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Coordinating the distribution networks in clinical supply chains

A case of AstraZeneca's pharmaceutical and lab kits networks

Master's thesis in the Master Program Supply Chain Management

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Supervisor: Michael Browne
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ABSTRACT

Decreasing profits and sharp globalized competition has driven the leading pharmaceutical companies to reduce the expenditures of new drug development by redesigning the clinical logistics processes. Under this context, the study managers of a clinical study of AstraZeneca in cardiovascular sector wanted to investigate the potential coordination of the distribution flows of the pharmaceutical kits and ancillary lab kits to the investigation sites as performed by the two strategic outsourcing partners, Fisher and Covance, respectively. As the study is at the last phase before the commercialization of the studied drug, multicentre trials on large groups of patients take place across the globe reaching 29 countries, 95 investigation sites and 13.500 patients. AstraZeneca's R&D department considers that there are potentials of reducing the logistics costs on a so expanded supply chain network.

The purpose of this study is to investigate the efficacy, the challenges and the potential benefits which can be reaped by the planned co-distribution channel, taking into account the performance of the two parallel supply chains which are mapped and evaluated considering the particularities of the regulatory framework that applies in the pharmaceutical industry. For the steps of the study various theoretical models from the literature have been used as a tool to gather and analyze the empirical data which are extracted by conducting semi-structured interviews with all the stakeholders that have a major role in the drug and lab kits supply chains and from internal documents of AstraZeneca. Identifying the weaknesses and the responsiveness of the two chains, a coordination plan is being proposed to reach to the future-state of the redesigned distribution network. This plan investigates the changes in the clinical logistics operations, the challenges and the constraints towards the completion of the co-distribution channel.

The findings show that the plan is feasible in terms of material and information coordination, but is should be cautious so that the efficacy and quality of the clinical study won't be affected. Close collaboration between the stakeholders is required but the roles in the new coordinated logistics network must be distinct and beneficial for all of them. The structure of the co-distribution channel has to be adapted to the diversity of the regulatory landscape in the importing countries and therefore scrutinized investigation is needed in that field so that the shortage risk, that encounters high costs can be mitigated. Finally, the applicability of the findings to coordination projects of supply chains with similar characteristics with the ones of the clinical pharmaceutical sector is discussed.

Keywords: "clinical studies", "clinical trial logistics", "pharmaceutical R&D sector", "AstraZeneca", "regulations in clinical studies", " drug import regulations", "supply chain coordination"

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_____ _____

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Abbreviations

3PL: Third Party Logistics

CRO: Contract Research Organization

DTS: Direct To Site

EMEA: European Medicines Agency

FDA: Food and Drug Administration (USA)

GCP: Good Clinical Practices

GDP: Good Distribution Practices

GLP: Good Laboratory Practices

GMP: Good Manufacturing Practices

IDEF: Integrated DEFinition

IL: Import Licensing

SCOR: Supply Chain Operations Reference

VD: Via Depot

VSM: Value Stream Mapping

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

In this chapter an introduction to the thesis project will be conducted. First of all, a general background on the pharmaceutical sector will be described, in order for the reader to acquire an overview of the challenges the clinical R&D sector faces nowadays. Additionally the business strategy of the pharmaceutical company AstraZeneca, for which this project is conducted, will be shortly presented. Subsequently, in the problem definition chapter the subject of the project will be clarified leading to the purpose of the thesis and the research questions that will be answered. Moreover, the delimitations of the project are identified and the outline of the project will be shown.

1.1 General background: The drug development in pharmaceutical sector

The scientific breakthroughs in chemical industry triggered the development of the pharmaceutical sector in Europe in the end of nineteenth century. The majority of the first pharmaceutical companies were located in Germany and Switzerland and fewer in Britain and France. The developed technology from the European companies was later adopted by the US-based companies. This was the main reason that US companies were heavily dependent on the European ones for a remarkably long period of time, until War World I. Undoubtedly the driving force of the development of pharmaceutical sector that period, was the intensive focus on clinical researches and development of new medicines, especially in the category of antibiotics. Investments on R&D departments were increasing, usually being funded by the governments and international organizations (Malerba and Orsenigo, 2015).

The pharmaceutical industry entered the era of globalization in the second half of the 20th century, after the end of the WWII, and still remains nowadays the dominant trend in the sector. Populations in developing economies are the new target markets companies commercialize their drug portfolios striving to increase their marginal profits in a highly fragmented and competitive business environment. During that period, high rates of return profits after taxes are recorded, reaching up to 22%. The research clinical studies that focus on developing and releasing new medicines to the markets, is the cornerstone of competitive advantage for the leading pharmaceutical companies in the world. (Malerba and Orsenigo, 2015)

Nowadays, the element of new drug development defines in a high extend the business strategy of the firms operating in the pharmaceutical industry. Based on that, a pharmaceutical company can be characterized either as originator or generic. An originator pharmaceutical firm focuses on producing new drugs after running clinical studies that last many years. Since the new drug is being released to the market, the manufacturing firm keeps the legal right of monopoly for the sale of it for some years. During those years of protected patent, the firm records high profits. Drug development though, is a high risk investment. After the exclusivity period of the new drug expires, generic pharmaceutical companies have the right to develop identical drugs to in a lower

price. For that reason, generic companies focus mostly on production efficiency, targeting on providing price-competitive drugs identical or similar to the initially patented ones. (ECORYS, 2009)

After the burst out of the crisis in 2008, the pharmaceutical sector is in a phase of slow recovery. As shown in Figure 1, this growth stems mainly from the positive figures of the sector in the developing economies of Asia and Latin America (growth increase by 11.6 % and 11.8% respectively) while the traditional market of EU is rather stagnated.

Figure 1: Global Pharmaceutical Sales (Source: AstraZeneca, pg.15)

Despite the positive future prospects, pharmaceutical R&D sector has to cope with significant challenges. The sharp competition from generic companies as patent periods get shortened, the decreasing number of successful clinical projects as the associated R&D costs increase and the strict regulations that lengthen the duration of the clinical study phases are the main issues originator pharmaceutical companies have to tackle in order to preserve the sustainability of their growth (AstraZeneca 2014, pg.14). Under this tightening environment, the logistics operations that support the new drug studies have drawn the attention of the clinical study managers who recognize that the efficiency of the supply chains in the clinical R&D sector is critical for the acceleration of new drug development process, an important cost cutting factor and vital for the efficacy and safety of the new product

1.2 Company background: AstraZeneca

British- Swedish AstraZeneca is one of the global leaders in the pharmaceutical sector operating in more than 100 countries and providing with medicines millions of patients each year. In 2014 the company was employing 57.500 employees worldwide of which 9.000 are employed in the Research and Development department, 10.200 in Manufacturing and Supply and 34.800 in Sales and Marketing (AstraZeneca 2014, pg. 2). AstraZeneca's revenues in 2015 reached $ 24.7 bn and positioning the firm in the seventh

place of the top 10 pharmaceutical companies in the world based on their market value (Financial Times Global 500, 2015).

