implications of defined continuous technology developments and readiness levels may be assessed (are certain routes to manufacture pre-disposed to continuous processing? What alternative routes *could* be?).

An E2E network performance analysis is then used to define overall system metrics, and to evaluate the current state configuration and trade-offs being made. Current-state supply and value network mapping techniques are used to define the existing sub-systems and the drivers/design factors that predominate in each sub-system. Associated impact variables may then be scored, setting out the potential scale of the benefit to patients, government health service providers and industrial value network partners. Here, technology interventions are assessed in terms of 15 impact variables, namely: *inventory; lead-time supply; lead-time to market; scale-up (going into); volume flexibility (mix and volume); process control (including reliability and safety); quality (purity); yield; IP protection and extension (including issue of counterfeits); cost (process, packaging and transport); investment cost (incorporating financial impacts and return on investment); fiscal/tax; environmental impact; viability/adaptability* and *asset utilisation*.

Future state process and network design scenarios, based on the emerging process technology options emerging from stage 2 of the assessment framework and future industry trends are then assessed. Future state models, in the form of value stream maps, generally explore several potential future states prior to a final decision. Alternative states may be based on emerging process and production technologies or AMTs that are still yet to be fully developed. In addition to key industry reports, central to the decision-making process, is continued access to, and engagement with industry, in order to assess future scenarios and the subsequent effect on the wider pharmaceutical landscape.

The research strategy we adopt enables cross-case analysis, in order to identify emerging patterns and other pharmaceutical drug products that may benefit from similar value network design and reconfiguration opportunities. The process also facilitates the development of a series of 'value network roadmaps', which may be both generic sector summaries, and product (category) specific. In the context of this research, these roadmaps may be defined as a visual representation, through time, of (disruptive) changes in 'activities' and 'actors' across the value chain, typically as a result of multiple technological disruptions in process (i.e. $T_1 \rightarrow T_2 \ldots T_n$) and/or a network reconfiguration of actors (i.e. $V_1 \rightarrow V_2 \ldots V_n$), usually resulting in the emergence of new products (i.e. $P_1 \rightarrow P_2 \ldots P_n$) – see schematic representation in Figure 3.

Within a pharmaceutical context, this stage can also support a performance assessment of several potential technological choices involving batch, continuous or hybrid routes, and involve a combination of:

(a) Providing a benchmark, in terms of potential yield and purity
(b) Evaluating various scenarios, which may involve alternative scale production footprints (dispersed, close-to-market, low-scale and integrated plants) and
(c) Developing alternative supply models that might now be possible, due to technological advances in ordering or replenishment.

In turn, architectural differences between batch, hybrid or continuous operations and associated implications for up-stream and down-stream value network configurations, structures, processes, and systems may be assessed across a series of product families. In practice, scenarios may depend on various disruptive influences that challenge the current value network model and introduce a series of possible product or product-service models.

Finally, stage 4 integrates business context/viability and technology readiness inputs (from supporting technology roadmaps) in order to evaluate value network reconfiguration opportunities, and develop a case for transformation. Inputs here include:

• Examining current and future states, in terms of key system metrics from stages 2 and 3
• Value propositions in making the transformation from a business context for key value network players, versus the investments required (potential impact on revenue, margin and inventory reduction)
• Key economic evaluation criteria in terms of batch versus continuous, for example, direct fixed capital, plant throughput, manufacturing cost and unit production cost
• Finally, feasibility and timescales on specific AMT interventions

