

# Emerging product-process archetypes in oncology: informing the sustainable provision of next- generation medicines

## **Abstract:**

The emergence of more targeted molecular therapies has contributed to accelerated growth within the oncology market. Projected to become the leading therapeutic area by 2017, forecast spends are expected to be in the range of \$74-84 billion. Coupled with its many specificities around pricing, insurance implications, and ethics, we argue that the oncology segment may best inform future pharmaceutical value network design characteristics - in supporting the sustainable manufacture and supply of next-generation medicines. Through exploration of future state scenarios and opportunities areas, driven by the adoption of emerging process and digital technologies, a base framework is extended to enable a systematic assessment of a series of candidates representative of the wider oncology market. These include niche, low volume drugs on-patent with high QALYs (quality-adjusted life years), through to higher volume generics with a history of supply shortages. A series of emerging product-process 'archetypes' in oncology are proposed – classified as 'New Niche', 'Old Niche' and 'Established Generics' – with associated models for reconfiguration, based on the clustering of potential supply benefits. A key application of this systems approach is the potential of informing economies of drug 'repurposing', through its extension from commercial to drug discovery, development and clinical trial contexts, and in matching emerging process capabilities to future adaptive supply requirements – for the sustainable provision of next-generation medicines.

**Key words:** Pharmaceuticals; Oncology; Value networks; Sustainable Industrial Systems; Futures

## **1. Introduction**

The Pharmaceutical industry landscape is continuing to face many business challenges, and these have been widely reported in the academic literature (Shah 2004; Singh 2005; Castner et al. 2007; Cepton Strategies 2009; Pedroso and Nakano 2009; KPMG 2011; Rossetti et al. 2011; Mayer 2012; Susarla & Karimi 2012; Scheel et al. 2013; Narayana et al. 2014; Srαι et al., 2015; Daly et al., 2015; Harrington, Philips, and Srαι 2016). A defining feature has been the decline of the 'one-size-fits-all' 'blockbuster' model: of the top twenty highest-grossing products in 2012, eighteen will have come off patent c. 2015 (Ehrhardt et al. 2012). This typically equates to a loss of 80% of volume in the first year, or worse still, 70% loss in just 45 days for Eli Lilly's Prozac (Singh 2005). Ehrhardt et al. (2012) also forecast that \$400 billion of revenues will be exposed to generic competition by 2015, with additional estimates that the industry could lose \$150 billion to generics between 2012 and 2018 (Mayer 2012). Furthermore, it is now rare to find such blockbuster drugs in the R&D pipeline, as the

market for high volume therapeutics is saturated with many existing options available to the patient (Shah 2004; Singh 2005; Ehrhardt et al. 2012).

In contrast, the oncology segment is growing at a faster rate. It has also made most progress in embracing a 'precision-medicine paradigm' – with the potential of informing 'proof of concepts' that may allow the rapid test and validation of new and existing treatment approaches across a variety of disease settings and patient cohorts (Huber and Howard 2016). With its many specificities (e.g. pricing, insurance implications, ethics issues), it is argued that this segment may best exhibit the characteristics of next-generation medicines (defined here as niche, personalised, low volume, targeted for sub-populations). The segment is also representative of growing complexity – with more than 300,000 new cancers (excluding skin cancers) diagnosed annually in the UK, across over 200 different cancer types (NICE 2016). Cancer is also now the leading cause of death worldwide, estimated to be in the order of 13%, with incidence rates also increasing globally - annual cases are predicted to grow from 14 million in 2012 to 22 million by 2032 (American Cancer Society 2011; WHO 2014). As a consequence, the oncology segment is fast becoming one of the major therapeutic areas in the pharmaceutical industry, capturing 31% of all R&D effort (Scheel et al. 2013), and experiencing the fastest growth amongst other therapy areas (KPMG 2011). Indeed, the oncology market is forecast to account for \$74 billion spending in developed countries per annum - making it the leading therapy area by 2017 (IMS Institute for Healthcare 2012). Furthermore, by 2020 targeted therapies and immunotherapies are expected to make up more than 70% of oncological treatments (Van Dyck et al, 2016).

The 'value network' is used as the basis in conducting our investigation. While Porter (1980) defined the 'value chain' to be "*the entire production chain from the input of raw materials to the output of final product consumed by the end user*", in studies of the pharmaceutical sector, 'network' terminology is now commonly used, with activities increasingly spread across networks of specialised firms (Edwards 2009; Harrington, Philips, and Srai 2016). Previous studies in pharma have largely focused on well-established drug products, with production volumes in the order of 100-10,000 tonnes/annum (Srai et al 2015). In line with the emergence of targeted molecular therapies to treat numerous sub-types of cancers, often with very small patient populations (Trusheim and Berndt 2012), this study focuses on the low – medium volume oncology (chemotherapy) segment. An analytical framework is adapted and extended to enable a systematic assessment of a series of candidates that are representative of the wider oncology market. These include niche drugs that are on patent, manufactured in low volume, with high QALYs (quality-adjusted life years) through to higher volume generics with a history of supply shortages. As the same molecular targets and pathways are often involved in driving two or more types of cancers that develop in different tissues or organs, the off-label use of drugs in oncology is now commonplace, as specialists increasingly investigate such possibilities (Casali 2007). Furthermore, with advances in DNA sequencing, and mutation identification, the idea of 'precision oncology' renders certain cancers vulnerable to already approved molecular medicines (Hall 2017). Hence, the selection process, developed as part of this study, also enables an exploration of 'adaptive' clinical trials in oncology - in that, the segment has the potential to

inform enormous economies of drug ‘repurposing’ - using a drug that has been approved to treat one particular disease to treat another quite different disease (Huber and Howard 2016).

Value network reconfiguration opportunities and future sustainable manufacturing scenarios - smaller, more cost-effective facilities (‘continuous’ processing; micro-factories), using smaller quantities of expensive ingredients and less energy, with more control over the final product quality and performance (Harrington, Philips, and Srai 2016) - are explored in these contexts.

The paper is structured as follows: Section 2 summarises pharmaceutical industry characteristics and the specificities of oncology, from the academic literature, to inform the development of both *Commercial Pharma* and *Oncology Value Networks*, the research question and aims of the study. Section 3 summarises the research methodology, and the 3-step approach employed. Section 4 outlines framework extension with respect to application and refinement in an oncology context. Section 5 presents our results and interpretations, involving a series of oncology product-process archetypes. Section 6 discusses current reconfiguration opportunities across the oncology value network, and how specificities in oncology may inform the future of Pharmaceutical industry. Finally, Section 7 presents conclusions, study limitations and future research activities.

## **2. Literature Review**

This section reviews the current state of knowledge derived from the literature in order to provide the relevant dimensions of analysis for the investigative phases of this research. Subsection 2.1 examines the pharmaceutical sector as a whole, representing key insights in the form of a value network. The focus of this paper – the oncology segment – is presented in more detail in 2.2, and how it differs from the wider pharmaceutical sector is outlined. This value network representation is then used in section 3 to frame the ‘current state’ of the sector, and in evaluating a set of future state scenarios based on the adoption of emerging process and digital technologies in section 4.

### **2.1. Pharmaceutical sector characteristics**

The main insights from the literature on the wider Pharmaceutical sector are summarised in figure 1. For ease of analysis, these are presented in the form of a *commercial pharmaceutical value network*, based on a mapping convention previously reported and used to represent a series of complex industrial systems across a number of different sectors (Srai et al., 2016; Srai 2017).

### **2.2. Oncology segment specificities**

This section summarises specific oncology market drivers and challenges from the academic literature, informing both the key actors, and activities - critical to the oncology value network. Oncology specificities were identified and classified, from the academic literature, and are summarised here in the following sub-sections, namely:

- Market growth in oncology
- 'Innovation movement'
- Economic incentives
- Insurance, ethics, shortages, and counterfeits

Based on insights from sub-sections 2.1.1 - 2.1.3, an alternative *oncology value network* is constructed, which is used as the basis of framing the 'future state', in terms of scenarios and opportunity areas in section 3 – see figure 2.

### 2.2.1. Market growth in oncology

An aging population has seen an increase in the prevalence of chronic illnesses, such as Diabetes, Cardio-Vascular diseases, and Cancer (Paul et al. 2013). For the oncology segment, QuintilesIMS (formerly know as IMS Health) (2012) reported growth of 6-15% between 2008 and 2013, as opposed to 1-7% for the wider pharmaceutical industry. In terms of other specific therapy areas, KPMG (2011) forecasts that the oncology market will continue to grow faster than others: 5-8% annually between 2010-2015 compared to 1-4% for Cardio-Vascular drugs. Furthermore, Bagwell et al. (2011) reported that oncology drugs went from 10% sales of the top 100 best-selling drugs in 1998, to 18% in 2009.

In terms of spending, QuintilesIMS forecast figures of between \$74-84 Billion in 2017 for developed nations, making it the leading therapeutic area, with the major drivers being increased incidence of cancer and therapeutic development (Jemal et al. 2010). Emerging markets are also gaining importance and influence across the wider Pharmaceutical sector (Ebel et al. 2013; Kandybin & Genova 2012; Cepton Strategies 2009; Arnum 2010). Indeed, KPMG (2011) forecasts such markets will make up 30% of the wider market by 2020, versus figures of 12% in 2010 – equating to an annual growth rate of 14% between 2010 and 2015, with revenues growing from \$170 billion in 2011 to \$230 billion in 2016 against an increase in the traditional markets from \$545 billion in 2011 to \$660 billion circa. 2016 (Ebel et al. 2013).

Converging and synergistic advances in biochemistry and digitalisation are enabling the creation of precisely targeted drugs, and tailoring their use to individual patients (Huber 2013). Another indication of growing importance is orphan drug designations, i.e. a pharmaceutical product aimed at rare diseases or disorders. In the EU, 50% of the top 20 indications fall within the cancer categorisation - with Non-Hodgkin's lymphoma (NHL) the indication most filed (EvaluatePharma 2015).

### 2.2.2. 'Innovation movement'

The concept of '*innovation movement*' is defined here as the combination of R&D dynamism, actor engagement, societal benefits recognition, and institution incentives, and is viewed as an essential driver in an oncology context. This phenomenon has lead to the development of new medicines, which have contributed to a 50-60% increase in cancer survival rates, over the last 40 years (Picard and Tarab 2012). Furthermore, Lichtenberg (2014) suggests that those cancers, attracting the most

research interest, have experienced the greatest reduction in mortality - illustrating the societal benefit driving innovation in oncology (e.g. overall a 14% reduction in cancer mortality from 2000 to 2009).