AstraZeneca's product portfolio is wide, including primary and specialty medicines which expand to the following therapy areas (AstraZeneca, 2014):

- Cardiovascular and Metabolic diseases
- Oncology
- Respiratory, Inflammation and Autoimmunity
- Infection and Neuroscience

AstraZeneca is a typical example of generator pharmaceutical company, having adopted an innovation-driven business strategy by focusing on the research and development of new medicines. The firm operates in the "…*span on the entire lifecycle of a medicine from research and development to manufacturing and supply…*" (AstraZeneca 2014, pg.2), which is its competitive advantage as few other pharmaceutical companies have this feature. Recording increased growth figures for 2014 (1% increase baseline 2013) (AstraZeneca 2014, pg.2) for the first times since 2010, AstraZeneca acknowledges that one reason of decreased growth the previous period was the fact that exclusivity period for marketed drugs of AstraZeneca had expired (AstraZeneca 2014, pg.5). Therefore, investments in the R&D sector of the firm will remain the key tool to respond to the growing competition and shortening marginal profits by renewing the product portfolio of patented medicines.

In 2014, 133 projects have been in the pipeline of AstraZeneca. Pipeline is called the life-cycle of the medicine, from the clinical research conducted for its production until its launch to the markets. 118 of them were in the clinical development process (which includes three phases) and 16 were approved to be marketed (AstraZeneca 2014, pg. 8).

1.3 Problem identification

As mentioned before, the state of the pharmaceutical sector is tightening the marginal profits of the generator companies that base their growth on releasing new drugs from their R&D clinical projects. This fact has driven them to adopt a cost cutting approach on their clinical studies especially in the logistics operations which account for almost 40% of the total clinical trial spending (Zhao and Fleischhacke, 2013).

The implementation of this cost-cutting policy which will result from the improvement or redesign of the clinical logistics operations is not an easy task though, as the supply chain of the pharmaceutical R&D sector is quite complicated presenting significant challenges. The main ones are the following:

1. Globalization of the clinical studies

Along with the expansion of the commercialized drugs to developing markets, the sector of the R&D clinical studies is going global too. In their effort to approach the

promising markets of the developing countries, pharmaceutical firms have turned towards these populations to recruit patients that will participate willingly in their clinical projects. Apart from sourcing of patients, the network of cooperating investigation sites, laboratories, manufacturing facilities is expanding in different countries. The globalization of clinical studies though has to be supported by the expansion of the clinical supply chains that operate in the background. (Rowland and McHanon, 2004)

2. Time management is very crucial

Clinical research is an exceptional paradigm of time-to-market sector. The highest profits from a new drug are made in the patent exclusivity period. The additional day it takes for a clinical research to be completed is one day less from the exclusivity period, which may worth $1 million for a typical drug (Clemento, 1999). It is obvious that clinical supply chains have to be efficient in a timely manner, as potential delays and bottlenecks will sharply increase the overall R&D cost by prolonging the duration of the clinical study.

3. Strict regulatory framework

Clinical trials are characterized by strict government and organizational regulations regarding the materials being used, the manufacturing process and the supply chain operations in order to preserve the safety of patients and the quality of conducted research. This element though may be contrary to the effort clinical managers do to reduce the overall costs, as these regulations usually lengthen the duration of the study and therefore increase the total cost.

Considering the complexity of the clinical logistics operations, as described previously, until recently the pharmaceutical companies used to neglect the logistics operations for another element of the clinical studies: the ancillary and lab kits products. Despite the fact that those products are crucial for the completion of the clinical studies as much as drugs are, they have been perceived by pharmaceutical companies as add-on elements to the main clinical trial logistics operations of drugs. For that reason, ancillary products are usually transported through a parallel to drug kits supply chain as a fully outsourced service. The attitude of the pharmaceutical companies towards this product group though, has already started to change driven by the need to improve clinical logistics processes and reduce their cost. (Klim, 2013)

Under this context, AstraZeneca is seeking ways to improve its clinical supply chain network, which is composed, by two parallel supply chains: one for the drug kits and a separate one for the lab kits. As it can be observed in the "As-is" map in Figure 2, both medicines and lab kits are delivered to the sites from different paths. The lab kits are sourced by an external CPO partner of AstraZeneca, Covance, which sends them to the sites (i.e. hospitals) in order to be filled with samples (i.e. blood) and be delivered back to its laboratory network. On the other path, the majority of the drug kits are delivered to the

sites from another partner of AstraZeneca, Fisher, which is a clinical 3PL service provider.

The two parallel supply chains of the drug and lab kits reach their destination, the investigation sites that recruit patients, in separate shipments. AstraZeneca considers that a potential co- distribution of the two products groups through a coordinated distribution network, will improve the efficiency of the clinical supply chain network with considerable cost benefits. The problem lies in the fact that the firm does not have a clear overview of the clinical logistics operations in the two chains as it has outsourced the distribution for both products to external partners and consequently ignores how the current logistics processes will be formulated in the new state, considering the particularities of the clinical supply chains.

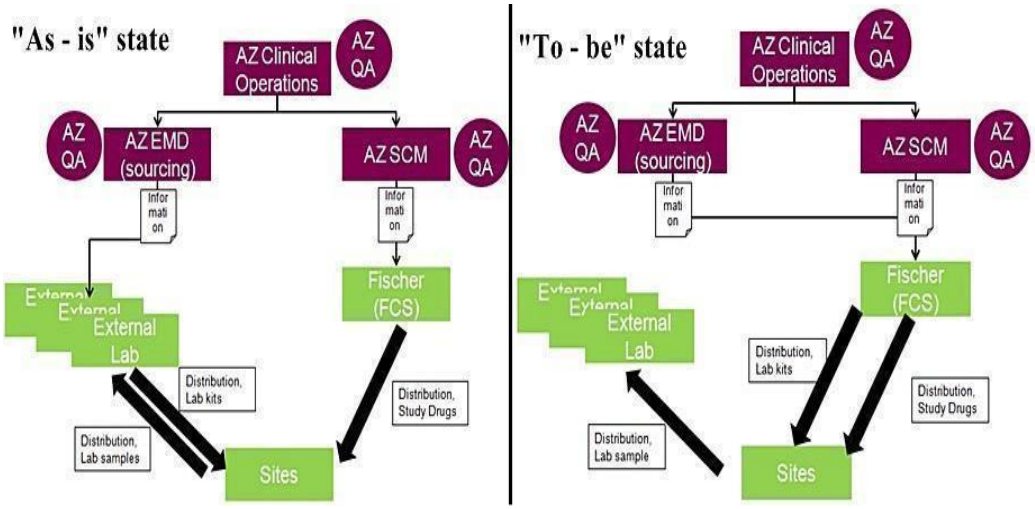


Figure 2: The current state of the distribution flows ("As- is" map) and the future state of coordinated distribution ("To- be" map.) (Source: AstraZeneca's internal document)