A series of emerging themes and insights from practitioners on the opportunities for technology-driven value network reconfigurations in the pharmaceutical sector are now outlined in the following section.
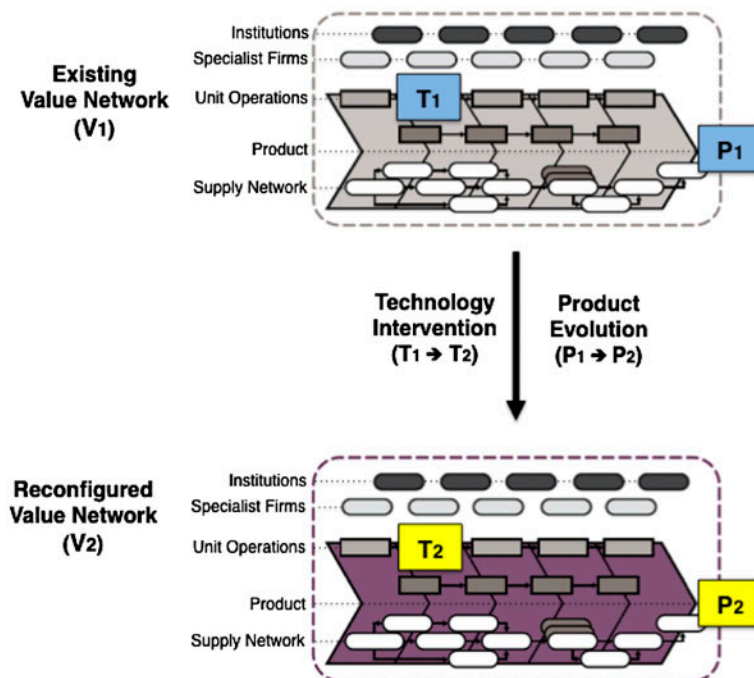
Figure 3. Reconfiguring pharmaceutical value networks: targeted interventions ($T_1 \rightarrow T_2$) changing the product and industrial landscape (P_1 and $V_1 \rightarrow P_2$ and V_2).

6. Results and implications

This section presents new sources in assessing the barriers to implementation, and the pathways for delivering future continuous manufacturing scenarios, using the framework and scenarios set out in Section 5.

While there is collective agreement from industry and academia that the funding model for drug discovery involving small molecules is becoming outdated and inefficient, there is level of disparity of viewpoints when it comes to adoption of 'continuous' manufacturing – in terms of opportunity areas, technological readiness levels and uncertainties and the transformation challenges (including behaviours) that lay ahead within the sector. Table 1 summarises outputs from workshop 1 involving industrial and academic experts who are actively involved in the areas of continuous flow R&D and process-technology adoption. Overcoming these barriers requires a coordinated and systematic approach when redesigning the entire value network. Our research suggests that barriers may be real or perceived, and arise from combinations of socio-political, technical and regulatory factors. *Content validity ratio (CVR) values were calculated[1] and range between −1 (perfect disagreement) and +1 (perfect agreement), with CVR values above zero indicating that over half of panel members were in agreement. For a panel size of 15, the critical level of agreement or disagreement (CVR $_{critical}$) is +/−0.6* (Ayre and Scally 2014).

Second, in assessing pathways to future continuous manufacturing scenarios, critical to this is how best to manage AMTs and best guide the selection of processes (continuous or batch). Identifying what adds value to the ultimate 'end-customer' is not just a technical consideration, but also requires a change in mind-set. The future influence of the patient was also cited as, potentially, the most disruptive factor across the entire industry. Hence, industry needs to design products and services based on patient needs, and not what an organisation 'wants to make'. Key insights on how the sector should approach 'manufacturing in a new way' to deliver value are summarised as follows:

- Technology interventions linked to E2E supply chain analysis should be a key deliverable in assessing any business case ('It's more than just a 'batch-to-continuous' agenda').
- While industry has committed to the principle of continuous processing, it may be better served to target 'tactical' AMT opportunities. Employing a phased approach, and scouting for opportunities where there are 'low effort/high yield' opportunities, confidence can be gained before applying more resources.
- It is argued that the industry, as a whole, doesn't currently operate its batch processes at an optimum level. In the future, how can the sector guarantee that continuous processes, enabled by AMTs, will operate any better? A key consideration is to acknowledge that benefits may be achievable without moving to a fully continuous route for some products. For example, continuous, batch, or hybrid solutions may well drive agile supply chains of the future.

Table 1. Barriers to the continuous manufacture of pharmaceutical drug products.

