Emerging product-process archetypes in oncology: implications for supply network design

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Abstract
Accelerated growth of the oncology market, within the pharmaceutical sector, has been widely reported in the literature e.g. predicted spends of $74-84 Billion by 2017, making oncology the leading therapeutic area. A series of emerging product-process archetypes and associated implications for future supply models in oncology are explored.

Keywords: oncology, pharmaceuticals**,** continuous manufacturing, supply networks

Introduction

The emergence of new technologies and therapies is driving the need and opportunity to radically transform pharmaceutical production processing and the end-to-end (E2E) supply chain (Srai, Badman *et al*, 2015; Daly *et al*, 2015). A future pharma model should look to incorporate such technologies that are compatible with the rapid scale-up of both new drugs and delivery formats, that enable late-stage customisation and manage multiple co-existing agile supply chains to cope with the potential of significantly increased stock keeping unit (SKU) counts (Daly *et al*, 2015). However, for such new technologies (e.g. alternative continuous processing technologies, inkjet printing etc.) to become more generally accepted within the wider healthcare sector, the (a) impact on current supply models, (b) opportunities for value chain re-configuration and (c) business case for transformation needs to be better understood (Harrington *et al*, 2014; Harrington and Srai, 2015b).

Supply network reconfiguration studies to-date in this area have largely focused on a series of high volume pharmaceutical candidates, in the range of 200-10,000 tonnes/annum (Srai, Harrington *et al*, 2015). Following a recent 'current state' review of the pharmaceutical sector (Harrington and Srai, 2014; Harrington and Srai, 2015a), a key objective of on-going research[1] is to cover the pharma landscape (examining low, medium and high volumes and SKUs – see fig.1) rather than just focusing on one specific area (i.e. large volume drug products). Hence, this research looks to focus on a series of extreme product families - selecting some representative products from each - in order to provide an informed view of the combinations of 'product' and 'process' 'attributes' that may benefit from adopting new continuous processing technologies.

It is argued that oncology may best exhibit characteristics of what may be the future of pharmaceutical industry (e.g. niche, personalised, lower volumes, targeting for sub-populations) and, hence, inform opportunities and benefits for e.g. continuous operations on the wider pharmaceutical industry (Harrington and Najim, 2014). It is also a key area of interest in research terms i.e. accelerated growth of the oncology market within the pharmaceutical sector has been widely reported in the literature e.g. oncology drugs went from 10% sales of the top 100 best-selling drugs in 1998 to 18% by 2009. In addition, the IMS Institute for Healthcare (2012) forecasts $74-84 Billion of spending by 2017, making oncology the leading therapeutic area.

Hence, a series of candidates that are representative of the wider oncology market e.g. including low volume, niche, patented drugs with high QALYs (quality-adjusted life years) through to higher volume generics with a history of shortages were previously identified for future study (Harrington and Najim, 2014). Preliminary scoping studies have shown these oncology candidates to 'cluster'- in terms of volume and product variety - into distinct groupings exhibiting very similar areas of benefit and at similar scale for patients and government health service providers (Harrington and Najim, 2014). Designated as 'product-process' archetypes[2] (Harrington *et al*, 2013), this simple classification system may enable ease of comparability to identify *other* drugs that may benefit from similar approaches. This research paper focuses on these emerging 'product-process' archetypes in oncology – classified as '*New Niche*', '*Old Niche*' and '*Established Generics*'

[1] Activities form part of an on-going research agenda at both the UK EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) and through the UK Department of Business Innovation and Skills (BIS) Advanced Manufacturing Supply Chain Initiative (AMSCI) funded project REMEDIES (RE-configuring MEDIcines End-to-end Supply)
[2] An '*archetype*' may be defined as "a typical example of something, or the original model of something from which others are copied" [Source: Cambridge dictionaries online].

(Harrington and Najim, 2014; Daly *et al*, 2015) - in order to explore a series of future scenarios, models for value chain reconfiguration and implications for supply network design.