1.4 Purpose and Research Questions

The purpose of the project is to investigate, on behalf of AstraZeneca, the potential coordination of the two separate outbound flows to the investigation sites. Given the two maps in Figure 2, which illustrate the current clinical logistics structure the two separate supply chains compose ("As-is" state map) and the potential supply chain structure with the unified distribution channel ("To-be" state map), the project will be developed in two steps. In the first step, the current state of the chains will be investigated in order to identify the factors that will judge the efficacy of the project and the challenges in coordinating the two chains. In the second step, all the issues regarding the changes in the clinical logistics operations will be investigated considering the assessment of the chains from the current state and the constraints of the clinical R&D sector. From the above, the

following research questions are being formulated, each one for the current-state and future- state steps:

Current-state research question:

1. Who are the actors, the logistics operations and distribution links in the two parallel supply chains? In what extent do the two supply chains correspond to the requirements and complexities of the clinical R&D sector?

Future- state research question:

2. How will the logistics processes be modified and which are the main challenges and constraints in coordinating the two supply chain flows? Which are the potential benefits that the stakeholders can reap from the implementation of the project?

1.5 Delimitations

Given the complexity of the project and the strict time framework for its completion, various types of delimitations have to be considered. Firstly, considering that the project focuses on the clinical supply chain of EUCLID study that expands to 29 countries, the geographical delimitation of the conducted investigation is evident. The investigation took place in the R&D headquarters of AstraZeneca located in Gothenburg, Sweden. Most of the interviews were conducted there, while contacts for interviewees that were located elsewhere were given by employees working in the R&D centre.

Additional delimitations regarding the area of investigation and the operations that will be investigated are defined by the company and the scope of the project. Specifically, the project focuses on the last phase of the EUCLID project which is in the research area of cardiovascular therapy. None of the other clinical projects of the firm are investigated. Moreover, the project focuses on the outbound flows of the drugs and lab kits supply chains towards the investigation sites. The inbound logistics of the two supply chains, like the sourcing of the contents of lab kits and the sourcing of the active ingredients for the manufacturing of the study drugs are not included in the investigation area. Additionally, the reverse flow of the lab kits (with samples) from the sites to the laboratories will only be slightly mentioned, just to recognize the potential implications it has to the co-distribution of the other two flows.

1.6 Project Outline

The project is divided in six chapters, including the introduction chapter. The structure of the project is:

Theoretical Framework

In this chapter various mapping methods are described and the most suitable method for the project will be selected. Also, the models of lean optimization, strategic fit and the triple-A supply chain will be presented in order for the reader to understand the models that will be used in the analysis. The constraints in the form of regulations that the pharmaceutical sector faces will be demonstrated.

Methodology

In this chapter the methodological approach, which will be used to work on the study, will be explained. More specifically, the methods that were applied in order to gather and process the empirical data will be presented.

Empirical Data

In this chapter the summary of the empirical data, which was gathered from interviews and internal documents, will be demonstrated. The empirical data will be presented according to the value stream mapping tool in order to map the two parallel supply chains and identify potential wastes that have to be considered in their potential coordination. In this way the first research question of the current state map is answered.

Analysis

In this chapter the empirical data will be processed according to the models of the theoretical framework in order to answer the second research question regarding the redesigned distribution network and the potential benefits it will bring to the stakeholders.

Conclusion

In this chapter, a summary of the answered research questions will be given and potential generalization of the results and future research will be discussed.

2. THEORETICAL FRAMEWORK

In this chapter, the theories which will be applied for the gathering and analysis of the empirical data will be presented.

2.1 Structure of the theoretical framework

Five topics formulate the theoretical background of the project: supply chain mapping, lean optimization, strategic fit model, the Triple-A supply chain principles and the role of regulations as a constraint factor in the clinical logistics operations. Firstly, the main supply chain mapping methods are presented and the most suitable one is selected for mapping the current-state of the project. Having mapped the two parallel supply chains, in the following stage the two chains are being assessed identifying wastes using the theory of the lean principles to identify the wasteful sources and the strategic fit model to picture their responsiveness to the uncertainty clinical studies present. Acquiring a clear view of the two chains, the logistics actions in the common distribution channel will be analyzed under the prism of the Triple-A supply chain model principles. Finally, theory regarding the regulations in the clinical drug development and their constraint role in the clinical logistics operations is being presented. The sequence of the steps that formulate the theoretical background is presented in the Figure 3.

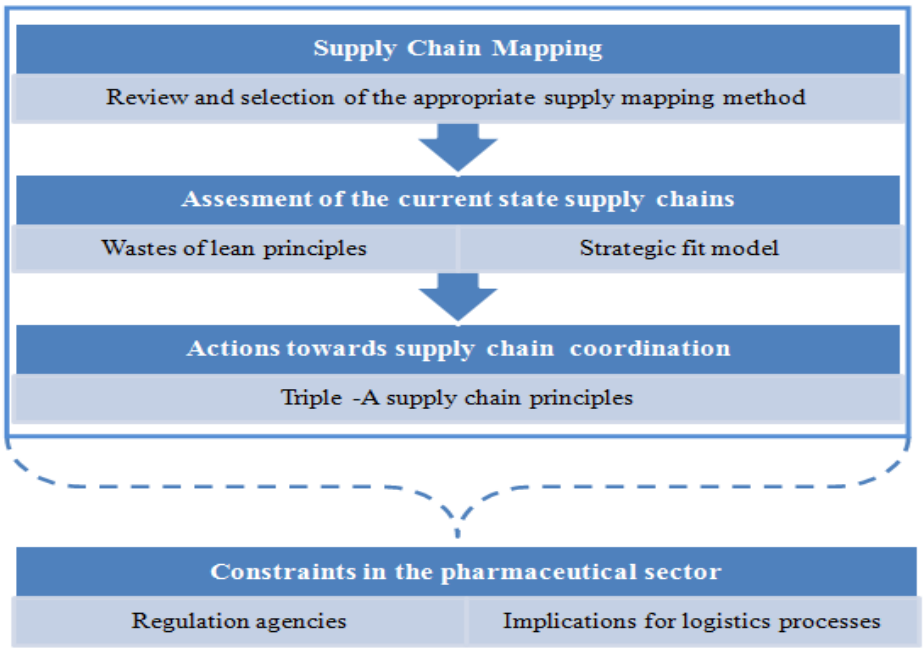


Figure 3: Visualization of the structure of the theoretical framework (Source: compiled by the authors)