As well as institutions and foundations (e.g. National Cancer Institute in the US, and Cancer Research UK) actively participating in innovation – through fundamental research and clinical trials, which are often purposely smaller, shorter and cheaper (Light and Kantarjian (2013), state-bodies and regulators also play a major part in incentivising oncology innovation. For example, the FDA has created several regulatory mechanisms to accelerate drug approval, especially in chemotherapy for late-stage malignancies (Senderowicz and Pfaff 2014; Horning et al. 2013). Consequently, this has resulted in oncology drugs constituting 25% of new approved drugs in the US, while they only account for 9% of drugs pending approval (QuintilesIMS 2012). Innovation around more ‘adaptive’ trials, with the potential of being integrated into clinical treatments that specialise in treating particular diseases is a focus (Huber and Howard 2016). A series of research programmes in UK (e.g. ReMediES: Reconfiguring Medicines End-to-End Supply) are looking to extend this ‘adaptive’ concept to clinical trial protocols and supply, which if designed to be flexible enough, may enable the investigation of different dosages and combinations, and identify opportunities for multi-drug therapies and other aspects of how a new or existing drug may be used.

Despite these initiatives, there are frequent calls for a need to reform the current complex system in order to achieve an appropriate and sustainable level of innovation in the global oncology enterprise (Garrison Jr 2009). Trusheim & Berndt (2012) argue that recent development of targeted therapies with smaller populations has resulted in (justified) premium pricing in order to recover R&D costs. In contrast, Light & Kantarjian (2013) disagree, arguing that taxpayers subsidise half the research in cancer, and state bodies pay for most of the basic research, thus, high prices are emerging from economic incentives.

### *2.2.3. Economic Incentives*

As outlined in the previous section, in order to fully understand the incentives to promote technology interventions and innovation in oncology, it is important to understand how these factors are tied together by the concept of economic value and sustainable provision in an increasingly global context (Garrison Jr 2009; Harrington, Philips, and Srari 2016). Important considerations relating to pricing and reimbursement policies in the oncology market, the role of the patent system, and how policies may affect incentives for R&D, should be incorporated into any business case assessment (Garrison Jr).

Bagwell et al. (2011) argue that revenue per cancer patient fuels the industry, and is steadily increasing – the average price for the top 10 branded prescription drugs has grown by approximately 14% to \$3,500 between 2007 and 2010). QuintilesIMS reported that the cost of branded oncology drugs has doubled in 10 years - from \$5,000/month in 2003 to \$10,000/month in 2013, while Icore Healthcare (2010) estimating the trend of increase in the cost of Injectables to be in the range of 11-34%. Furthermore, due to its specific nature, Danzon & Taylor (2010) argue that the patents and the level of insurance coverage for oncology drugs has resulted in lower price-sensitivity in patients and

professionals, allowing the firms to meet target sales with high prices. For Light & Kantarjian (2013), this is especially true in the US, where prices are usually twice those of Europe and Canada (congress prohibits against Medicare i.e. The American Public Health Insurance negotiating discount prices on drugs). This constitutes extra earnings, as they argue pharmaceutical companies can make healthy profits at European and Canadian prices, but still charge more in America (ibid).

#### 2.2.4. Insurance, Ethics, Shortages, and Counterfeits

High costs and pricing in oncology has raised many issues from an Insurance and Ethics point of view (Mackey & Liang 2012). Indeed, as oncology drug costs soared, insurers experienced increasing financial pressure (Trusheim & Berndt 2012). This has resulted in an increased cost-sharing (i.e. the portion of a drug price paid by the patient) to 20-25%, resulting in an increased price sensitivity from patients and oncologists (Light & Kantarjian 2013; Garrison 2010).

Brock (2010) and Danzon & Taylor (2010) warn of the possible financial risks of such measures for patients, when products are costly, coupled with lower access to appropriate therapies. This results in many ethical issues, which ultimately lead to the development and refinement of a set of methods broadly known as “Cost-Effectiveness Analysis”(Garrison 2010), which involves e.g.

- A relative indicator, *the Incremental Cost Effectiveness Ratio (ICER)*: comparing the added cost of a new therapy, versus the standard, and in light of additional health benefit(s)
- An absolute indicator, *the Cost/Quality Adjusted Life Year (QALY)*: transforming a drug’s health benefit into a common measure (i.e. Quality Adjusted Life Year, by adjusting life years gained for changes in the quality of life from treatment e.g. immobilisation in bed) and comparing this to the cost the drug

Brock (2010) argues these will help the scarce societal resources to be used in an effective way, as they should not be focused on last chance, very high cost, low benefit treatment (i.e. new pricy oncology drugs that extend life by a couple of months at a high cost). For instance, the National Institute for Health and Clinical Excellence (NICE) recommends coverage for drugs with a Cost/QALY lower than £30,000/QALY.

In addition to issues around *cost* and *ethics*, the oncology segment experiences frequent shortages in essential drugs (e.g. Methotrexate, Paclitaxel). The sector ranks second in terms of shortage (Anna Gu et al. 2011), and generics are the drug segment with the highest incidence rate (Gatesman & Smith 2011). These shortages originate from multiple reasons, e.g.

- Lack of financial incentives driving cost-containment in production through use of old production lines and lower inventories (Gatesman & Smith 2011; Chabner 2011; Mackey & Liang 2012a; McKeever et al. 2013);
- Increased demand for generics stressing existing scarce production lines (Chabner 2011);
- Quality issues (Mackey & Liang 2012).

These not only result in preventing patients from receiving appropriate treatment, but also have numerous other effects, e.g. increased cost of healthcare through use of higher cost brand-name drugs as a replacement, and increase in time and effort required to manage the shortages e.g. estimated \$216 million additional spending in the US in 2010 (Gatesman & Smith 2011); and increased prevalence of the grey market (i.e. distribution channels which, while legal, are unofficial), especially from Internet, with sometimes 3,000% mark-up on drugs, exacerbating the incentives for counterfeits (Chabner 2011; Mackey & Liang 2012).

### **2.3. Mapping the Oncology Value Network**

The previous sections summarised the literature related to the wider pharmaceutical sector, and oncology segment in particular, in order to first understand the current business context and its criticality. It also captured the different challenges, drivers and possible opportunities and future trends in order to allow a deeper understanding of the future vision.

To do so, we adapt an analytical framework previously developed, to extend to an oncology context. Based on section 2.2 an *oncology value network* is constructed, which is used as the basis of framing the 'future state', in terms of scenarios and opportunity areas in section 3. In summary, this paper aims to address the following research question:

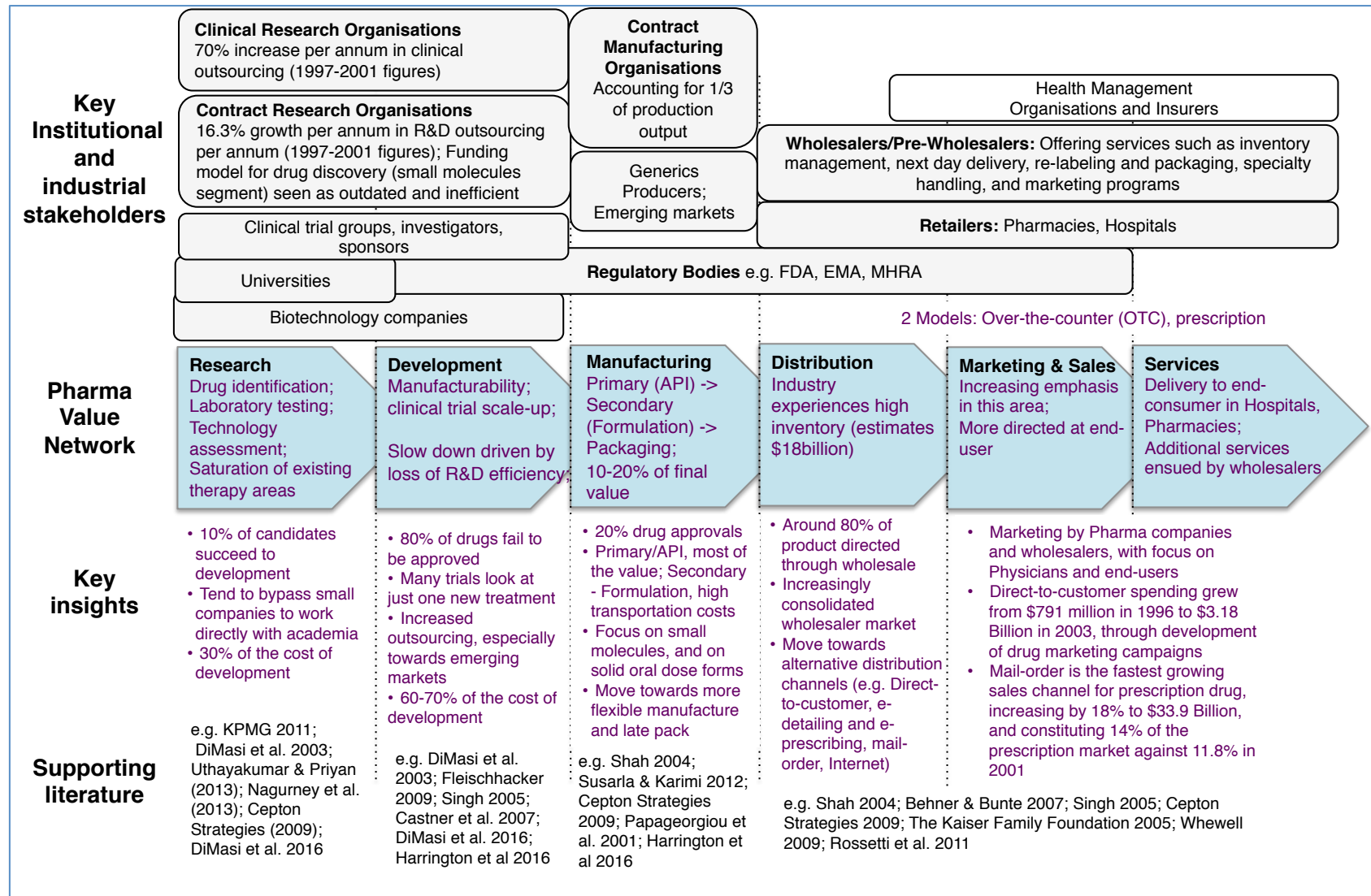
#### **RQ: How may specificities in oncology inform next-gen pharma value networks and the future industrial system?**

To answer this research question, the following sub-questions are explored:

- What are the current reconfiguration opportunities across the oncology value network?
- How may an analytical framework be adapted for oncology to detect and evaluate these opportunities?
- How may reconfigurations opportunities and specificities in oncology best translate to inform the future of Pharmaceutical industry (i.e. development of oncology product-process archetypes)?