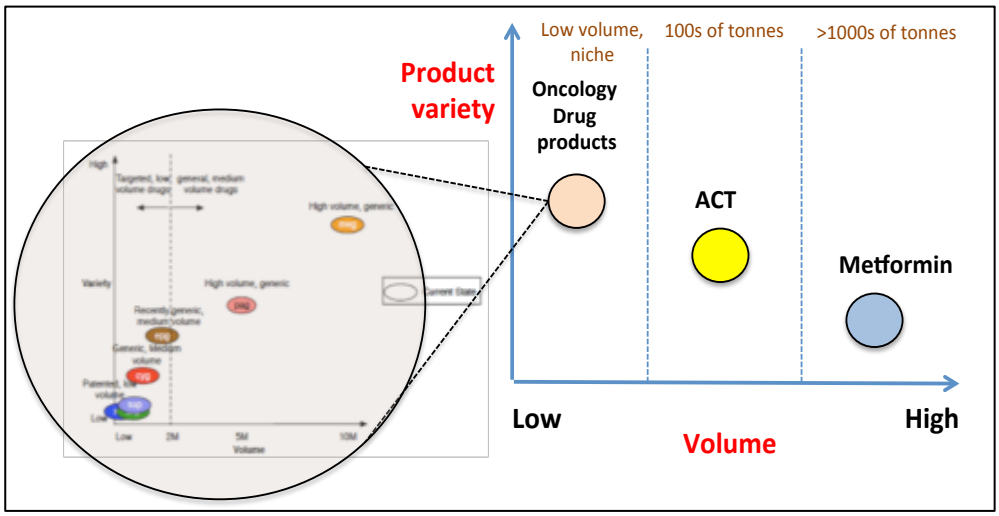

Fig. 1. Product variety-Volume Matrix (adapted from Srai et al, 2014) - covering the pharma landscape, targeting low (oncology), medium (e.g. ACT) and high volumes (e.g. Metformin) and a range of SKUs

Oncology context

Cancer remains the leading cause of worldwide deaths, estimated to be in the order of 13% (American Cancer Society, 2011; WHO, 2014) and incidence rates are predicted to also increase worldwide e.g. from 14 million annual cases in 2012 to 22 million within the two decades (WHO, 2014). In terms of demographics, incidence and mortality rates for most cancers are increasing more quickly in (a) developing countries with the adoption of western lifestyles (Jemal *et al*, 2010) and (b) ageing populations. Hence, cost of care is becoming a critical issue because of the lower purchasing power of these two segments.

The IMS Institute for Healthcare (2012) has reported growth rates of 6-15% for the oncology market between 2008 and 2013, as opposed to 1-7% for the wider pharmaceutical industry. In addition, KPMG (2011) forecasts that oncology will continue to grow faster than other leading therapy areas: 5-8% annually between 2010-2015 compared to e.g. 1-4% for Cardio-Vascular drugs).

Currently, cancer care consists of a combination of the three available treatment types (i.e. Surgery, Radiotherapy, Chemotherapy) with success dependent on type of cancer treated, stage discovered, and treatments available (American Cancer Society 2011). This research specifically focuses on the chemotherapy drug treatment area of care and the opportunities for technology-enabled value chain (VC) reconfiguration, which may reduce cost, and satisfy 'unmet needs' within these segments.

Methodology and intervention case examples

A number of cases exploring technological interventions to develop new or radically different product-process reconfiguration models that may support major breakthroughs are currently under examination and inform this research (Harrington *et al*, 2013; Harrington *et al*, 2014; Srai *et al*, 2014; Srai, Christodoulou and Harrington, 2014; Harrington and Srai, 2014; Srai, Badman *et al*, 2015; Daly *et al*, 2015). Although a small majority of the models examined have reached industrial viability, these conceptual network redesign studies look to highlight different product, process and business models that may enable new production processing and/or delivery models, redesign alternatives and open up new or previously elusive markets. These include:

- Exploring continuous-processing in previously batch-process-oriented Pharmaceuticals
- Potential applications where inkjet printing may enable continuous and semi-continuous manufacturing, e.g.:
    - High-throughput API "system discovery" techniques
    - Delivery of inherently scalable technologies to enable rapid transition to clinical trials