2.2 Supply Chain Mapping

Nowadays, firms recognize that competition is being performed between the supply chains they are part of and that competitive advantage is gained through efficient supply chain performance which adds value to the end customer. Thus, it is crucial for the firms to keep control over their supply network, identify the weaknesses and improve the effectiveness and efficiency of the supply chain operations.

Supply chain mapping is the most useful tool in order to acquire all the aforementioned benefits. But the main benefit is its linking role between strategic planning processes and supply chain strategy. Moreover it facilitates the evaluation of alignment between these two elements (Gardner and Cooper, 2003). The visualization the mapping gives a holistic and comprehensive view of the actors and the logistics processes interconnecting them.

Across the bibliography there is a variety of mapping models with terms which overlap with each other under the umbrella of supply chain mapping. This is due to the fact that those mapping models originate from different industries, serving different purposes and focusing on different business models. In addition to this, map characteristics may differ even within the same mapping model in terms of geometry, perspective and implementation.

The main supply chain mapping methods as identified in the literature are the following (Figure 4):

- The SCOR model which focuses on improving the buy-make-deliver operations focusing on the inter-company relationships
- IDEF Detailed Process mapping model
- The value supply chain mapping model, which was initiated by the Lean Institute, and that it will be analyzed further. Some tools of the Value Stream Mapping are the Process Activity Mapping, the Decision Point Analysis and the Supply Chain Matrix that will be analyzed further in this chapter.

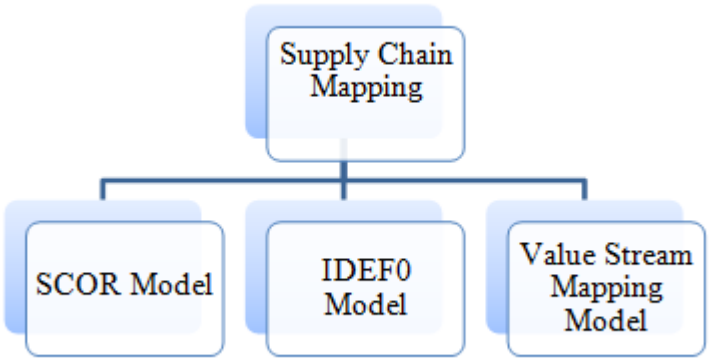


Figure 4: The main supply chain mapping methods (Source: made by the authors)

Despite that process mapping is the core activity for all aforementioned mapping methods, they follow different approaches towards mapping intra and intercompany processes, as they implement in their technique values and elements from different business sectors (Lambert and Cooper, 2000).The basic difference is found between value stream mapping and the other two mapping methods. The latter two methods are more effective in the operations inside the firms, as they have a more traditional approach towards supply chain management. This is the reason that they focus more on the borders of the processes. On the other hand, value stream mapping adopts a more holistic approach towards supply chain and additional mapping techniques focus on detailed segments of the chain (SupplyChainOpz, 2014).

2.2.1 SCOR model

The SCOR model was introduced by the Supply Chain Council in 1996 and performs as a supply chain mapping tool having an operational perspective. They acronym stands for Supply Chain Operations Reference (SCOR). The model includes the processes customer interactions, physical transactions and market interactions. The basic advantage of the model is its standardized structure of process mapping which can be implemented in a diversity of industries (Stewart, 1997). Despite its resemblance to Value Stream Mapping method, the SCOR model does not map the value stream neither targets on detecting the waste across the chain, like VSM does. SCOR structure is composed of three levels of processes (Zhou et al, 2011) (Figure 5):

- Level 1 defines the SCOR model's scope and content by setting the core processes on which competition performance is formulated. These are the processes of PLAN (P), SOURCE (S), MAKE (M), DELIVER (D) and RETURN.

- Level 2 contains the four process categories which characterize the operations strategy the specific supply chain follows. These are: Make-to-Stock (1), Make-to-Order (2), Engineer-to-Order (3) and Retail Product.

- Level 3 is where the process decomposition takes place and where each company follows practices in order to compete successfully in the specific market. The decomposition defines the inputs, outputs, the performance metrics and best applicable practices for each process. These sub-processes have standardized relationships with the associated Level 2 processes.

- Level 4 is where the implementation of specific supply chain practices in operational level takes place in order to have a competitive advantage. The implemented practices are not standardized for all firms but they differ from one industry to another and even from one company to another within the same sector.

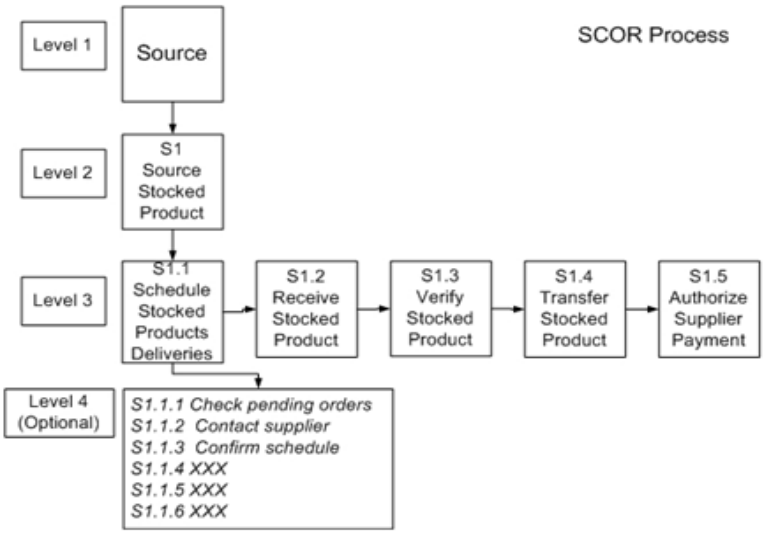


Figure 5: "SOURCE" SCOR process analysis through the four levels of the mapping method (Source: SupplyChainOpz)

2.2.2 Integrated DEFinition (IDEF) detail mapping model

Detailed process mapping finds best application in the model of Integrated DEFinition (IDEF) that was developed by the United States Air Force in 1970s.IDEF is both a mapping model and language which visualizes the intra-company relationships of the activities and functions. The model has developed 14 methods, varying from functioning to object oriented analysis. All the methods are coded from IDEF0 to IDEF14. (IEEE, 1998)

The methods which are related to the business process mapping are IDEF0 and IDEF3. IDEF0 is used on mapping the business functions which compose a process and, in addition to that, IDEF3 enriches the map with the decision points providing an overview of the business process (Brianhunt.org, 2013).