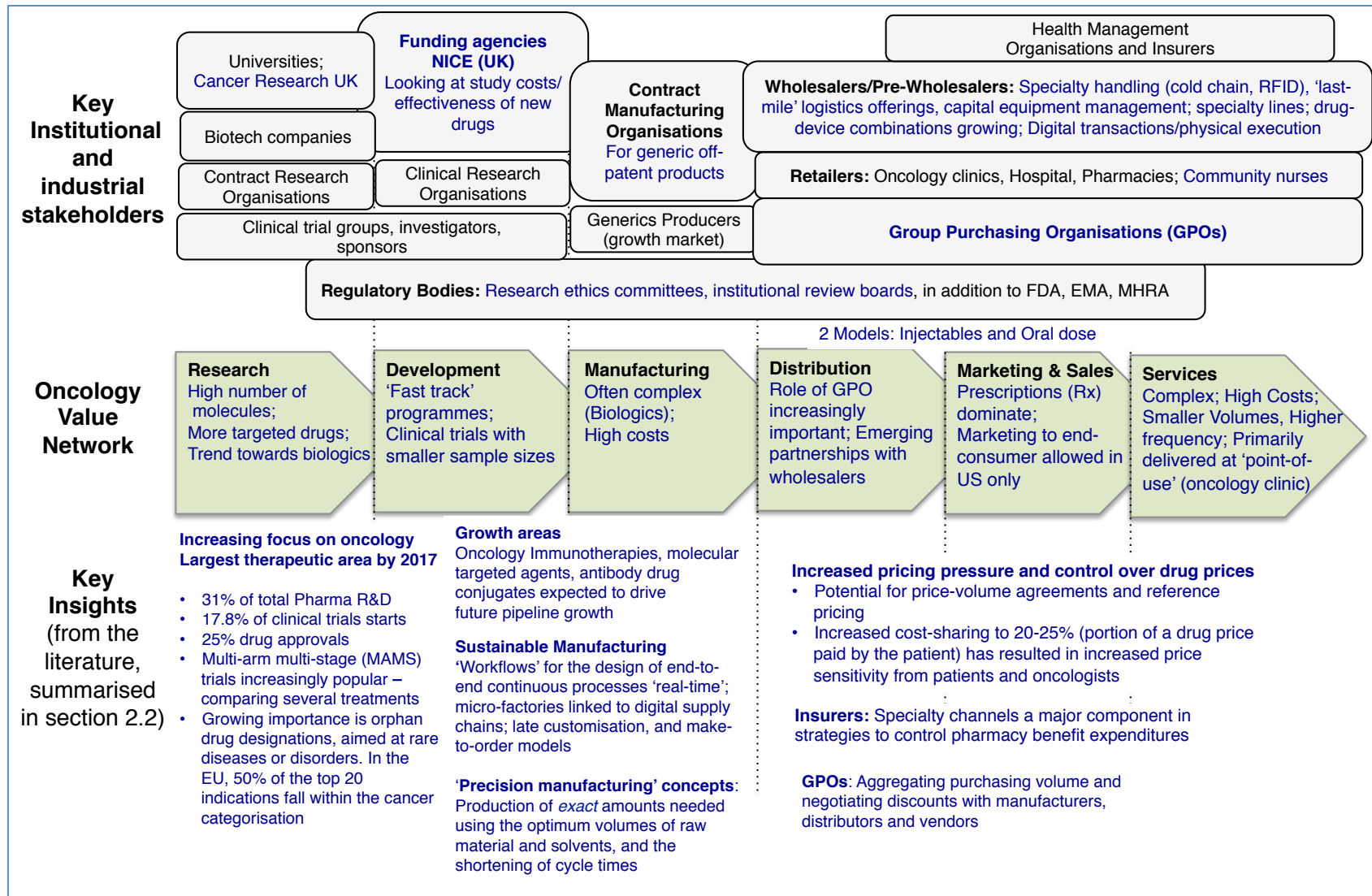
The overall aim of this research is to identify product-process archetypes for the oncology segment, to identify reconfiguration opportunities across the Oncology value network, and inform the future structure of the wider Pharmaceutical sector.

**Figure 1.** Framing the 'current state': representation of a commercial pharmaceutical value network – key stakeholder mapping and insights from the academic literature





**Figure 2.** Framing the ‘future state’: representation of an oncology value network – key stakeholder mapping and insights from the academic literature



### 3. Research Methodology

This section summarises the research methodology (philosophy, approach, rationale, and strategy) that has been used in this paper. An empirical approach is preferred and an interpretivist philosophy is adopted as the study uses business context and real case applications to explore future of the pharmaceutical and oncology value networks, which are both human constructions (Kothari 1990; Remenyi 1995; Meredith 1998; Myers 2008; Pizam & Mansfeld (2009).

The research was specifically focused on the oncology segment, within the wider pharma sector, and involved a 3-step approach. In summary:

- Firstly, as set out in the literature review section, secondary data (academic journals in addition to reports and online resources) was used in order to generate a prototype commercial pharma and oncology value networks – see figures 1 and 2.
- The next step involved adopting a methodology in order to inform the underlying rationale for the oncology drug candidate selection process, based on the idea of *sub-systems integration* (Srai et al 2015; Harrington, Philips, and Srai 2016), was used as a base framework to capture and test the potential of specific value network reconfiguration opportunities. In determining the oncology case studies with the highest potential outcomes, selection criteria included i.e.
  - Candidate(s) representative of the wider oncology segment, with low-medium volume and differing SKU profiles
  - Candidate(s) with interesting business case for reconfiguration to add substantial value in an oncology context e.g. opportunities for repurposing
  - Candidates with a sufficient amount of data to be able to conduct the case study (This is especially critical in oncology, where specific data on products and value networks is often very difficult to access due to commercial sensitivities)
  - Case studies with higher probability to undergo technology-enabled reconfigurations, e.g. exhibiting viable business cases to benefit from a specific technology disruption (moving from traditional batch manufacturing paradigm to more sustainable manufacturing practices, such as continuous processing, in the context of this study)
- Finally, semi-structured interviews were then used, in order to get a better coverage of the different aspects and dimensions, allow addition of new information (i.e. exploratory aspect), and dig deeper into specific areas of the study. Interviewees were also selected based on specific criteria e.g. (a) subjects were currently in, or recently held, a senior (managerial/technical) role in pharma/healthcare, (b) had relevant experience/knowledge of wider pharma and oncology segments, and (c) had an understanding of acute and chronic diseases, and their respective treatments. This ensured appropriateness and enabled capture of a broad range of perspectives across both value networks (wider pharma and oncology)

and specific drug candidates that were selected. In total, ten interviews were completed, details of which are summarised in table 2.

**Table 1.**

<b>Interview</b>	<b>Organisation</b>	<b>Role</b>	<b>Focus/insights</b>
1	Academia (UK)	Research on technology interventions and value network reconfiguration	Sustainable manufacturing practices such as continuous process technologies— pharma and oncology contexts
2	Public Health (Europe)	Oncologist	Specificities and validation of the oncology value network mapping exercise
3	Multi-national Pharma	Plant Manager - Continuous Manufacturing	Sustainable manufacturing practices - continuous processing
4	Public Health (Europe)	Oncology manager	Specificities and validation of the oncology value network mapping exercise
5	Multi-national Pharma	Marketing and Sales	Expert opinion, assessment and validation for case studies data
6	Multi-national Pharma	Supply Chain Manager	Expert opinion, assessment and validation for case studies data
7	Multi-national Pharma	Supply Chain Manager	Expert opinion, assessment and validation for case studies data
8	Public Health (Europe)	Oncology Manager	Specificities and validation of the oncology value network mapping exercise
9	Multi-national Pharma	Chemical Engineer	Continuous manufacturing feasibility assessment in case studies
10	Multi-national Pharma	Former head of global supply chain	Continuous manufacturing feasibility assessment in case studies; Specificities and validation of the oncology value network mapping exercise

Christensen (1997) and Doorneweert (2012) claim disruptive innovation makes it possible to challenge existing value networks and replace them with new networks. Application of the base framework, in conjunction with review of the value networks, was used to examine current and future state scenarios. With successful implementation not solely dependent upon the technical requirements of each process step, it is critical that the business case and impact on current industry value network configuration(s) were well understood and captured (Harrington, Philips, and Srai 2016).

Future state scenarios, supporting a tailored future configuration aligned with the specific benefits identified enabled through the adoption of sustainable continuous manufacturing concepts in pharmaceutical industrial were used to evaluate reconfiguration opportunities for each sub-system (i.e. clinical trials, primary manufacture, secondary processing, pack/distribute, and end-2-end supply) versus a set of impact variables. The purpose of this step was to present a holistic view on the possible opportunities for reconfiguration, and propose *product-process archetypes* from the analysis.

#### **4. Base framework extension - Candidate selection**

Section 4.1 focuses on framework extension with respect to application and refinement in an oncology context. Section 4.2 then presents the output from application of the this extended framework, in selecting the candidate drugs from the available oncology therapies, then using the base framework to analyse the candidate drugs selected.

##### ***4.1. Base framework extension – Oncology context***

This section first briefly summarises refinements of the base framework changes in an oncology context. A selection process was first required to inform more targeted criteria in oncology in terms of business cases, data availability, and applicability of technology disruption for value network reconfiguration opportunities. For the purpose of this research, special focus was placed on developing an alternative business case – based on the adoption of alternative technologies. More flexibility was allowed on criteria such as supply chain data availability, because of the nature of the oncology segment (data protection). The 4-stage process of selection is outlined as follows:

- Stage 1: Assessment of different oncology drugs at a molecule level, deleting duplicates from drugs produced by different manufacturers, as well as drug combinations
- Stage 2: Drug segmentation constitutes the next selection criterion. Two segments exist: e.g. small molecules and biologic drugs. For small molecules, production processes are often well known and straightforward, while biologics are often produced through very complex, difficult to certify processes (Garrison 2010). Here, we focus on small molecules, as they are more amenable to a continuous manufacturing disruption – from an economic and/or environmental point-of-view. However, they are more subject to generic competition (because of the low barrier to entry after patent expiration compared to a higher manufacturing barrier to entry in biologics).
- Stage 3: First data availability screening examined process chemistry, data availability and molecule chemistry. The objective here was to understand the production or chemical process for synthesising the drug with special focus on API, as it encompasses most of the value (Singh 2005). Access to data is critical in order to evaluate the opportunities for amenability to a technology disruption
- Stage 4: the drugs' business context is examined. By capturing e.g. target population, therapy area, price, patent state, re-purposing opportunities, the aim was to detect interesting business states that may benefit from a possible reconfiguration (e.g. inaccessible drug because of price or cost, drug with frequent shortages), and amenability to a technology disruption e.g. feasibility of manufacturing the drug product in an alternative way (batch -> continuous). Availability of supply chain data served to highlight the drug candidates with highest potential for reconfiguration, with enough data to compare reconfiguration opportunities and future states and scenarios with current states.