  - Manufacturing as (a) a primary process (i.e. API manufacture) or (b) a secondary process (i.e. delivery format fabrication)
  - Packaging and Distribution (e.g. security tags printed directly to product)
  - Final drug delivery method (e.g. aerosol technology, needle-free injection)
- Implications of additive manufacturing in component manufacture
- Other post-dosing product finishing models that enable more near-market supply

An analytical framework previously developed (Srai *et al*, 2014) and tested (Srai, Harrington *et al*, 2015) was utilised to enable a systematic assessment of a series of candidates that are representative of the wider oncology market e.g. including low volume, niche, patented drugs with high QALYs (quality-adjusted life years) through to higher volume generics with a history of shortages. In summary, step 1 of the methodology involved exploration of current state process models. The conceptual network redesign studies (above) and other considerations (operational, technical, social data coupled with e.g. chemistry inputs on amenability) inform step 2, which involved mapping future process and network design options and scenarios involving each of the candidate products. As the overall purpose of the analytical framework is to test, propose and forecast potential reconfiguration opportunities, it is of paramount importance to select the case studies with the highest potential outcomes, i.e.:

- Candidates with an interesting business context for reconfiguration
- Candidates with a sufficient amount of data to be able to conduct the case studies (secondary data)
- Case studies with higher probability to experience reconfiguration, and thus in this case, higher chance to benefit from a technology disruption

Oncology Drug Candidate Selection

This section summarises the approach previously developed (Harrington and Najim, 2014) to select the case study oncology candidate drugs, e.g.:

- *Step 1: Assessment of oncology drugs at a molecule level*: this enabled the deletion of duplicates and combinations produced by different firms

- *Step 2: Drug segmentation*: Two segments exist - small molecules and biologics. For small molecules, production processes are often well understood and straightforward, while biologics are often produced through very complex, difficult to certify processes (Garrison 2010). Thus, on one hand, small molecules are more amenable to technology disruption (because of ease and level of understanding of their production processes), on the other hand, they are more subject to generic competition (because of the low barrier to entry after patent expiration compared to the high manufacturing barrier to entry in biologics).

- Step 3: *First data availability screening*: this involved examination of the process chemistry, data availability and molecule chemistry. The objective here was to be able to understand the production or chemical process for synthesising the drug, with special focus on API as it commonly encompasses most of the value. Access to data is critical at a later stage of screening, as it is beneficial in order to evaluate the opportunities for amenability to a technology disruption.

- *Step 4: Business context*: this involved capturing e.g. target population, therapy area, price, patent state, etc., with the purpose of detecting interesting business cases that may benefit from a possible reconfiguration (e.g. inaccessible drug because of price or cost, drug with frequent shortages etc.) Finally, amenability to technology disruption e.g. continuous processing and readily available supply chain data serves to highlight the drug candidates with highest potential for reconfiguration in order to compare reconfiguration opportunities and future states/scenarios with current states.

Using this candidate drug selection rationale, a shortlist of potential candidates for future research was determined. In summary:

- Step 1: **369** oncology drugs were identified as being currently in the pipeline (i.e. in clinical test or at commercialisation). At the molecule level, a deletion of duplicates from competing brands or combinations resulted in **144** molecules of interest.
- Step 2: the focus of this research e.g. small molecules consisted of **110** of these 144 candidates
- Step 3: **47** of the 110 small molecules had current state 'data' readily available
- Step 4: Assessment of the business case led to the selection of **7** candidate drugs from the 47 shortlisted drugs e.g.