The first step in IDEF0 model is to track which functions are performed for the specific business process and gather all related information for these functions .The information should be about the five elements which compose a function according to IDEF0 model: the input which is needed to start the process, the activity (or process) which transforms the data, the output which are converted from the activity objects, the constraints of the activity and the mechanism that supports the activity (Figure 6).The method gives a comprehensive view of the daily operations within the firm, while the documentation produced during performance of the method can be used for further system analysis and potential improvements (Kawai et al., 2012).

The major advantage of IDEF0 is that it allows an easy integration between different segments of the accumulated processes which can be mapped separately in the same time. As the language of IDEF0 and syntax is in a high percentage standardized, the resulting mapping models are quite flexible and can find appliance in varying situations and

conditions (Waissi et al., 2015).The major disadvantage though, is that the IDEF0 process is limited in mapping the process within a company, without being able to capture the whole concept of supply chain mapping. Moreover the maps can become too technical and complicated (Jørgensen 1995, pp. 345)

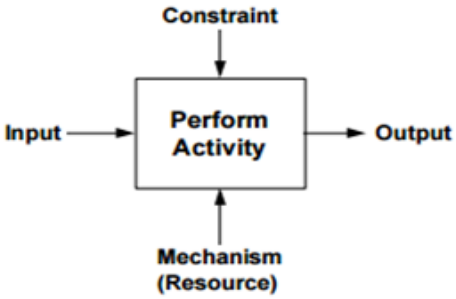


Figure 6: IDEF0 Representation (Source: Jørgensen 1995, pp. 345)

2.2.3 Value stream mapping

The definitions of the Value Stream Mapping (VSM) across literature describe the method as a tool of tracking material and information flows across value chain, from the supplier to the end customer, bypassing without interruption the corporate boundaries (Seth and Gupta, 2005; Pavnaskar, Gershenson and Jambekar, 2003; Womack and Jones, 1996).

The origin of the model explains its purpose to detect waste (muda) across the supply chain, adopting the principles of lean manufacturing which were developed from the Japanese automobile industry of 60s .The business strategy of firms which have implemented lean thinking in their operations, targets on eliminating waste not only from the internal processes but from the value stream across the supply chain, bypassing the corporate boundaries (Pavnaskar et al. 2003).

The method has a holistic approach visualizing graphically the value flow door to door across an enterprise. Value Stream Mapping (VSM) categorizes the process into two groups: the Value Adding (VA) processes and the Non Adding Value (NVA) processes. Both types of processes are tracked upstream and downstream of the supply chain reaching suppliers and end customers (Seth and Gupta, 2005). A graphical map of the current flow of the processes is the outcome of the VMA method. The map can reveal possible bottlenecks in inventory and lead time supporting additionally decision making and process improvement procedures. Moreover the VMA map can be as a future state visualization tool (Rohac and Januska, 2015) giving the opportunity to compare the current and a potential future structure of supply chain flows:

- A Current State Map (CSM) (“as is”) which depicts the current state of the process and value flow and reveal potential improvements

- A Future State Map (FSM) ("to be") which depicts the process and value flow after eliminating the detected wastes.

The comparison between the two maps can give answers on the efficacy and effectiveness of a supply chain redesign process.

Additional value stream mapping tools have been developed to fill the gaps the high level and big picture of value flow value stream mapping visualizes. Depending on the selected level of detail in the mapping and the nature of the sector the mapped supply chain belongs, these tools are useful in tracking waste in different segments of the chain (Hines and Rich, 1997).

The general guidelines of value stream mapping though, especially for maps which are geographically oriented are the following (SupplyChainOpz, 2014):

1) The actors of the mapped supply chain: The stakeholders that participate in the supply chain operations have to be clearly identified. The potential wastes that will be identified at the end of the VSM stem from processes the participating actors perform.

2) The product of the mapped supply chain: Value stream mapping tool is useful to supply chains that operate on one product (or group of products). Therefore investigators must select which product will be the subject of the mapping.

3) Mapping of the distribution network: Having decided upon the product, the material flow upstream and downstream of the supply chain has to be traced. The specific case study focuses on the downstream flow of lab and drug kits to sites is the segment and therefore the distribution network that supports the two products will be mapped.

4) Physical location and lead times: The geographical aspect of the map is developed at this stage, recording the physical locations that supply chain operations take place. The performed lead times and inventory position are also tracked at this step.

5) Information flow: The information flow between the actors regarding the logistics operations is tracked in this step of VSM.

6) Identification of wastes in the last stage of the process.

The main advantage of VMA is that it approaches mapping under the dominant, nowadays, prism of creating value for the end customers On the other hand, VMA can map only one product family requiring extensive data and thus the first step of the model is to identify which product family is going to be mapped (Lopes dos Santos et al., 2014).

2.2.4 Selection of the supply chain mapping method for the project

As it can be observed from the Table 1, the methods differ from each other making them be more or less appropriate depending on the purpose of supply chain mapping. In

contrast to SCOR model and VSM, IDEF0 is focused on the intra company operations approaching the notion of supply chain as separate nodes of actors. The model is not suitable for the specific project as the investigated supply chains are mainly handled by external partners of AstraZeneca. The main dilemma is choosing between SCOR model and VSM, as the methods present similarities. The SCOR model focuses more on the marketing value of the supply chains, and specifically on revealing potentials of enhancing competitive advantage through supply chain operations while VSM focuses on optimization of supply chain performance by eliminating the identified wastes. As the project requires the evaluation of a potential improvement redesign of the distribution network, VSM is considered to be more appropriate. The specific mapping tool will provide a general overview of the current "As is" state detecting potential wasteful processes, and in a next stage, assess the feasibility and effectiveness of the "To – be" distribution flow.