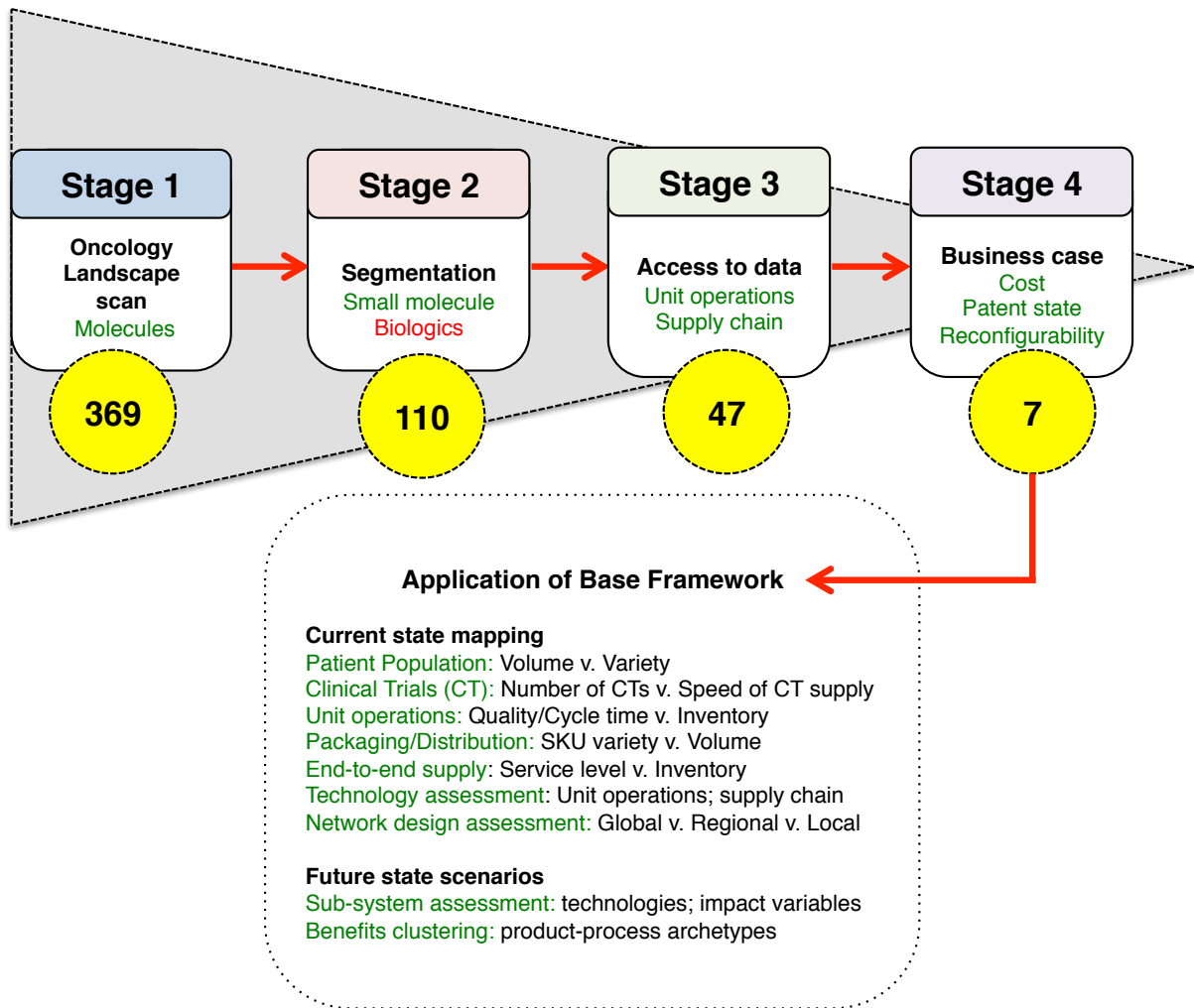
In extending the base framework to an oncology context, this research introduces a *Clinical trials/Supply Chain speed* analysis - comparing the volumes of clinical trials being launched to the speed of the clinical trial supply chain. This analysis reveals the potential speed and ease of testing the drug, and highlights the extent of opportunities in unlocking new therapy areas, and in promoting future adaptive clinical trial protocols and supply. Business case assessment, as part of the framework, was also adapted to take into consideration a series of subtleties and specificities with respect to the oncology market. It is proposed that the following components should be investigated:

- The measure *Cost/QALY* is proposed to assess the business case in relation to increasing drugs' cost. This is particularly critical in oncology, where it is regarded as a good indicator of cost of the drug, its efficiency, its accessibility to target population, and its financial burden on insurers and payers
- Not only are *clinical trials* an important component of oncology (high volume of these in progress), but also, they indicate potential scale ups when drugs are approved, and in unlocking new therapy areas
- *Drug heritage*, as well as the *patent state*, is argued to be important component as they can offer a better understanding of the drug profile, production configuration, economic incentives, and possible exclusivity.

#### **4.2. Application of the extended base framework - Oncology candidate selection**

A shortlist of oncology drug products was selected for this research, through application of the extended base framework. These candidates were representative of the wider oncology segment - including generic drug products with medium-high volumes, through to lower volume, niche and patented variants. An overview of the selection process is presented in Figure 3. In summary:

- *Landscape scanning*: 369 oncology drug products currently in the pipeline (i.e. in clinical test or commercialised) were assessed at the molecule level. A deletion of duplicates from competing brands or combination drug products resulted in refining this list down to 144 molecules of interest.
- *Segmentation*: For the purposes of this study, biologics were excluded at this stage of investigation. The small molecules segment made up 110 of these 144 candidates of interest
- *Access to data*: 47 of the 110 remaining drug candidates were found to have readily accessible supply chain, manufacturing unit operations data, or reported chemical production processes.
- *Business case*: From these 47 shortlisted drugs, focus on the oncology business case as per the criteria set out led to the final selection of 7 candidate drugs for this research. Table X summarises the profile of each candidate. The commercial names of the drug products have been anonymised for data protection purposes.



**Figure 3:** Selection process – identifying 7 oncology candidates shortlisted for this research

**Table 1:** Profile of Oncology drug product case studies

Drug	Patient population	Therapy area	Firm Profile	Patent state	No. of Clinical trials	Cost/QALY	SKU Mix	Supply Chain configuration insights; sources	Production process mapping insights; sources
<b>XAP</b>	500,000	Non-small cell lung cancer; highly personalised, very low target population	Single firm	Patent until 2025	28	\$170k	2	Production and packaging integrated; Worldwide production at 1 facility; Potential for major scale up based on current clinical trials; Interviews and secondary data sets	50% of the overall process (unit operations) is known; technical challenges (heterogeneous phase chemistry); Medium amenability of process to technology disruption
<b>AXP</b>	750,000	Renal cell carcinoma (RCC)	Single firm	Patent until 2020	28	\$160k	2	Production and packaging integrated. Worldwide production in 1 facility. Potential for major scale up based on breast cancer clinical trials; Interviews and secondary data sets	7-step process; 60% Yield; Very low amenability of process to TD: Low API volumes, technical challenges (heterogeneous phase chemistry)
<b>SUP</b>	3.6 Million	RCC; Gastrointestinal stromal tumours (GIST)	Single firm	Patent until 2021	81	\$50k	3	Basic data on volume and supply chain; 1 primary plant and 1 secondary/packaging plant; Preparing for generic introduction;	5 step process; Medium cycle times; Interviews and secondary data sets
<b>EPG</b>	6.25 Million	Breast cancers already surgically treated	At least 10 firms	Expired in 2007	98	Medium - High	3	Basic data on supply chain; Interviews and secondary data sets	25-step process with some technical challenges; 25% Yields; Interviews and secondary data sets
<b>CYG</b>	720,000	Blood cancers; Acute myeloid leukaemia (AML); Non-Hodgkin lymphoma	At least 7 firms	Long expired	268	Medium - Low	3	Basic data on supply chain; firms facing high competition; Interviews and secondary data sets	3-step straightforward process; Interviews and secondary data sets
<b>PAG</b>	15 Million	Various types of solid tumour cancers (e.g. Ovarian, breast and lung, bladder)	Multiple	Generic	398	\$20k	8	Long lifecycle product with 2 parallel supply chains: BMS using plant cell fermentation, and NPI using Biomass extraction; Secondary data sets	Process from raw material straightforward. Biosynthesis route available but not used; Secondary data sets
<b>MEG</b>	30 Million	High volume generic applied to many cancers	Multiple	Generic	186	Low	12	Multiple supply chains Secondary data sets	Non-complex 3-step process Secondary data sets

## 5. Results and interpretation

The oncology drug candidates were analysed and clustered - based on similar areas of benefit and scale for manufacturers, patients and payers – into three different segments e.g.: *New Niche*, *Old Niche*, and *Established Generic*. Designated as “product-process archetypes” (Daly *et al.*, 2015), this simple classification system enables ease of comparability to identify other drugs that may benefit from similar approaches – see table 2. The following sub-sections (5.1-5.5) summarise the research findings in terms of pricing, shortages, clinical trials, sustainable manufacturing/packaging, and systems analysis/benefits clustering.

Table 2: Product-Process archetypes characteristics and definition

Archetype	'New niche'	'Old niche'	'Established generic'
<b>Drug products</b>	XAP, AXP, SUP	EPG, CYG	PAG, MEG
<b>Volumes (Current state)</b>	Low	Medium	High
<b>Cost</b>	High	Medium	Low
<b>Patent</b>	Yes	Recently expired	No
<b>Inventory</b>	High	Medium	Low
<b>Production attributes</b>	In-house; high quality (final)	Downgraded factories; mixed levels of quality (right-first-time)	Outsourced; low quality (right-first-time)
<b>Clinical trials</b>	High potential	Lower potential	Support drugs
<b>Service levels</b>	High	Medium	Low
<b>Shortages</b>	Tending to zero	Rare	Frequent
<b>Potential reconfiguration benefits through technology interventions</b>	Lower inventories; shorter times to market; Easier scale up (e.g. through continuous processing)	Enhanced process control and product quality	Enhanced process control, product quality, and lower costs

The *New Niche* segment represents patented drugs recently discovered and approved (e.g. XAP and AXP in 2011 and 2012 respectively). These drug products are more targeted e.g. XAP is most efficient for a specific 'allele' (variant form of a given gene) type, and are expensive with costs in the range of \$13,000 for 60 capsules of XAP, driven by a combination of high R&D costs, and low volumes (340,000 units/year for SUP; 89,000 units/year for XAP). These drugs are generally manufactured in newer facilities - resulting in increased levels of efficiency. However, associated supply chains for this niche segment are designed to carry excessively high levels of inventory (raw materials through to final product), to avoid the risk of shortages (some in excess of 700 days).

Conversely, the *Established Generic* segment is comprised of older and off-patent drugs, (e.g. MEG, PAG). While volumes may be considered high in an oncology context (e.g. 10 million units/year for MEG), prices are typically low (\$40 for 12 tablets of MEG). Often produced in older facilities, or outsourced (e.g. CYG), they experience frequent shortages as a result of poor economic incentives that have led to cost-cutting, higher risk taking with lower inventories, product/process quality issues and disruptions e.g. contamination problems resulting (McKeever *et al.* 2013).