	Barriers	Panel size (N)	n_e	Content validity ratio (CVR)
Social	General belief is that continuous processing is only suitable for large volumes	15	5	−0.333
	Lack of experience and fear of the unknown is delaying the implementation of continuous technologies	15	9	0.2
	Common view is that conversion, from current batch production equipment to continuous production equipment, will not bring a good return on investment	15	8	0.067
	Common misconception is that continuous processing is not flexible	15	12	**0.6**
	Uncertain market conditions/customer demands and shorter product life cycles are key challenges for continuous manufacturing	15	11	0.467
Economic	Resources required at the start-up of the continuous process and availability of the equipment is a key consideration	15	8	0.067
	Lack of financial justification for investment in continuous processing while holding excess existing batch capacity (sunk cost and over capacity)	15	11	0.467
	Specialised people or the up-skilling of current staff to control the continuous process is required	15	9	0.2
Regulatory	The existing regulatory system (or perception of it) is rigid and unfavourable to the introduction of new innovative systems	15	6	−0.2
	Lack of definition: If a continuous process is used within pharma, 'batch size' definition needs to be discussed and agreed with the regulatory authorities	15	8	0.067
	Sterility is viewed as an issue as contaminants and by-products build up within the system in a multi-product environment	15	8	0.067
Technological	Losses that occur during start-up and shut-down periods, and control of such, is a major challenge for continuous technologies	15	3	**−0.6**
	Handling material that does not meet specifications is a major quality assurance issue in continuous processing	15	8	0.067
	Continuous technology is still more challenging in terms of crystallisation, isolation, filtration and drying	15	12	**0.6**
	Solid formation, in general, can block reaction channels and it is currently difficult to overcome this problem	15	9	0.2
	The challenge in micro and tube reactors is to make the reaction possible in solid phase	15	9	0.2
Process	Continuous manufacturing control systems constitute one of the major design challenges	15	6	−0.2
	Good online measurement tools (PAT and QbD systems) and integration between the generated data and control software is challenging in a continuous context	15	8	0.067
	Current batch processes must be fully understood before transferring to continuous mode	15	3	**−0.6**
	Implementing continuous processing requires a change in processes that have already been validated	15	9	0.2
	Process management and its execution (incorporating QC documents and management) will be key factors when switching from batch to continuous	15	14	**0.867**

For many of the emerging niche and high-cost candidates discussed as part of this study, scenarios often involve exploring opportunities to reformulate in order to increase bioavailability. This opens up the potential to reduce 'dosages', hence, volumes are required for new formulations. There were cases where more combinations are likely to be required in the future, where single-use derivatives are actively discouraged due to risk of drug resistance (as in this case of ACTs in Appendix 3), complex hybrid solutions involving more combinations and reformulations and, finally, cases where significant increases in volumes will require additional capacity close to emerging markets. Combining such criteria may also be used to identify clusters of candidate drug products with attractive business cases that may exhibit similar areas of benefit and scale for patients and government health service providers, made possible in the context of adopting specific continuous processing technologies. This emerging 'library' of 'product-process archetypes' can inform a classification system that enables ease of comparability in identifying other drug candidates and new molecules that may benefit from specific technology interventions and opportunity areas.

Thirdly, in a future pharma context, it is argued that collaboration may be the key to success, but clear deliverables, timelines and specific targets must be established to make alliances work. The management of AMT is not so straightforward in this scenario. Decisions on partner selection should involve not only assessing the type of AMT that is

appropriate for a particular manufacturing and business situation, but also its specification, integration and use. Key considerations from industry on 'continuous capability and supplier development' are as follows:

- Where are the 'solution spaces' (large volumes, elimination of working capital, speed of supply reducing inventories and customising for the patient) where continuous processing can deliver value?
- What are the specific continuous AMT interventions, and associated technical challenges, that need to be overcome to achieve delivery of these 'solution spaces'?

It is suggested that the ideal supply chain may be composed of a mix of internal fixed-capacity, with some degree of external variable capacity. With a growing patient-centric focus and a move towards 'outcomes-based' business models, it is argued that future pharma may well be better served to focus on R&D and commercialisation, leaving emerging CMOs to provide the 'solution space' or capacity to become an attractive 'test-bed' for rolling out new drug products. There may be a requirement for more of a supplier development focus given that the industry needs to grow external manufacturer capability to enable continuous manufacturing to develop. A critical counter argument here is increased dependencies, especially external, may lead to suppliers of AMTs or input chemicals becoming future competitors as they develop more core competencies in the focal firm's key processes.