After implementing the VSM tool on both the supply chains, the researchers will have a clear view on the procedures, while potential wastes in the two parallel chains will be will be identified according to the principles of lean optimization.

Table 1: A summary of the three analyzed supply chain mapping methods (Sources: Brianhunt.org, 2013; Jørgensen, 1995; Steward, 1997; Zhou et al, 2011; Seth and Gupta, 2005; Pavnaskar, Gershenson and Jambekar, 2003; Lopes dos Santos et al., 2014; Hines and Rich, 1997)

Characteristics	SCOR Model	Detailed Process Mapping (IDEF0)	Value Stream Mapping (VSM)
Target	Provide an overview of the supply chain management and support improvements to gain competitive advantage	Accommodate the design and integration of the internal functions of the company	Detect and reduce the waste according to lean principles
Area of mapping	Supply chain	Processes within a company	Supply Chain
Objects of mapping	End- to- end descriptions of the material & information flows of the core processes. Focus on relationship between supply chain partners	Internal processes and information flows	Material and information flows

2.3 Lean Principles and Optimization

In this chapter the basic concepts of lean optimization will be presented. Also, a quite important part in our study is the seven wastes that derive from lean thinking.

2.3.1 Lean approach to business processes

Business processes is a series of activities which lead to a product. The accumulation of these business processes targets on adding value to the customers, which can be internal or external. Apart from this main goal, business processes have an administrative role setting the regulatory framework for the inte- and intra- company relationships (Mohaptra 2013, pp. 1-2). The adding value element lies in the core of Porter's value chain model, which supports that the value for the customer will be maximized providing the firm competitive advantage, only if the business processes across the supply chain are approached in a holistic view (Porter 1998, pp 33-52).

In the middle of 90's the principles of the value chain met the concept of lean manufacturing which had expanded by then from its roots in Japanese automobile industry to other businesses sectors. The integration of lean thinking across supply chain took place when the philosophy and approach of lean manufacturing concepts, like "Just-in-Time" and the pull-based "Kanban" method, found application out of the borders of the firms, in the inter-organizational business processes with suppliers and customers. The focus towards providing value to the customer enhanced the implementation of lean values across the supply chain, targeting on eliminating the waste sources (Hines, Holweg and Rich, 2004).

Apart from the adding value concept, the element of cost savings was another issue that enhanced the coordination of lean principles in the field of the supply chain. As the supply chain corresponds to almost 50-80% of the total cost of sales (Myerson, 2012), firms considered that operational cost reduction in the supply chains was an easier task than a goal of increasing the sales, especially in the globalized and competitive environment.

In order to implement lean optimization in a company, both top-down management commitment and bottom-up participation are necessary. The culture of the company should promote the creation of a team-based endless optimization mentality following a top-down approach. Considering that an intra-company process of optimization is complicated by itself, the coordination process across a supply chain is way more complicating, needing supportive tools in order to be successful (Myerson, 2012). Value Stream Mapping is the most commonly used tool in lean optimization coordination. Train-do method is the most suitable in integrating lean thinking inside the companies.

2.3.2 Types of wastes in the supply chain

As mentioned previously, lean thinking originates from the Japanese automobile sector of 1960's, and specifically from Toyota. The firm production system has defined seven

types of wastes lean manufacturing is coping with, and they have dominated in the related literature. These are: inventory waste, transportation or movement Waste, motion waste, waiting waste, overproduction waste, over processing waste and defect or error waste.

Inventory waste has the form of cost which emerges for maintain the inventory. The inventory cost is composed of capital, storage and tax costs and it can fluctuate between 15 and 30 per cent of the product's value. As companies need to have stock, they focus their efforts on holding the lowest possible inventory costs and at the same time, provide high quality service to their customers (Myerson, 2012).

Transportation or movement waste consists of a series of processes and actors, like locating, loading, unloading, information and people. The loading/ unloading points across a distribution network are the most wasteful sources in terms of time consumption, efficiency and manpower. The optimal way requires a minimum number of those points across a routing. But in real conditions materials are stocked and moved several times before reaching their final destination. The waste has also economic aspects, as there is an associated cost involved in moving the materials (i.e. fuel consumption) and additionally the possible damages during their move. (Myerson, 2012)

The idea behind motion waste could be illustrated by the concept of placing the objects or materials that are needed more close to you and the objects or materials that are needed less are placed away. Motions that are not needed or that could have been prevented are identified as wastes, as they do not add any value in the product. The waste is mostly met in the warehouses or in the production line, where their ergonomics have to be taken into account in order to minimize the motion waste (Myerson, 2012).

Myerson (2012) defines waiting waste as the time that passes waiting for materials, information, supplies and people that are necessary in order to perform an action. This time does not add any value in the product. In a great number of procedures, it can be observed that a significant part of lead time is spent on waiting, which may be generated from the next procedure. The waiting waste can result in bigger Work In Process (WIP) inventory.

Overproduction is defined as ordering, manufacturing or processing a product sooner than it is necessary. This element results is generating other types of waste, like inventory, waiting waste due to longer lead times and defect waste due to larger batches. It also restrains the optimal flow of the materials. (Myerson, 2012)

The situation when time or effort is invested in a procedure that does not add value to the product, is defined as the overprocessing waste. Another aspect that could be characterized as overprocessing is the use of expensive equipment, a complicated and time consuming method for a procedure. In those cases not only any value is added but instead the cost increases. For example over-packaging of a product is a type of overprocessing (Myerson, 2012).

The necessity of repairing, reworking or reprocessing a product is considered as a defect or error waste. The waste is bigger when the defect is observed in the late stages of the production phase, as the necessary rework will be more extensive. The worst scenario is when the product is returned from the end customer due to defects. The repairing or reworking is considered of a no value added procedure.

2.4 Strategic Fit

In order for a company to thrive in today's economic environment, it is essential that its supply chain and its competitive strategy are aligned. This alignment is called strategic fit. Failing to achieve strategic fit may doom a company to fail, because antithesis will emerge between different functional objectives within the company or between the objectives in different supply chain points. The model is presented by Chopra and Meindl (2013) and is composed of the three steps The first two steps define the position of the investigated supply chain in the axes of implied uncertainty (horizontal axis) and the responsiveness spectrum (vertical axis) while in the final third step it will be mapped if the specific chain is in the strategic fit zone. The outcome is the resultant of the two previous steps.