The *Old Niche* segment includes drugs that have recently come off patent (2007 for EPG), with medium volumes (e.g. 1.7 Million units/year for CYG), and prices (e.g. \$275 for a 10mg vial of EPG). Newly introduced competition has gradually led the segment to lose economic incentives, with cost-cutting leading to reduced inventories, production in downgraded facilities, resulting in occasional shortages and quality problems (e.g. recent incidences of contamination in vials for both CYG and EPG). This archetype may be described as a hybrid of niche and generic – with a mixture of characteristics from the two, and the academic literature does not clearly characterise this segment to a great extent; however, the potential benefits from a technological disruption point-of-view are very high (e.g. continuous processing may offer process patent extension opportunities), as drugs become susceptible to generic competition.

Segmentation, in terms of Injectables v. oral dose forms, was also captured during the analysis. Most recent drugs are presented in an oral format (e.g. XAP, AXP, SUP), compared to the vial option for older drug products (e.g. PAG, MEG, CYG, EPG). This is in line with recent research demonstrating an acceleration in oral therapies compared to Injectables (Fitch *et al.* 2010). This also influences the opportunities for reconfiguration in secondary processing. Indeed, while oral dose forms may benefit greatly from a technology disruption such as continuous manufacturing, the production process involving vials currently represents a series of technological and process challenges (e.g. freezing and sublimation steps), that may lead to opportunities for more radical disruptions.

### **5.1. Pricing**

A negative correlation between drug age and cost for the candidate drugs was demonstrated. Literature supports this trend (Light and Kantarjian 2013), with Cost/QALY particularly demonstrating this in an oncology context (e.g. XAP in 2012, \$170,000/QALY v. PAG from the 1960s, \$20,000/QALY). This pricing increase can be explained by the increasingly high cost of R&D for new drugs 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). For the oncology segment, this is compounded by lower volume (e.g. XAP targets a specific allele, resulting in a global patient population of just 500,000 people) (Brock 2010). In some cases, cost/QALY can be difficult to determine, e.g. SUP, for which the original manufacturer determined a cost/QALY of £29,000/QALY, NICE's evaluation revealed a £72,000/QALY for the same drug (this is an exemplar case, as NICE uses <30,000/QALY as a tipping point for recommending coverage of a drug). This highlights specific insurance and ethical issues, and the difficulty in adequately addressing these currently, in oncology.

As manufacturing and supply chain complexity increases (with a move towards biologics), this stage in the value chain will hold increasing value – potentially capturing >20% of the final product value (Papageorgiou *et al.* 2001), thus, increasing the opportunities for the reduction of drug costs. With the transfer of many elements of clinical trials to commercial inherently built-in (manufacture and supply), it is argued that the real opportunities lies in development through e.g. the adoption of continuous manufacturing and the targeting of drug repurposing (Harrington, Philips, and Srαι 2016). Such technology solutions and strategies could drive alternative clinical supply chain designs at an earlier phase, that are more adaptable to changing customer

demands - specifically in delivering 'precision manufacturing' for improved product quality, in addition to speed of supply, inventory savings, and less waste (Ibid).

## **5.2. Shortages**

The case studies revealed a prevalence of shortages in oncology, which are mainly in the old niche and established generic segments (e.g. currently 19 for PAG, 7 for MEG, 6 for CYG). Numerous supporting reasons including low economic incentives to produce PAG and MEG, the often unexpected increases in demand, coupled with production and quality issues (Singh 2005; Mackey and Liang 2012a; McKeever et al. 2013). The emergence of process and digital technologies have the potential to enhance the economic incentive (decreasing production cost), in increasing production flexibility, reducing production and supply chain wastages, and improving product/process quality through process analytical technologies (PAT) - addressing the major root causes, and in turn, reducing the prevalence of shortages.

## **5.3. 'Adaptive' Clinical trials**

Despite current clinical trials accounting for over 50% of estimated drug development costs (Huber and Howard 2016), clinical trial supply is often viewed as being of secondary importance, compared to the commercial supply chain. Commercial shortages, as outlined in section 5.2, often result in a redirection of existing inventories from clinical trial, slowing down and disrupting many of the trials. Hence, clinical trials in oncology are an area of high opportunity, as per 'innovation movement' parameters set out in section 2.2.2. Two different profiles have been identified, as part of this study:

- Clinical trials for new drugs, lower in volume compared to other drugs (e.g. 28 trials for XAP, 28 for AXP), aiming to prove drug efficiency and safety for new specific therapy areas (e.g. Breast cancer for AXP, Anaplastic large cell lymphoma for XAP)
- Clinical trials involving older generics, higher in volume (e.g. 398 for PAG and 186 for MEG), where the drug is mostly used in a combination, or as a comparator (determining potential and benefits of a new drug, versus the existing best-in-case drug offering).

Many shortages and subsequent effects are also compounded by a growing internationalisation of clinical trials (Fleischhacker 2009), increasing the complexity of the supply chain, and the uncertainty of drug demand relating to the specific trial. However, buffering such trials with inventory is often not viable (because of limited shelf life and increased cost), increasing the need for an more agile supply chain (Singh 2005).

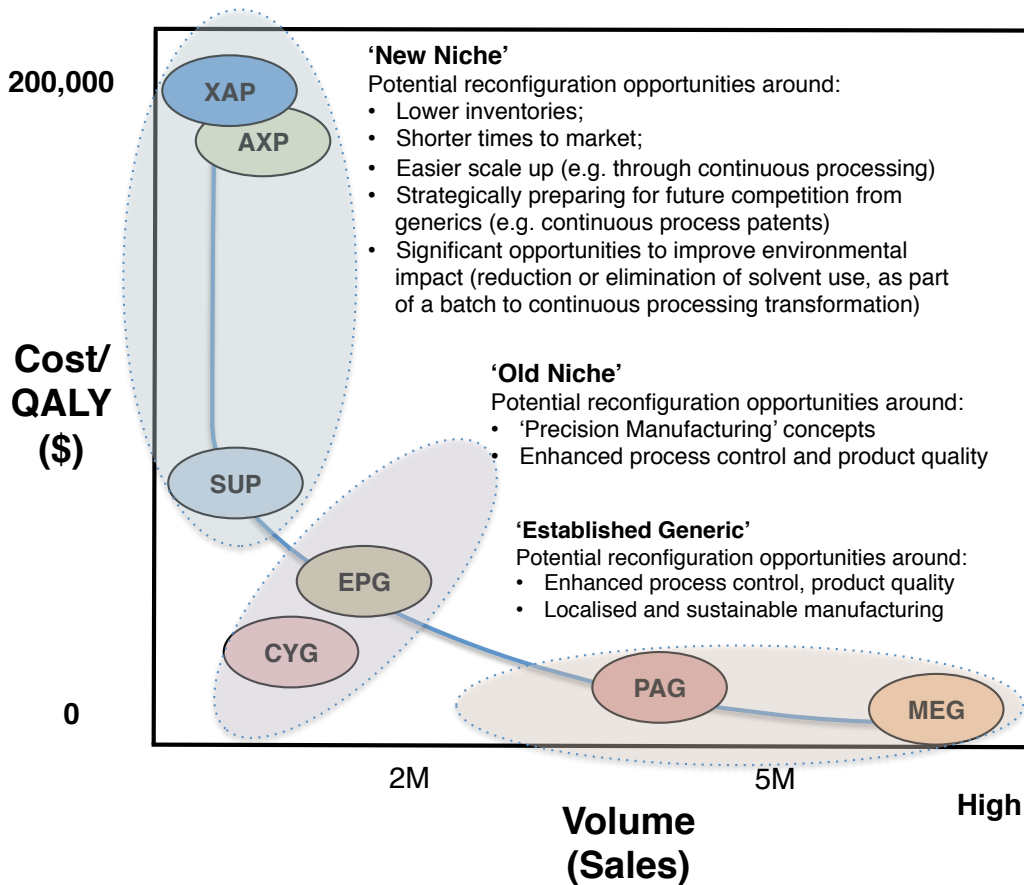
In addition, clinical trials also contribute substantially to greenhouse gas emissions and waste - driving an opportunity for the adoption of renewable energy sources, sustainable 'continuous' manufacturing and packaging practices, and more efficient energy use (BMJ 2007; Harrington, Philips, and Srari 2016), and. In terms of waste (kits), it is estimated that costs are in the order of stg£10-100M annually by company; which equates to between 25% - 70% of total clinical trial supply (CTS) production. This is an area of focus for project ReMediES (Reconfiguring Medicines End-to-End Supply), technology disruptions are currently being targeted in this area that will enable increased agility – with the additional benefit of waste reduction and optimisation - unlocking the potential to secure 'adaptive' and sustainable clinical trial drug supply (ReMediES 2017).

#### 5.4. Systems analysis

Hamel (2000) suggests that it is at the system level where the real benefits of disruptive innovation can be achieved. The base framework, extended in this paper, examined the interactions between sub-systems in oncology for the three archetypes, representing dissimilar product examples to demonstrate the utility of the approach. Appendix I summarises a comparative analysis across the three archetypes – assessing a set of impact variables in the context of how emerging technology concepts may promote paradigm shifts for each cluster, in terms of following sub-systems: clinical trials, primary/secondary processing, packaging, and E2E supply respectively. Figure 4 illustrates one example of how the product-process archetypes may cluster within different sub-system analysis visualisations and demonstrate patterns with respect to sub-system analysis dimensions (e.g. in this case Cost/QALY v. Volumes).

Assessment of specific ‘continuous’ interventions for the three cases and the potential scale of opportunities across the E2E supply chain are outlined here, as follows:

- ‘*New Niche*’: With global production served by 1-2 locations, primary and secondary manufacturing/packaging processes are typically integrated in the same line. The segment exhibits high potential benefit in lowering inventory (from primary to end-to-end). Other potential benefits are envisaged 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 high potential in allowing more clinical trials to unlock new therapy areas, and to be able to scale up production accordingly, in an easier manner. Inefficient supply chains, due in large to the drug’s patented state, may be improved – with opportunities to lower inventories, cost, and strategically preparing for future competition from generics (e.g. continuous process patents), with significant opportunities to improve environmental impact (reduction or elimination of solvent use, as part of a batch to continuous processing transformation).



**Figure. 4.** Product-process archetypes and reconfiguration opportunities segmented in terms of Cost/QALY v. Volume

- *'Old Niche'*: This segment presents highest potential benefit in enhanced process control, reliability and safety (across all the sub-systems), and improved quality, purity and consistency (in secondary, packaging and end-to-end supply), which may help lower the frequency of shortages. Cost reduction potential (especially in primary manufacturing) may help this segment recover from lower economic incentives resulting from recent expiration of patent.
- *'Established Generic'*: This segment exhibits highest potential benefit in enhanced process control, reliability and safety, and improved quality, purity, consistency (across all the sub-systems) – which may help reduce the number of recalls and shortages occurring in the segment. Another important potential benefit is cost-reduction (from primary to end-to-end), which may increase economic incentives for this segment. Established generics tend to have many production sites located globally, with a higher number of secondary processing and packaging sites compared to primary manufacturing locations - usually separated (e.g. 19 primary sites versus 34 secondary for MEG; 11 primary sites versus 18 secondary for PAG). Strategic technology interventions, such as continuous processing can significantly re-shape the global footprint of this segment (Harrington, Philips, and Srai 2016) - resulting in lower CapEx, smaller production lines and flexible production, and enabling an increase in more integrated and localised primary-secondary-packaging configurations.