A fourth theme that emerged was whether the real opportunities for AMT adoption lay in 'development' stages. With the transfer of many elements of clinical supply to commercial supply inherently built-in, should industry concentrate on alternative clinical supply chain designs at an early phase, which may drive technology solutions to deliver precision, speed, integration, inventory savings, increased flexibility, improved product quality and quicker response to new customer demands? This would involve a focus on speed-to-market for system or drug discovery, with commercial and 'development' phases using continuous technologies to enable rapid synthesis and speed/efficiency as an optimal pathway to E2E integration. The importance of continuous AMT implementation in 'discovery' could also enable rapidly shorter supply chains where there may be less of a stability requirement for a final drug product. This could open up potential opportunities for a new range of targeted molecules with a stability of a few weeks (i.e. radiopharmaceuticals).

Finally, while the adoption of specific AMTs in pharma may be used to serve existing markets more effectively, or deliver unmet end-user needs, individual drug products may also be assessed, in the context of new continuous capabilities and technology interventions that may create opportunities with respect to new and emerging markets. These could include (a) drug products previously considered uneconomical to deliver via traditional batch processing routes, (b) more established generic products which may need to 'evolve', in response to future trends and changing markets, in addition to (c) new chemical entities for an initial assessment. High levels of investment in continuous AMTs may well remove cost benefits (initially), but once a maturity level is achieved and a technology is no longer proprietary but widespread (like the example of laser printing), there will be opportunities for return on investment. However, continued uncertainty with respect to timescales on certain continuous technology developments and implementation, versus changing cost profiles of high cost and emerging countries remains a key concern for the sector.

7. Conclusions and future research agenda

Pharmaceutical organisations are now actively reviewing their global footprints and questioning whether they have the optimal architecture and technologies for manufacturing in the future. In this study, we draw on a categorisation of AMTs that may enable a shift from the traditional centralised and batch manufacturing paradigm of 'make-to-stock', towards more re-distributed 'continuous' manufacturing operations and 'make-to-order' models. The research strategy employed enabled an investigation of the scope, challenges and opportunities of specific AMT innovations, in the area of continuous manufacturing and crystallisation, where current adoption rates within the pharmaceutical sector remain low. This paper then presented new sources, in our study of AMT adoption in a global context – assessing the barriers to implementation, and the pathways for delivering future continuous manufacturing scenarios – using a four-stage assessment framework as a basis for data capture.

While our studies have highlighted a desire for improved integration, openness, collaboration and trust between stakeholders, our findings also capture the high level of disparity in viewpoints that exist across the pharmaceutical value network, emphasising the many uncertainties and transformational challenges that lay ahead. Secondly, the widespread take-up of AMTs, in the area of 'continuous' manufacturing, is not solely dependent upon the technical requirements identified. Overcoming the barriers to adoption requires a coordinated and systematic approach to understanding and quantifying the benefits across the entire value network, in local and global contexts, in order to develop the business case for the implementation of continuous AMT solutions.

In conducting this study, some limitations are evident which, however, present interesting opportunities for future research. First, and inherent to the nature of emerging AMTs in Pharma, was access to a significant number of case

examples at this juncture. While the assessment framework was developed using an extensive literature review, testing and refinement was restricted to four workshops, with validation restricted to application using two in-depth case studies to-date that were assessed by an expert panel. The second limitation of this study is a focus on small molecules, and on solid oral dose forms. With the trend towards more biopharmaceuticals and more drug device combinations, future research plans will include testing and refining the framework using case studies involving other industry segments e.g. macro-molecules, stratified medicines and extending the approach to health care contexts (e.g. medical devices and digital e-health care technologies) – all of which will require some additional AMTs in process analytics, diagnostics, and across the extended supply chain. These activities form part of an ongoing research agenda, as part of project ReMediES (Re-configuring Medicines E2E Supply), which explores

- Implications of digitalisation – from the perspective of AMT disruptions on traditional supply chains, solutions to customise and address customer needs, and the effect on downstream supply chains to patient delivery.
- Development of 'smart' packaging AMTs, for security and anti-counterfeiting.
- Implications, in terms of AMT challenges in formulation, and the wider supply chain.
- The impact of regulatory trends, together with affordability and access to care/markets.