Step 1: Understanding the Customer and Supply Chain Uncertainty

In the first step the company attempts to measure the uncertainty stemming from both sides of customers and suppliers. Chopra and Meindl, define this measured uncertainty as implied. That means that this uncertainty concerns the supply chain operations due to changes in the customer's needs and the capabilities of the suppliers For that reason, the firm has to clarify the customer's needs and evaluate the suppliers' capabilities in order to measure the implied uncertainty they cause to the chain. Table 2 presents the key aspects that have to be considered for the customer and supply uncertainty.

Table 2: The key aspects in measuring the customer and supplier implied uncertainty (Source: Chopra and Meindl 2013, pg. 35-36)

Customer Demand Uncertainty	Supplier Capability Uncertainty
Quantity of product required in each shipment	Frequent breakdowns
Lead times customers can tolerate	Unpredictable and low yields
Variety of products customers need	Poor quality
Service level customers require	Limited supply capacity
The price of the product	Inflexible supply capacity
Required level of innovation in the product	Evolving product process

Step 2: Understanding the Supply Chain Capabilities

In the second step, the firm has to identify the capability of the supply chain in terms of how efficient and/or how responsive it can be and place a score in the responsiveness spectrum (vertical axis). In figure 7 the Responsive Spectrum, as it was introduced by Chopra and Meindl (2013), is presented. Full efficiency and full responsiveness are perceived as two opposite attributes, as an efficient supply chain has cost benefits but it is poorly responsive, while in the opposite case the highly responsive supply chains presents high operational costs. The attributes that have to be examined to label a supply chain responsive or efficient are the following:

- Responsiveness to ample ranges of quantities needed
- Ability to meet short lead times
- Ability to manage a wide variety of products
- Ability to produce extremely innovative products
- Ability to provide service level
- Ability to manage supply uncertainty

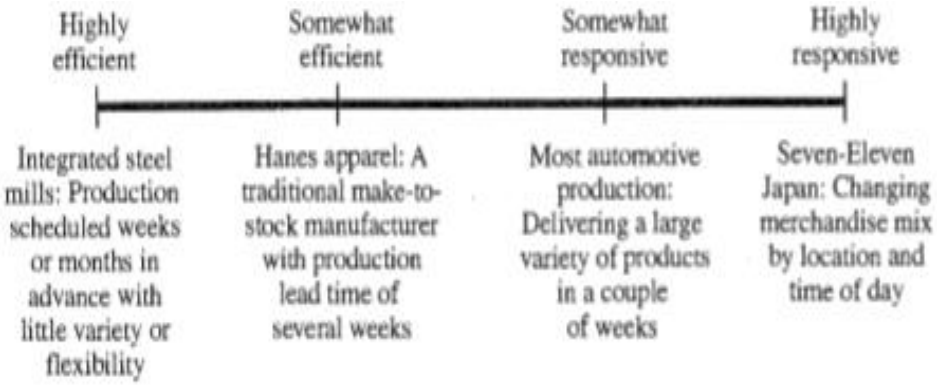


Figure 7: The Responsiveness Spectrum (Source: Chopra and Meindl 2013, pg.39)

Step 3: Achieving Strategic Fit

Having investigated and mapped the position of the supply chain in the two axes from the previous two steps, in is feasible in the third step to identify whether the supply chain is in the strategic fit or not. This is done with the use of the diagram (Figure 8). If the supply chain is not in the strategic fir zone, the firm has to proceed in actions that will change the position in the vertical axis, making the supply chain more responsive or more efficient.

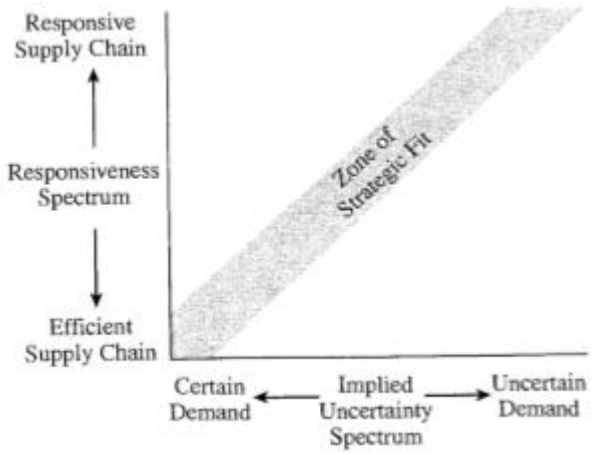


Figure 8: Finding the zone of Strategic Fit (Source: Chopra and Meindl 2013, pg. 40)

2.5 The triple-A supply chain

Knowing the position of a supply chain regarding the strategic fit zone, it is possible to take actions that will improve the responsiveness and efficiency of that chain. These actions align with the principles of triple-A model. These principles are: (Lee, 2004):

- Agility: The aspect of agility in a supply chain is necessary in order to react immediately to changes that occur in demand or supply with the minor possible cost, especially in today's global business environment.

- Adaptability: On the hand, the element of adaptability focuses on the permanent changes supply chains have to do in order to adjust to the evolution of the market structures and strategies.

- Alignment: The element of alignment, which is the most crucial aspect of the coordinated supply chain of lab and drug kits, is focused on bringing closer the interest of the involved companies to the aims and interest the main actor has set. Supply chain coordination is the strategic aspect of this attribute, as through its centralized and decentralized decision making mechanisms (e.g. Collaborative Planning and Forecasting, Vendor Managed Inventory) coordinates the information, material and financial flows of the supply chain and aligns the goals and benefits for the stakeholders.

In Table 3 the three characteristics are summarized towards the goal and the methods that should be followed in order to achieve them.

Table 3: Summary of the Triple-A characteristics (Source: Lee, 2004)

	Agility	Adaptability	Alignment
GOAL	• Respond to short-term changes in demand or supply quickly • Handle external disruptions smoothly.	• Adjust supply chain's design to meet structural shifts in markets • Modify supply network to strategies, products, and technologies.	• Create incentives for better performance.
METHOD	• Promote flow of information with suppliers and customers. • Develop collaborative relationships with suppliers. • Design for postponement. • Build inventory buffers • Have a dependable logistics system or partner. • Draw up contingency plans and develop crisis management teams	•Spot new supply bases and markets. •Evaluate needs of ultimate consumers—not just immediate customers. •Create flexible product designs. •Determine where companies' products stand in terms of technology cycles and product life cycles	• Co-exchange information and knowledge freely with vendors and customers. • Lay down roles, tasks, and responsibilities clearly for suppliers and customers. • Equitably share risks, costs, and gains of improvement initiatives

2.6 Constraints and regulations in clinical R&D sector

A major constraint element in the potential coordination of the drug and lab kits are the regulations that dominate in the R&D pharmaceutical sector affecting the clinical logistics operations. The logistics operations in the common distribution network will be modified and this change has to comply with the legislative framework that regulates the clinical studies.