## 6. Discussion

As summarised in section 1 and 2, there is growing interest in pharmaceutical sector research as current state manufacturing and its associated supply chains exhibit numerous inefficiencies (e.g. long lead times, high inventories; low quality; high waste). In this paper, we argue that the oncology segment may best exhibit the characteristics of next-generation medicines (defined here as niche, personalised, low volume, targeted for sub-populations), and the wider pharmaceutical sector as a whole, hence, we explore how complex value networks in oncology may be reconfigured – with a focus on the adoption of sustainable manufacturing practices such as continuous processing. This section discusses the key insights emerging through the analysis phase, and relates the findings to the existing knowledge in literature. In summary, there is potential for different levels of reconfiguration, driven by technology interventions, across the oncology value network, e.g.

- Opportunities in R&D and clinical trials are high due to the emerging capabilities in sustainable manufacture of small quantities of drug product in an increasingly cost-effective way (micro-factories, enabled by continuous processing). Technology adoption also opens up opportunities to increase speed in terms of clinical trial approval and repurposing. Multi-arm multi-stage (MAMS) trials are increasingly popular – comparing several treatments, resulting in therapy areas being unlocked, faster, for more drugs to serve previously ‘unmet’ needs. As a result, the target patient population increases for certain new drugs (especially attractive in the case of XAP and AXP).
- ‘Precision manufacturing’ concepts: there are opportunities to target primary production costs (lower CapEX, production of *exact* amounts needed using the right amount of raw material and solvents, resulting in decreased waste), and the shortening of cycle times - from integration of processes, reducing or eliminating waiting time between processes, improved processes, improved kinetics due to better heat and mass transfer (Brown et al., in review). While there are exciting opportunities for footprint reduction, barriers to enabling technologies (e.g. process understanding, perceived regulatory resistance, change management) often result in lower than expected adoption rates at first, as was reported for sustainable manufacturing concepts, such as continuous crystallisation unit operations (Harrington, Philips, and Srari 2016).
- In terms of secondary processing and packaging, there are opportunities to ‘get closer’ to the ‘end-consumer’, allowing late customisation, and make-to-order models to serve an increasing need for flexibility associated with greatly increased stock-keeping units (SKUs) and drug product combinations. In terms of personalisation, this is particularly critical in oncology where dosages are important and often depend on the specific patient (e.g. weight, age). For the focal firm, this may have major implications for existing value network structure and role, and in a firm’s position within the value network (Gebremeskeltesfaye et al., 2012).
- A potential increase in the number of (micro-) factories, located closer to end-consumer markets will greatly impact a focal firm’s internal supply chain logistics. Proliferation of SKU variety, compounded by the emergence of aforementioned late-customisation, and make-to-order models will likely increase logistics complexity, especially in terms of refills. In order to keep the same level of service (e.g. 24h delivery), this may drive further consolidation of wholesalers and pre-wholesalers, to improve supply chain efficiencies and increase economies of scale (Behner and Bunte 2007). A logistics service

provider's current configuration may change with the increased handling and transportation needs of the manufacturing supply chain, while wholesalers' configuration may also shift with the changing needs in 'last-mile' logistics – resulting in novel solution design in this area (Harrington et al., 2016). As production costs decrease, the role of the Group Purchasing Organisations (GPOs) may be of paramount importance in capturing maximum value, increasing the importance of more strategic agreements between GPOs and Wholesalers.

- 'New' service provision: such 'last-mile' solution designs for more personalised delivery is informing a series of potential technologies, with a view to delivering customised/made-to-order products and drug-device combinations directly to the patient. Currently this only holds true for oral dose forms, while Injectables still need the monitoring and administration expertise of hospitals and oncologists. However, with the trend towards the development of oral therapies in the future (Fitch et al. 2010), direct to consumer route is likely to develop fast, with implications for various stakeholders across the oncology/pharma value network.
- 'Workflows for Sustainable Manufacturing': this mode of operating uses data gathered during the manufacturing process itself to make drug development and manufacture more efficient at every stage of production. Process analytical techniques (PAT) in conjunction with workflow allows for the design of end-to-end and continuous processes real-time, and 'adapt' parameters and protocols, essentially controlling not just the quality but also the end products - increasing overall service levels, and decreasing inventory across multiple nodes in the supply chain. These approaches inform a better understanding of more complex processing schemes and reduce approvals lead-time for the manufacturer, as well as educating regulatory bodies (e.g. FDA in the US; MHRA in the UK; EMA in Europe) emerging disruptive technologies – resulting in a review and revision of current regulation processes.

Today, the Oncology market exhibits many characteristics of what the future Pharmaceutical sector may look like (e.g. Low volumes, targeted therapies, higher costs, specialty distribution routes). Therefore, the structure of a sustainable pharmaceutical industrial system may be inferred from our investigation of a future reconfigured Oncology value network. In summary,

- As the wider pharmaceutical sector shifts towards more targeted therapies, coupled with the requirement to manage higher flexibility and drive lower production costs from technology implementation, there is likely to be a rise in more targeted R&D and clinical trial activities – evidenced by increasing activities in the digital development of Pharmaceutical therapeutics, and adoption of sustainable continuous processes in development (Harrington, Philips, and Srai 2016). Clinical trials specifically may experience the highest benefits as Fleischhacker (2009) argues it currently faces high pressure with loss of high inventories from a failure of clinical trials, and loss of production efficiency and scale economy from the production of small batches. With the globalisation of clinical trials (in order to meet patient/subject recruitment objectives), secure drug supply is listed as the main remaining challenge for the clinical trial supply chain (ibid). The strategic adoption of continuous processing in developmental phases, resulting in ease of subsequent transfer and ramp-up to a commercial context, may enable this through flexible and lower costs of production. One result likely will be an increase in

number and speed of clinical trials, and may translate in an increased number of new actors emerging in the Clinical Research space.

- As Sousa et al. (2011) argue primary manufacturing is most affected by changing demand and the bullwhip effect, this sub-system will benefit from continuous processing implementation (through increased flexibility and speed) to better adapt to fluctuations. The whole production process will likely benefit from the suppression of waiting time between processes and decreased waste. Lower inventories and costs are likely to follow with late-customisation and made-to-order models arising with the potential of newly acquired agility (i.e. flexibility and speed). Product and process quality may also be improved with the implementation of PAT.
- While the need for improved production logistics will increase from the increase and spread of production units, pressure on distribution will come from the increased number of SKU variety (resulting from late-customisation). Emphasis on 'last-mile' delivery may push wholesalers to reconfigure in supporting novel service supply models, with further consolidation likely to happen at this stage of the value network (Behner & Bunte 2007). Furthermore, as more targeted therapies develop - resulting in increased drug prices (Trusheim & Berndt 2012), more GPO-type actors are likely to emerge with a view to increasing bargaining and negotiation power in distribution.
- Development of direct-to-consumer distribution (e.g. mail order, web pharmacies, direct shipping; 'pillpack' models) from increased customisation, coupled with current trends in Pharma (Rossetti et al. 2011) may well see a decrease in the importance and role of pharmacies in a future industrial system.
- End-to-end supply: while the Pharmaceutical value network gains in agility decreasing the bullwhip effect and inventory levels in the manufacturing SC, increases in SKU variety from the acquired flexibility may increase the pressure on wholesalers who already have to make available 10,000 SKUs to pharmacies within 12 hours with fill rates superior at 99% (Singh 2005). Increase in product quality may lower recalls, which may have a substantial positive impact on network efficiency and cost. Rossetti et al. (2011) argue that the cost of reverse logistics (drugs' recall management) adds substantial expenses to actors, and is usually underestimated. Increase in manufacturing flexibility and decrease in lead-time may also significantly lower shortages.

## 7. Conclusion

This research paper explored how specificities in the oncology segment may inform the development of future pharmaceutical value networks, and support the sustainable manufacture and supply of next-generation medicines.

Oncology and pharmaceutical value networks were first derived from the academic literature and used to explore the 'current state' and a series of 'future state' scenarios and opportunities areas, driven by the adoption of emerging process and digital technologies.

A base framework was then extended to enable a systematic assessment of seven drug candidates representative of the wider oncology market. These include niche, low volume drugs on-patent with high QALYs (quality-adjusted life years), through to higher volume generics with a history of supply shortages. A series of

emerging product-process 'archetypes' in oncology are proposed – classified as 'New Niche', 'Old Niche' and 'Established Generics' – with associated models for reconfiguration, based on the clustering of potential supply and manufacturing benefits. In summary, these included e.g. lower inventory, shorter lead time to market and easier scale up for 'New Niche', in addition to significant opportunities to improve environmental impact (reduction or elimination of solvent use), as part of a batch to continuous processing transformation to strategically prepare for future generics competition, enhanced process control and product quality – 'precision manufacturing' - for 'Old Niche', and enhanced process control and product quality, lower costs, and more sustainable and localised practices for the 'Established Generic'. A key application of adopting this systems approach was the potential of informing economies of drug 'repurposing', through its extension from commercial to drug discovery, development and clinical trial contexts, and in matching emerging process capabilities to future adaptive supply requirements. Analysis using a series of impact variables has shown that each of these product-process archetypes may benefit differently from technology disruption, such as the adoption of continuous manufacturing

The research has contributed to the existing literature by proposing (a) product-process archetypes for the oncology sector, (b) reconfiguration opportunities related to each of these archetypes, (c) possible future reconfiguration of oncology and pharmaceutical value networks (d) and an adapted analytical framework assessing reconfiguration opportunities for the oncology case. Moreover, analysis of the different candidate drugs has provided insights into the oncology market. In extending the base framework, new parameters were considered in an oncology context – e.g. candidate selection logic and segmentation, clinical trial analysis, business case development in terms of Cost/QALY, patent state, and drug candidate heritage. Analysis of the candidate drugs has shown highest potential benefits for the oncology segment in production cost for the primary, secondary and packaging sub-systems. Appendix I summarises the opportunities in oncology, incorporating the seven case studies'. This may be replicated and further adapted to multiple therapy areas.

In terms of limitations, data is highly protected and often difficult to access (Clift 2007), as the high cost of R&D and new drug development prohibits companies in disclosing their manufacturing processes and/or in providing data in great detail. Study of other therapy areas could also offer supporting and alternative insights into the wider pharmaceutical value network. Further investigation is required in terms of Supply Chain and Process configurations, with regards to other specific technology disruptions (e.g. inject printing) and could constitute the focus of future work.