Several diverse pharmaceutical products have also been identified as part of this on-going study, in order to provide the basis for exploring alternative product-process supply network options and value chain implications arising from a technology intervention. These case studies were chosen as they represent products at different stages of their product life cycle, have dissimilar product volume and pack complexity profiles, and varying transformation challenges if an alternative process, value network and/or business case is implemented. In turn, this will inform a classification system (in development) that will enable ease of comparability to identify and connect drug product, AMT, and device, where 'combinations' of technologies may well benefit from similar value network design and reconfiguration opportunities.

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Note

1. The CVR (content validity ratio) is a linear transformation of a proportional level of agreement on how many experts within a panel rate an item 'essential' calculated in the following way (Ayre and Scally 2014): $CVR = n_e - (N/2)/(N/2)$, where CVR is the content validity ratio, n_e is the number of panel members indicating an item 'essential,' and N is the number of panel members.

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Appendix 1.

Six intervention points where research on the inkjet printing of pharmaceutical drug products will focus on (adapted from Daly et al., 2015)
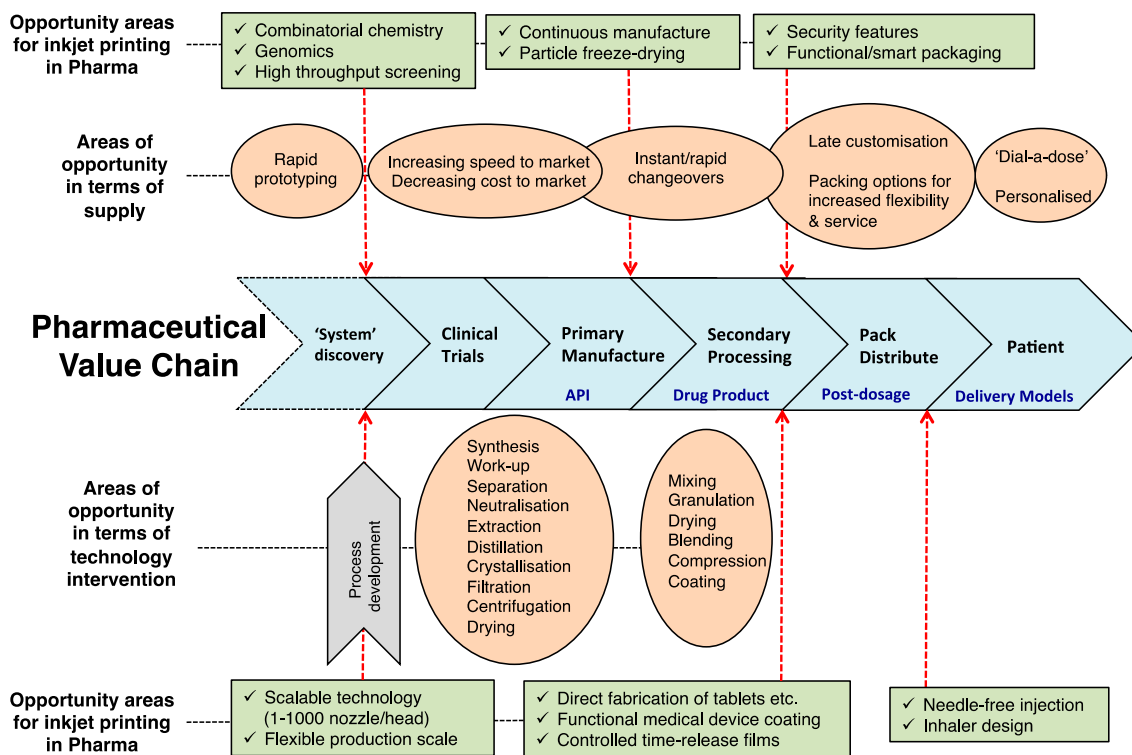
Appendix 2.