    - 'XAP' – high cost personalised product under patent, with a very low target population,
    - 'AXP'- product under patent, with high cost/low target population
    - 'SUP' – product under patent, high cost/low target population, facing generic competition in the short to mid-term future.
    - 'EPG' – product recently off patent, large target population (breast cancer)
    - 'CYG'- product off patent, facing high competition
    - 'PAG' – high volume generic drug, with a long cycle time
    - 'MEG' – high volume generic drug, applicable to many forms of cancer treatment

Case study analysis

Three emerging product-process archetypes in oncology previously reported (Harrington and Najim, 2014) formed the basis of this study i.e. in terms of supply network design, current-state supply and value network mapping techniques were used to define the existing sub-systems for these archetypes (e.g. Clinical trial, Primary, Secondary, Packaging and E2E) and the drivers/design factors in each sub-system. This enabled an end-to-end network performance analysis to be performed in addition to defining overall system metrics to challenge the current state configuration design parameters and trade-offs being made (illustrated in figures 2-4).

An initial assessment of future/alternative processing models was then conducted where alternative chemical process scenario analysis considered opportunities for e.g. more flow-through continuous processing. These scenarios were evaluated in terms of a 'delta' or relative benefits against key system level operational benefits that might emerge. This step in the process generated potential step change possibilities in the key metric(s) or impact variable under consideration (e.g. inventory, lead-time supply etc. - see figures 1-3)

New Niche					
Conti Impact Variables	**linical Trial**	**Primary**	**Secondary**	**Packaging**	**E2E**
Inventory	✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
Lead time supply	✔✔	✔✔	✔✔	✔✔	✔✔
Lead time to market	✔✔	✔✔✔	✔✔✔	✔✔	✔✔✔
Scale-up (going into)	✔✔	✔✔✔	✔✔✔	✔✔	✔✔
Volume Flexibility (mix and volume)	✔	✔	✔✔	✔✔✔	✔✔
Process Control; Reliability; Safety	✔	✔	✔	✔	✔
Quality; Purity; Consistency	✔	✔	✔	✔	✔
Yield	O	O	O	O	O
IP Protection/extension/counterfeits	O	O	✔✔	✔✔	✔✔
Cost (Proc/Pkg/Transport)	✔✔	✔✔	✔✔✔	✔✔✔	✔✔
Investment Cost	O	O	O	O	O
Fiscal/Tax	O	O	O	O	O
Environmental impact/solvent	O	O	O	O	O
Mobility/adaptability	✔	✔	✔✔✔	✔✔✔	✔✔
Asset Utilisation	O	O	O	O	O

Fig. 2. "New niche" product-process archetype – potential areas of benefit

The '*New Niche*' archetype – see fig. 2 (incorporating inputs from 'XAP', 'AXP' and 'SUP') - exhibits a high potential benefit in lowering inventory (from primary to E2E). Other potential benefits are proposed e.g. lowering lead-time to market (primary, secondary and end-to-end), easier scale up (primary and secondary), cost (secondary, packaging) and mobility/adaptability (secondary, packaging). This segment has also potential in

clinical trials and in unlocking new therapy areas, and to be able to scale up accordingly, in a potentially easier manner. Inefficient supply chains, driven by the drug patent state may be improved e.g. lowering very high inventories, cost, and preparing for future generic competition.

The '*Old Niche*' archetype – see fig. 3 (incorporating inputs from 'EPG' and 'CYG') - presents highest potential benefit in enhanced process control, reliability and safety (across all of the sub-systems), and improved quality, purity and consistency (in terms of secondary, packaging and E2E), which may help lower shortages' frequency. Cost reduction potential (especially in primary) may help this segment regain recently lost economic incentives (e.g. from loss of patent). There is potential in unlocking therapy areas, supported by medium potential benefits for easier scale-up.

Old Niche

Conti Impact Variables	Clinical Trial	Primary	Secondary	Packaging	E2E
Inventory	✔	✔✔	✔✔	✔✔	✔✔
Lead time supply	✔	✔	✔	✔	✔
Lead time to market	✔	✔	✔	✔	✔
Scale-up (going into)	✔✔	✔✔	✔✔	✔✔	✔✔
Volume Flexibility (mix and volume)	✔✔	✔	✔✔	✔✔	✔✔
Process Control; Reliability; Safety	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
Quality; Purity; Consistency	✔✔	✔✔	✔✔✔	✔✔✔	✔✔✔
Yield	O	O	O	O	O
IP Protection/extension/counterfeits	O	O	✔✔	✔✔	✔
Cost (Proc/Pkg/Transport)	✔✔	✔✔✔	✔✔	✔✔	✔✔
Investment Cost	O	O	O	O	O
Fiscal/Tax	O	O	O	O	O
Environmental impact/solvent	O	O	O	O	O
Mobility/adaptability	✔	✔	✔✔	✔✔	✔✔
Asset Utilisation	O	O	O	O	O