Appendix I. Comparative analysis across the three archetypes using a set of impact variables

New Niche					
Impact Variables	Clinical Trials	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	○	○	○	○	○
IP Protection/extension/counterfeits	○	○	✓	✓	✓
Cost (Proc/Pkg/Transport)	✓	✓	✓✓	✓✓	✓
Investment Cost	○	○	○	○	○
Fiscal/Tax	○	○	○	○	○
Environmental impact/solvent	○	○	○	○	○
Mobility/adaptability	=	=	✓✓	✓✓	✓
Asset Utilisation	○	○	○	○	○

Old Niche					
Impact Variables	Clinical Trials	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	○	○	○	○	○
IP Protection/extension/counterfeits	○	○	✓	✓	=
Cost (Proc/Pkg/Transport)	✓	✓✓	✓	✓	✓
Investment Cost	○	○	○	○	○
Fiscal/Tax	○	○	○	○	○
Environmental impact/solvent	○	○	○	○	○
Mobility/adaptability	=	=	✓	✓	✓
Asset Utilisation	○	○	○	○	○

Established Generic					
Impact Variables	Clinical Trials	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	○	○	○	○	○
IP Protection/extension/counterfeits	○	○	✓✓	✓✓	✓
Cost (Proc/Pkg/Transport)	✓	✓✓	✓✓	✓✓	✓✓
Investment Cost	○	○	○	○	○
Fiscal/Tax	○	○	○	○	○
Environmental impact/solvent	○	○	○	○	○
Mobility/adaptability	=	=	=	✓	=
Asset Utilisation	○	○	○	○	○

Key	○	=	✓	✓✓
Opportunity	TBD	Neutral	Some	Significant

## References

- Abel, G. a et al., 2006. Direct-to-consumer advertising in oncology. *The Oncologist*, Vol. 11, No. 2, pp.217–26. DOI: 10.1634/theoncologist.11-2-217
- Adner, R. and Kapoor, R., 2010. VALUE CREATION IN INNOVATION ECOSYSTEMS : HOW THE STRUCTURE OF TECHNOLOGICAL INTERDEPENDENCE AFFECTS FIRM PERFORMANCE IN NEW TECHNOLOGY GENERATIONS. *Strategic Management Journal*, Vol. 31, pp.306–333.
- Afuah, A., 2000. HOW MUCH DO YOUR CO-OPETITORS ' CAPABILITIES MATTER IN THE FACE OF TECHNOLOGICAL CHANGE ? *Strategic Management Journal*, Vol. 21, pp.387–404.
- Afuah, A., 1998. *Innovation Management : Strategies, Implementation and Profits*. Oxford University Press
- Afuah, A.N. & Bahram, N., 1995. The Hypercube of innovation. *Research Policy*, 24, pp.51–76.
- Alford, J., 2013. Understand the Basics of Process Analytical Technology. *CHEMICAL ENGINEERING* .... Available at: <http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Understand+the+Basics+of+Process+Analytical+Technology#3> [Accessed April 3, 2014].
- American Cancer Society, 2011. *Global Cancer Facts & Figures 2nd Edition*,
- Anes, J. & Fernandes, P., 2013. Towards the continuous production of fructose syrups from inulin using inulinase entrapped in PVA-based particles. *Biocatalysis and Agricultural Biotechnology*, pp.1–7. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S1878818113001394> [Accessed April 3, 2014].
- Anna Gu, M. et al., 2011. Drug Shortages in the US – Causes, Impact, and Strategies. , pp.1–8.
- Arnum, P. Van, 2010. Big Pharma ' s Manufacturing Strategy : What Is the Next Move ? , (August).
- Bagwell, B. et al., 2011. *Oncology Market Overview : Barriers , Challenges and Value ONCOLOGY MARKET OVERVIEW : BARRIERS , CHALLENGES AND VALUE*,
- Baig, V.A. & Khan, T., 2007. Supply Chain Management; Value Chain and Value Network Logics.
- Bair, J., 2005. Competition & Change Global Capitalism and Commodity Chains : Looking Back , Going Forward. , 9(2), pp.9–10.
- Behner, P. & Bunte, M., 2007. *Getting to Grips with The Supply Chain How Pharmaceutical Companies can Enhance Patient Safety and Protect Revenues by Increasing Their Control Of Drug Distribution*,
- Biem, A. & Caswell, N., 2008. A Value Network Model for Strategic Analysis. *Proceedings of the 41st Annual Hawaii International Conference on System Sciences (HICSS 2008)*, pp.361–361. Available at: <http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=4439066>.
- BMJ 2007. Towards sustainable clinical trials, Vol. 334, pp. 671 doi: <http://dx.doi.org/10.1136/bmj.39140.623137.BE>

- Brock, D.W., 2010. Ethical and value issues in insurance coverage for cancer treatment. *The oncologist*, 15 Suppl 1, pp.36–42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20237216> [Accessed April 21, 2014].
- P. G. Casali, 2007, The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). *Ann Oncol* 18 (12): 1923-1925. doi: 10.1093/annonc/mdm517
- Castner, M., Hayes, J. & Shankie, D., 2007. The Global Pharmaceutical Industry: International Trade and Contemporary Trends. , pp.2–5.
- Cepton Strategies, 2009. *Strategic outsourcing across the pharmaceuticals value chain*,
- Chabner, B. a, 2011. Drug shortages--a critical challenge for the generic-drug market. *The New England journal of medicine*, 365(23), pp.2147–9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22040167>.
- Chatterjee, S., 2012. Fda on continuous processing. In *IFPAC Annual Meeting, Baltimore*.
- Chen, J. et al., 2011. Pharmaceutical Crystallization Published as part of the Crystal Growth & Design 10th Anniversary Perspective. , pp.887–895.
- Christensen, C.M., 1997. *The Innovator's Dilemma; when new technologies cause great firms to fail*,
- Clift, C., 2007. Data Protection and Data Exclusivity in Pharmaceuticals and Agrochemicals. In *Sharing the Art of IP Management*. pp. 431–435.
- Cote, B., 2007. Evolution of the Oncology GPO. , (November), pp.28–36.
- Cottrill, K., 2011. TRANSFORMING THE FUTURE OF SUPPLY CHAINS THROUGH DISRUPTIVE INNOVATION. *MIT CTL WHITE PAPER*.
- Daly R, Harrington TS, et al (2015) 'Inkjet printing for pharmaceuticals - A review of research and manufacturing', *International Journal of Pharmaceutics*, Vol. 494, No. 2, pp. 554-567. DOI: 10.1016/j.ijpharm.2015.03.017
- Danzon, P.M. & Taylor, E., 2010. Drug pricing and value in oncology. *The oncologist*, 15 Suppl 1, pp.24–31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20237214> [Accessed April 2, 2014].
- DiMasi, J. a, Hansen, R.W. & Grabowski, H.G., 2003. The price of innovation: new estimates of drug development costs. *Journal of health economics*, 22(2), pp.151–85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12606142> [Accessed May 23, 2014].
- Doorneweert, B., 2012. Value Chain Generation: Disruptive innovation and sustainable development., pp.38–39. Available at: <https://valuechaingeneration.com/2012/07/25/disruptive-innovation-and-sustainable-development/> (accessed 23 Jan 2017)
- Ebel, T. et al., 2013. *Building New Strengths in the Healthcare Supply Chain Pharmaceuticals and Medical Products Operations*,
- Edwards, P. J. 2009. "Value Networks Identify Innovation in 21st Century Pharmaceutical Research." *Drug Discovery Today* 14 (1-2): 68–77. doi:10.1016/j.drudis.2008.09.015.
- Ehrhardt, M., Hutchens, R. & Higgins, S., 2012. Five Steps toward a Revitalized Pharmaceutical Supply Chain. , (66), pp.1–5.

- Eisenhardt, K.M., 1989. Building Theories From Case Study Research.
- EvaluatePharma, 2015. Orphan Drug Report, 3rd Edition (October). Available at: <http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdf> (accessed 12 Jan 2017)
- Ferguson, S. et al., 2014. Use of Continuous MSMPR Crystallization with Integrated Nano filtration Membrane Recycle for Enhanced Yield and Purity in API Crystallization.
- Fitch, K., Iwasaki, K. & Pyenson, B., 2010. *Parity for Oral and Intravenous / Injected Cancer Drugs*, New York, NY Milliman
- Fleischhacker, B.Y.A., 2009. AN INVESTIGATION OF CLINICAL TRIAL SUPPLY CHAINS An Investigation of Clinical Trial Supply Chains by Adam Fleischhacker.
- Gable, G.G., 1994. Integrating case study and survey research methods: an example in information systems. , 3, pp.112–126.
- Garrison Jr, L.P., 2010. Rewarding value creation to promote innovation in oncology: The importance of considering the global product life cycle. *The Oncologist*, 15 Suppl 1, pp.49–57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20237218> [Accessed April 21, 2014].
- Gatesman, M.L. & Smith, T.J., 2011. The Shortage of Essential Chemotherapy Drugs in the United States. , pp.1653–1655.
- Gebremeskeltessfaye, H., Nguyen, T.H.N. & Bengtsson, M., 2012. Incumbent firms and Response to Disruptive Innovation through Value Network Management : Lessons from Eastman Kodak's failure in the digital era.
- Gereffi, G., 2003. THE GLOBAL APPAREL VALUE CHAIN : What Prospects for Upgrading by Developing Countries.
- Gereffi, G. & Fernandez-stark, K., 2011. GLOBAL VALUE CHAIN ANALYSIS : A PRIMER.
- Gereffi, G., Humphrey, J. & Sturgeon, T., 2005. The governance of global value chains. *Review of International Political Economy*, 12(1), pp.78–104. Available at: <http://www.tandfonline.com/doi/abs/10.1080/09692290500049805> [Accessed July 9, 2014].
- Hall, J.K. & Martin, M.J.C., 2005. Disruptive technologies , stakeholders and the innovation value-added chain : a framework for evaluating radical technology development. *R&D Management*, Vol. 35, No. 3, pp.273–284.
- Hall, SS., 2017 The Cancer Lottery, *MIT Technology Review*, Vol. 120. No. 1, pp. 34-43
- Hamel, G., 2000. LEADING THE REVOLUTION. , (August).
- Handfield, R., 2012. *Biopharmaceutical Supply Chains : Distribution, Regulatory, Systems and Structural Changes Ahead* C. Press, ed., Taylor & Francis Group LLC.
- Harrington TS, Phillips MA, and Srari JS. 2016 'Reconfiguring global pharmaceutical value networks through targeted technology interventions', *International Journal of Production Research*. Published online: 18 August. DOI: 10.1080/00207543.2016.1221541
- Harrington TS, et al. 2016. 'Identifying design criteria for urban system 'last-mile' solutions – a multi-stakeholder perspective', *Production Planning and Control: The Management of Operations*, Vol. 27, No. 6, pp. 456-476. DOI: 10.1080/09537287.2016.1147099