Expert informants, by role, and their contribution to the 5 workshops

Workshop 1: Royal Society of Chemistry Symposium
Workshop 2: MIT Continuous Manufacturing Symposium
Workshop 3: Cambridge International Manufacturing Symposium
Workshop 4: Process technology applications and linkages
Workshop 5: Expert panel assessment

Interviewee/source	Role/contribution area	Organisation	Workshop
1	Operations Director	National Centre – Continuous Manufacturing	1,2,4
2	Research Director, co-Principle Investigator, Pharma Supply Chains	Academia (UK)	1,2,3,5
3	Senior Researcher, Chemistry	Academia (UK)	1
4	Director of National Centre, Principle Investigator, Pharmaceutical sciences	Academia (UK)	1,2,5
5	Head of Process Technology	CMO – UK & India	1
6	R&D Chemical Engineer	MNC – Global Pharma, health, cosmetics	1
7	Director, Manufacturing projects	CMO – Global Pharma R&D	1,4
8	Group Technical Director	MNC – Global Process Engineering	1,2
9	Senior Project Engineer	CMO – Petro-chemicals, food processing	1
10	Manufacturing Technical Project Lead	MNC – Global Pharma Manufacturing	1
11	Capability Lead for Clinical Operations	MNC – Global Pharma Clinical Trials	1
12	Technology Lead, Continuous technologies	MNC – Global Pharma Manufacturing	1
13	Senior Scientist	MNC – Global R&D	1
14	Professor, Flow chemistry	Academia (UK)	2
15	Director, Continuous technologies	MNC – Global Pharma Manufacturing	2
16	Director, Advanced process analytics	MNC – Global Pharma Manufacturing	2
17	Senior Researcher, Emerging technologies	Academia (UK)	1,2,3,4,5
18	Professor, Global Manufacturing	Academia (US)	3
19	Professor, Supply Chain Management	Academia (US)	3
20	Researcher, Supply Chain Data Analytics	Academia (UK)	3,4
21	Researcher, Policy and Standards	Academia (UK)	3
22	Senior Researcher, Sustainable Operations	Academia (EU)	3
23	Senior Researcher, Sustainability	Academia (EU)	3
24	Senior Researcher, Supply Chains	Academia (UK)	3
25	Former Head of Global Pharma Supply Chains	Academia (UK)	3
26	Researcher, Sustainable Supply Chains	Academia (UK)	3
27	Researcher, Supply Chain Design	Academia (UK)	3
28	National Programme Advisor	National Funding Body	4
29	Director of National Programme, Clinical Trials	MNC – Global Pharma Clinical Trials	1,2,4
30	Technical Lead, API Manufacture	National Centre – Continuous Manufacturing	4
31	Technical Lead, Secondary Manufacture	MNC – Global Pharma Manufacturing	4
32	Business Development and Technical Lead,	CMO – Advanced Manufacturing Technologies	4
33	Technical Lead, Pharma packaging	MNC – Global Pharma Manufacturing	4
34	Project Lead, Smart packaging in Pharma	National Centre – Process Industries	4
35	Technical Lead, Advanced flow technologies	MNC – Global Pharma Manufacturing	4
36	Technical Director, Process design	SME – Process Industries	4
37	Project Manager, Innovation capability	CMO – Global Process Engineering	4
38	Director, Continuous technologies	CMO – Global Manufacturing Development	4
39	Managing Director	CMO – Intelligent Process Monitoring	4
40	Head of Strategy, Pharma and Life Sciences	National Centre – Skills development	4
41	Product Manager, Continuous technologies	CMO – Modular Equipment Design	4

Appendix 2. (*Continued*)