Fig. 3. "Old Niche" product-process archetype – potential areas of benefit

The '*Established Generic*' archetype – see fig. 4 (incorporating inputs from 'PAG' and 'MEG') - exhibits highest potential benefit in enhanced process control, reliability, safety; and improved quality, purity, consistency (across all the sub-systems). This may help lower the frequent recalls and shortages that are occurring in this segment and drive cost reduction (from primary to E2E).

Established Generic

Conti Impact Variables	Clinical Trial	Primary	Secondary	Packaging	E2E
Inventory	✔	✔	✔	✔	✔
Lead time supply	✔✔	✔✔	✔✔	✔✔	✔✔
Lead time to market	✔✔	✔✔	✔✔	✔✔	✔✔
Scale-up (going into)	✔✔	✔✔	✔✔	✔✔	✔✔
Volume Flexibility (mix and volume)	✔✔	✔	✔	✔	✔
Process Control; Reliability; Safety	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
Quality; Purity; Consistency	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
Yield	O	O	O	O	O
IP Protection/extension/counterfeits	O	O	✔✔	✔✔	✔
Cost (Proc/Pkg/Transport)	✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
Investment Cost	O	O	O	O	O
Fiscal/Tax	O	O	O	O	O
Environmental impact/solvent	O	O	O	O	O
Mobility/adaptability	✔	✔	✔	✔✔	✔
Asset Utilisation	O	O	O	O	O

Fig. 4. "Established Generic" product-process archetype – potential areas of benefit

Conclusions

An analytical framework, previously developed and tested for large volume Pharmaceutical candidates, was used as part of this study to explore value chain reconfiguration opportunities for a series of oncology candidates and scope out implications for supply network design. A series of candidates that are representative of the wider oncology market e.g. including low volume, niche, patented drugs with high QALYs (quality-adjusted life years) through to higher volume generics with a history of shortages were selected.

Current state profiles for seven oncology drug candidates were developed, capturing the critical sub-systems that may be affected by a shift to e.g. continuous manufacturing using a range of scenarios that could emerge by adopting alternative product-process-business model innovations. These alternatives were based on emerging process and production technologies or even technologies that are still yet to be fully developed (initial focus on continuous processing and crystallisation in pharmaceuticals here).

Building on previous scoping studies, this research have shown oncology candidates to 'cluster' into distinct groupings exhibiting very similar areas of benefit and at similar scale. These 'product-process archetypes' – classified as '*New Niche*', '*Old Niche*' and '*Established Generics*', in an oncology context - provide a simple classification system that may enable the classification of *other* drugs, with comparable characteristics, to benefit from similar technological interventions and supply network design.

Future work

This research aims to utilise a well-understood linkage between technology platforms and final product innovations. However, limited attention is paid to the *industrial system* that 'connects' technology developments to final products e.g. how the *value chain* (VC) reconfigures to provide a linkage between technologies and technology options to product iterations. The approaches, presented in this paper, will be extended to a set of in-depth case studies involving additional drug candidates (e.g. Metformin, Paracetamol, Piroxicam, Caramazepine, Carvedilol, Albendazole, Fenofibrate, Lactose, Budesonide and Ibuprofen), in order to (a) explore current and future state VC considerations and (b) develop a series of "value chain roadmaps[3]", which may be both generic sector summaries and product (category) specific.

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[3] In the context of this research, "VC roadmaps" are defined as a visual representation, through time, of (disruptive) changes in 'activities' and 'actors' across the VC, typically as a result of technological changes (i.e. product, process) and/or a network reconfiguration of actors - usually resulting in the emergence of new products.

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