- Herper, M., 2010. The World ' s Most Expensive Drugs. *Forbes Magazine*, pp.1–5.
- Herriott, R.E. & Firestone, W. a., 1983. Multisite Qualitative Policy Research: Optimizing Description and Generalizability. *Educational Researcher*, 12(2), pp.14–19. Available at: <http://edr.sagepub.com/cgi/doi/10.3102/0013189X012002014> [Accessed August 16, 2014].
- Horning, S.J. et al., 2013. Developing standards for breakthrough therapy designation in oncology. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 19(16), pp.4297–304. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3745545&tool=pmcentrez&rendertype=abstract> [Accessed April 1, 2014].
- Huber, P., 2013,
- Huber, P., and P. Howard, 2016. Biopharmaceutical Policy for American Leadership in the 21st Century, in, *Unleashing Opportunity: A Project of National Affairs Volume I: Policy Reforms to Advance Innovation*, eds., Y. Levin and E. MacLean, National Affairs, Washington, D.C.
- Icore Healthcare, 2010. *MEDICAL INJECTABLEs & ONCOLOGY*,
- IMS Institute for Healthcare, 2012. Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report.
- Jemal, A. et al., 2010. Global patterns of cancer incidence and mortality rates and trends. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 19(8), pp.1893–907. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20647400> [Accessed July 9, 2014].
- Kandybin, A. & Genova, V., 2012. BIG PHARMA ' S UNCERTAIN FUTURE. , (66).
- Kaplinsky, R., 2000. Spreading the gains from globalisation: what can be learned from value chain analysis? *Institute of Development Studies*, 635.
- Kaplinsky, R. & Morris, M., 2000. A HANDBOOK FOR VALUE CHAIN. , (September).
- Kormawa, P.M., 2009. *Developing a Value Chain Diagnostics Tool for Common Practice at UNIDO*,
- Kothari, C.R., 1990. *Research Methodology, Methods and Techniques*, New Age International Publishers.
- KPMG, 2011. *Future Pharma: Five strategies to Accelerate the Transformation of the Pharmaceutical Industry by 2020*,
- Kumar, A. et al., 2013. Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production--a critical review. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V.*, 85(3 Pt B), pp.814–32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24056091> [Accessed April 3, 2014].
- Lambert, D.M. & Cooper, M.C., 2000. Issues in Supply Chain Management. *Industrial Marketing Management*, 29(1), pp.65–83. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0019850199001133>.
- Lichtenberg, F.R., 2014. Pushing Innovation Into Oncology : Restructuring Clinical Trials. , pp.2–4.

- Light, D.W. & Kantarjian, H., 2013. Market spiral pricing of cancer drugs. *Cancer*, 119(22), pp.3900–2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24002792> [Accessed April 1, 2014].
- Musante, C., Ramanujan, S., Schmidt, B., Ghobrial, O., Lu, J. and Heatherington, A. (2017), Quantitative Systems Pharmacology: A Case for Disease Models. *Clin. Pharmacol. Ther.*, 101: 24–27. doi:10.1002/cpt.528
- Mackey, T.K. & Liang, B. 2012. Oncology and the Internet: regulatory failure and reform. *Journal of oncology practice / American Society of Clinical Oncology*, 8(6), pp.341–3. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3500477&tool=pmcentrez&rendertype=abstract> [Accessed June 5, 2014].
- Mayer, A., 2012. *Supply Chain Metrics That Matter: A Focus on the Pharmaceutical Industry*,
- McKeever, A.E., Bloch, J.R. & Bractic, A., 2013. Drug Shortages and the Burden of Access to Care. , pp.1–9.
- Meredith, J., 1998. Building operations management theory through case and field research. , pp.441–454.
- Miroudot, S. & De Backer, K., 2012. *Mapping global value chains*,
- Myers, M.D., 2008. *Qualitative Research in Business & Management*.
- Nagurney, A., Li, D. & Nagurney, L.S., 2013. Pharmaceutical supply chain networks with outsourcing under price and quality competition. *International Transactions in Operational Research*, 20, p.n/a–n/a. Available at: <http://doi.wiley.com/10.1111/itor.12031> [Accessed April 1, 2014].
- Narayana, S.A., Kumar Pati, R. & Vrat, P., 2014. Managerial research on the pharmaceutical supply chain – A critical review and some insights for future directions. *Journal of Purchasing and Supply Management*, 20(1), pp.18–40. Available at: <http://www.scopus.com/inward/record.url?eid=2-s2.0-84886857082&partnerID=tZOtx3y1> [Accessed March 20, 2014].
- Oxford Dictionary, 1997. Oxford Dictionary.
- Papageorgiou, L.G., Rotstein, G.E. & Shah, N., 2001. Strategic Supply Chain Optimization for the Pharmaceutical Industries. *Industrial & Engineering Chemistry Research*, 40(1), pp.275–286. Available at: <http://pubs.acs.org/doi/abs/10.1021/ie990870t>.
- Paul, C., Wei, J. & Moser, R., 2013. How Institutional Change Reconfigures Successful Value Chains: The Case of Western Pharma Corporations in China. , 49(0), pp.153–172.
- Pedroso, M.C. & Nakano, D., 2009. Knowledge and information flows in supply chains: A study on pharmaceutical companies. *International Journal of Production Economics*, 122(1), pp.376–384. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0925527309002011> [Accessed March 24, 2014].
- Penny, T., Collins, M., Whiting, A. and Aumônier, S. (2015), *Care Pathways: Guidance on Appraising Sustainability*, <http://www.sduhealth.org.uk/>
- Picard, E.H. & Tarab, A., 2012. Recognizing Value in Oncology Innovation.

- Pizam, A. & Mansfeld, Y., 2009. Consumer Behavior in Travel and More About the Authors Customers viewing this page may be interested in these sponsored links Customer Buying Journey. , pp.28–30.
- Plumb, K., 2005. Continuous Processing in the Pharmaceutical Industry. *Chemical Engineering Research and Design*, 83(6), pp.730–738. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0263876205727556> [Accessed June 2, 2014].
- Porter, M.E., 1980. *COMPETITIVE STRATEGY: Techniques for Analyzing Industries and Competitors*,
- Remenyi, D., 1995. So you want to be an academic researcher in business and management studies !
- Rossetti, C.L., Handfield, R. & Dooley, K.J., 2011. Forces, trends, and decisions in pharmaceutical supply chain management. *International Journal of Physical Distribution & Logistics Management*, 41(6), pp.601–622. Available at: <http://www.emeraldinsight.com/10.1108/09600031111147835> [Accessed March 20, 2014].
- ReMediES, 2017. 'Clinical Supply Chain Platform', Available at: <https://remediesproject.com/research-2/project-structure/clinical-supply-chain-platform/> (accessed 23 Jan 2017)
- Saerens, L. et al., 2014. Process monitoring and visualization solutions for hot-melt extrusion: a review. *The Journal of pharmacy and pharmacology*, 66(2), pp.180–203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24433422> [Accessed March 27, 2014].
- Saunders, M., Lewis, P. & Thornhill, A., 2008. *Research methods for business students* Fifth edit. F. P. Hall, ed., Pearson Education.
- Schaber, S.D. et al., 2011. Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study. *Industrial & Engineering Chemistry Research*, 50(17), pp.10083–10092. Available at: <http://pubs.acs.org/doi/abs/10.1021/ie2006752>.
- Scheel, O., Wintermantel, T. & O’Keefe, J., 2013. *Unleashing Pharma from the R & D Value Chain*,
- Schrickel, J., 2013. Continuous processes - sustainable manufacturing. , 31(June), pp.3–6.
- Senderowicz, A.M. & Pfaff, O., 2014. Similarities and Differences in the Oncology Drug Approval Process between FDA and European Union with Emphasis on In Vitro Companion Diagnostics. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 20(6), pp.1445–52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24634467> [Accessed March 19, 2014].
- Shah, N., 2004. Pharmaceutical supply chains : key issues and strategies for optimisation. , 28, pp.929–941.
- Singh, M., 2005. The Pharmaceutical Supply Chain : a Diagnosis of the State-of-the-Art The Pharmaceutical Supply Chain , Thesis available at: <https://dspace.mit.edu/handle/1721.1/33354> (accessed 4th January 2017)
- Sousa, R.T. et al., 2011. Global supply chain planning for pharmaceuticals. *Chemical Engineering Research and Design*, 89(11), pp.2396–2409. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0263876211001420> [Accessed April 1, 2014].

- Srai JS, Harrington TS, and Tiwari MK (2016) 'Characteristics of redistributed manufacturing systems: a comparative study of emerging industry supply networks', *International Journal of Production Research*, Vol. 54, No. 23, pp. 6936–6955. DOI: 10.1080/00207543.2016.1214765
- Srai, J.S. 2017. 'Mapping industrial systems – a supply network perspective on enabling technologies, processes and actors', *Int. J. Manufacturing Technology and Management*, Vol. 31, Nos. 1/2/3, pp.82–99.
- Stabell, C.B., 1998. CONFIGURING VALUE FOR COMPETITIVE ADVANTAGE : ON CHAINS , SHOPS , AND NETWORKS. , 19(November 1996), pp.413–437.
- Sturgeon, T.J., 2001. How Do We Define Value Chains and Production Networks? \*. *IDS Bulletin*, 32(3), pp.9–18. Available at: <http://doi.wiley.com/10.1111/j.1759-5436.2001.mp32003002.x>.
- Susarla, N. & Karimi, I. a., 2012. Integrated supply chain planning for multinational pharmaceutical enterprises. *Computers & Chemical Engineering*, 42, pp.168–177. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0098135412000804> [Accessed April 1, 2014].
- The Kaiser Family Foundation, 2005. *Follow The Pill: Understanding the U . S . Commercial Pharmaceutical Supply Chain*,
- Thorelli, H.B., 1986. Networks: Between Markets and Hierarchies.
- Trout, B., 2009. Continuous Manufacturing of Small Molecule Pharmaceuticals The Ultra Lean Way of Manufacturing.
- Trusheim, Mark R. and Berndt, Ernst R., 2012, "The Segmentation of Therapeutic Populations in Oncology", *Health Management, Policy and Innovation*, 1 (1): 19-34
- Uthayakumar, R. & Priyan, S., 2013. Pharmaceutical supply chain and inventory management strategies: Optimization for a pharmaceutical company and a hospital. *Operations Research for Health Care*, 2(3), pp.52–64. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S2211692313000155> [Accessed April 2, 2014].
- Webber, M. & Labaste, P., 2007. *USING VALUE CHAIN APPROACHES IN SUB-SAHARAN AFRICA*,
- Whewell, R., 2009. Supply Chain in the Pharma industry.
- WHO, 2014. *World Health Organization- Fact sheet N°297*,
- Yin, R.K., 2009. *Case Study Research: Design and Methods*, SAGE Publications.