Interviewee/source	Role/contribution area	Organisation	Workshop
42	Managing Director	CMO – Continuous Processing Systems	4
43	Business Development Manager, R&D	CMO – Advanced Manufacturing Technologies	4
44	Senior Engineer, Automation	CMO – Customised Technical Solutions	4
45	R&D Team Lead	MNC – Global Biopharma Technologies	4
46	Operations Director	CMO – Advanced Manufacturing Technologies	4
47	Technical Director	MNC – Global Biopharma Technologies	4
48	Developer, Process systems	SME – Advanced Process Modelling	4
49	Director, Business Development	SME – Pharmaceutical Development Services	4
50	Professor, Pharmacy and Biomedical Sciences	Academia (UK)	5
51	Professor, Chemical and Process Engineering	Academia (UK)	5
52	Professor, Chemical Engineering	Academia (UK)	5
53	Research Fellow, Chemistry	Academia (UK)	5
54	Research Fellow, Process Engineering	Academia (UK)	5
55	Research Fellow, Chemical Engineering	Academia (UK)	5
56	Manufacturing Fellow, Chemistry and Process	Academia (UK)	5
57	Senior Lecturer, Modelling	Academia (UK)	5
58	Researcher, Medicinal Chemistry	Academia (UK)	5

Appendix 3:

Four-stage framework, with case study example, to assess the feasibility of adopting continuous manufacturing technologies for the production of pharmaceutical drug products

Stage	Step	Description	Case study example – Global supply of Artemisinin-based combination therapies (ACTs)
	1	Gather basic data on drug candidate (e.g. Therapy Area, Patient Population, Treatment profile(s) Cost, Volumes)	Therapy/disease area: Malaria; Patient population (global context): 104 countries; Treatment profile: currently 220 M cases, with an estimated 280 M treatments per annum; Dosage: Medium-High (Coatrem-24 tablets; dose is 4 tablets); Frequency: Full course of treatment is 6 doses of Coartem, taken over 3 days); Duration: 7–14 days; Other: Diagnostic test required; Volumes: 200 tonnes/annum (current); Cost of API: $500–600/kg (plant-derived), $350–400/kg (biosynthetic route); Strengths: Coatrem: fixed at 20 mg Artemisinin; 120 mg of Lumefantrine; Pack sizes: 12 and 24.
Pre-screening	2	Rapid opportunity/barrier analysis (e.g. operational and societal data)	Overview: ACTs remain the first-line response for the treatment of malaria. There were 660,000 deaths in 2011. Eighty per cent of deaths occured in just 17 countries, the majority of which have household incomes of less than $1.25 per person per day. Intent is to reduce treatment cost to circa $0.50 per dose. Timescale yet to be defined. Funding: To address a lack of funding, the Global Fund, in partnership with the UN, WHO and World Bank have created the Affordable Facility for Manufacturing – malaria (AMFm), as a vehicle to provide financial subsidies for qualified commercial treatment products to qualifying countries. Global funding for malaria prevention and

(*Continued*)

Appendix 3. (*Continued*)

Stage	Step	Description	Case study example – Global supply of Artemisinin-based combination therapies (ACTs)
			treatment was US$2.3B (in 2011), which is still less than required to support WHO goals.
			Treatment profile: Diagnostics tests are required to confirm malaria and source of infection. This represents the most significant cost in treatment (over $4 per patent). Due to the cost and potential delay, most fever is treated presumptively (i.e. an anti-malarial is given as a precaution – estimated at 60 M treatments in 2011).
			Quality assurance: It has been estimated that only around 59% of malaria cases are treated with quality ACT, with implications for demand. Counterfeits are prevalent in many countries leading to high risk and mortality.
	3	Rapid volume/variety analysis (e.g. future predicted volumes and SKU counts)	Volumes: From 200 tonnes to 300 tonnes/annum (future). Currently, it is estimated that 10,000 sites are producing 60,000 metric tonnes of raw material, very low yields. SKUs/Variety: Future requirement to develop more combinations as use of a single Artemisinin derivative is actively discouraged due to risk of drug resistance. ACT derivatives have also shown utility in treating other diseases, such as cancers, but this has had limited clinical development to-date.
	4	Unmet needs (e.g. business context)	Future costs: AMFm is sustainable at country level under the conditions that the subsidy level for ACTs remains at its current level (approximately 92%) and that prices of ACTs do not increase during the five-year period of interest (2013–2017); Diagnostics tests required to confirm malaria and source of infection represent the most significant cost in treatment (> $4 per patient).
	5	Process chemistry (e.g. is the 'process' predisposed to Continuous manufacturing?)	Opportunity as current chemical synthesis (batch route) is difficult and expensive, due to the complex nature of the molecule. (Criteria assessed here includes: molecule; polymorph; chirality; number of process steps; particle engineering; kinetics; stability; bioavailability; final dosage form and ease of scale-up/scale-out).
	6	Critical Review & Opportunity Scoping – Gate 1	High potential – value network reconfiguration opportunities end-2-end (E2E) in adopting continuous manufacturing technologies, in developing diagnostics, and in implementing 'smart' anti-counterfeiting packaging.
Current State process mapping	1	Application of supply network configuration tools (in specific contexts)	Current global manufacturing footprint: 16 × Artemisinin producers – China (8) Vietnam (5) Kenya (1) Uganda (1) Madagascar (1); 10 × WHO Prequalified API Manufacturers – India (6) China (3) Italy (1); 12 × WHO/EMA Prequalified ACT Manufacturers – India (6) Germany (2) Italy (1).
	2	Current state analysis (sub-systems)	The overall lead time from crop planting to final product shipment is approximately 14 months, and highly variable (being impacted by weather and local economic factors) and, is expensive compared to the target treatment cost. There is also a large variation in Artemisinin content in the leaves of plants from different origins and regions.(Criteria assessed here examines potential for impact by technology interventions across sub-systems e.g. clinical trials, primary and secondary manufacturing, packaging and E2E supply).
	3	Populate Opportunity Grid (assessment versus 15 impact variables)	Identifying the potential benefits using a continuous manufacturing technology intervention outcomes matrix shows potential for improved quality and supply reliability, and a reduction in overall product cost.
	4	Current state flow chart (e.g. current process technology in use)	Plant extraction/purification and multi-stage batch (Focus on synthesis; purification; isolation; formulation; packaging).
	5	Critical Review & Opportunity Scoping – Gate 2	High potential – continuous technology 'interventions', from synthesis right through to packaging and labelling, to be considered in developing and assessing a series of alternative supply models.

Appendix 3. (*Continued*)

Stage	Step	Description	Case study example – Global supply of Artemisinin-based combination therapies (ACTs)
Future state model(s)	1	Sub-systems (clinical trials, primary and secondary manufacturing, packaging and E2E supply) – future state analysis	Alternative continuous manufacturing route derived with the aim of reducing overall process lead-time from an estimated 30–90 days (currently) to 5–10 days. Future scenarios developed as part of a current-future state analysis, namely: A: Reformulate in order to increase bioavailability. Potential here to reduce the 'dosage', hence, volumes required for a series of new formulation(s). B: Develop more combinations for ACTs due to risk of drug resistance C: Hybrid solution involving more ACT combinations and reformulations D: Volumes set to increase dramatically, with opportunities in other therapy areas
	2	Explore Continuous manufacturing technology options (leveraging latest experimentation data and/or literature)	
	3	Generate alternative process and supply network design option(s)	
	4	Expert Panel Assessment	High potential – opportunities to reduce cycle times and inventory, by adopting continuous processes that also reduce solvent use. Several technology developments are considered with maturing technology readiness levels, which suggest promising routes to commercialisation and adoption.
Case for adopting specific technology intervention(s)	1	Assessment Framework Output (current state vs. future state(s))	Currently, there is a lack of transparency in the supply chain hampered by inaccurate and untimely country demand forecasts. Opportunities to significantly reduce lead-time and increase service levels.
	2	Business Context/Viability	Currently, a fragmented extraction and manufacturing market with high transaction costs. Potential for cost and inventory reduction.
	3	Technology Readiness	Several continuous schemes have been developed which demonstrate potential feasibility and benefits.
	4	Develop case for transformation dossier	High potential – in adopting manufacturing scenario A, initial projections suggest potential to reduce product cost to around 60% of current prices, and the treatment adherence burden in a relatively short time frame (compared, say, to a new drug combination) thereby maximising the impact benefit for patients and society.