Clinical trials are regulated by agencies which focus on preserving the efficacy and safety of the candidate to be marketed drug. Their utmost mission is the protection of the safety, welfare and individual rights of participating human subjects (recruited patients) (Wall and Wiernas 2015, pp. 231**)**.

These regulatory agencies may be federal or independent. Each country has its own regulatory agency which sets the regulations all the imported drugs (marketed and under development) have to comply. Some of the most important agencies are the Food and Drug Administration (FDA) which is the federal regulation agency of the United States and the European Medicines Agency (EMEA) which is regulatory instrument of the EU member states. The challenging for the pharmaceutical companies that perform clinical studies across the world is to get approval for the developed drug by a wide range of countries which present high heterogeneity in their legislative framework. Despite the differences between the regulatory agencies across the world, steps have been made in harmonizing the regulations landscape regarding the drug development. (Handoo, Shweta et. al, 2012)

In order for a developed new drug to be imported in a country, the respective regulatory agency has to give an import license approval. The license is given only after the inspection and assessment of the preclinical and clinical study which has applied for clinical trial approval. These procedures are based on the principles of Good Clinical Practices (GCPs).GCPs are ethical and scientific quality standards that have to be met in all stages of the clinical trials. The compliance with these standards ensures that the rights, safety and well-being of humans are protected according to the Declaration of Helsinki. There are three main types of GCPs on which regulatory agencies base their requirements and rules: (EMEA, 2015)

1. Good manufacturing practice (GMP) and Good distribution practice (GDP): They are related aspects on assuring that the products are serving their intended use and that the quality is maintained throughout the distribution network.

2. Good clinical practice (GCP): It sets the standards that clinical trials have to comply in terms of design, recording and reporting their data and results assuring the safety of human subject and the credibility of the research.

3. Good laboratory practice (GLP): It defines quality standards and criteria regarding the practices and conditions in the laboratories during the clinical studies.

Apart from those types of GCP, there are certain regulations regarding the conditions under the logistics processes of the clinical supply chains have to be performed. Therefore, there is also the Good Distribution Practices (GDP) protocol that sets regulations regarding the premises and storage conditions, the use of containers and their labeling, the transportation of the drugs, their dispatching and the associated documentation (World Health Organization, 2005). It is crucial that in the potential coordination of the distribution of lab and drug kits that these regulations will be met.

Apart from these regulations that directly affect the clinical supply chain operations and therefore the investigated project, there are also regulations associated to the study design of each project and have indirect implications on the logistics processes of the outbound

channel to the investigation sites. For example, the number of the different types of drugs that will be used in a specific clinical study is a characteristic that makes more complicating the potential consolidation of the drug and lab kits. In EUCLID, the investigated clinical study, two types of drugs are being used the developed and a competitor's, having an active treatment label as a study (Table 4).

Table 4: Types of controlled clinical trials (Source: e-Code of Federal Regulations, 2016)

	Types of concurrent controlled trials		
Clinical trial characteristics	**Placebo trial**	**Active treatment trial**	**Dosage comparison trial**
Types of drugs used	1. The study drug 2. A placebo which resemble the study drug as far as possible	1. The test drug 2. A marketed drug which aims at the same therapy area	At least two dosages of the same test drug
Mechanism of the trial	Comparison between the study drug and the placebo to assess the efficacy and safety of the clinical drug	Comparison between the marketed and the study drug and assessment of the therapeutic effectiveness and differentiation of the clinical drug	Investigation of dosage factor as an affecting element on the efficacy, safety and effectiveness of the clinical drug.

Blinding is another vital element on the clinical studies, where regulatory agencies set strict requirements. Blinding's mission is to mitigate the bias element by hiding (or not) characteristics and information regarding a clinical study from the actors that participate: the sponsor, the investigator and the patients. In this way, the efficacy and credibility of the study results are protected. Therefore five types of blinding are formulated depending if the actors are blinded or not and the mechanism of the conducted study (See Table 5).

Table 5: Types of blinding studies (Source: Wall and Wiernas, 2015 p. 237)

Trial blinding description	Patient blinded	Investigator blinded	Sponsor blinded
Open-label	No	No	No
Single-blinded (or masked)	Yes	No	No
Double-blinded (or masked)	Yes	Yes	Yes
Observer (or investigator)-blinded (or masked)	Yes	Yes	Usually
Double dummy (in order to blind dissimilar dosage forms, investigational product or placebo are given to each patient, e.g., active suspension + dummy tablet or dummy suspension + active tablet)	Yes	Yes	Usually

In all types of blinding, uniformity in the physical aspects of investigation elements is the most crucial element in order to prevent bias in the clinical supply chain. The elements of sight, sound, taste, smell and touch must not reveal any information to the blinded groups as this may threaten the credibility of the study results (Monkhouse and Rhodes, 1998 as cited from Wall and Wiernas, 2015). For example, for the purposes of sight uniformity, packaging and labeling procedures are under scrutinized control by regulatory agencies so that they won't reveal any information about the drugs to the participating blinded groups. The masking of packages and containers used for the storing and transporting of drugs is a common practice, especially for those studies where different types of blinding may be used in different stages of the project

EUCLID is a double blinded, double-dummy clinical study where Brilinda, the study drug and a competitor's one are given to patients by the doctors without both knowing which type of drug is given.

As it can be concluded regulation agencies across the world set legislations that set barriers regarding the operation of the clinical logistics processes. The import license processes affect mainly the performed lead times, while the blinding rules affect the distribution processes through the CDP protocol. The potential consolidation of the drug and lab kits has to comply with the constraints these regulations set.

3. METHODOLOGY

The research elements that compose the methodology of the project will be presented in this chapter. Firstly, the research and design process is explained. The research and design process is divided in the three phases that are presented below. This is followed by the data collection methods and the data analysis which will be adopted. Finally, the evaluation of the study is analyzed, which is divided into the reliability and the validity of the project.

3.1. Research Design and Process

The thesis is conducted as a project of AstraZeneca. As the firm provided a very specific topic to be investigated within its environment (the clinical R&D sector) the most suitable methodological approach is the one of case study (Bryman and Bell 2011, pg .41-44). Additionally, the fact that the project examines the complexity of implementing a supply coordination project in the context of clinical trials sector, is another reason for approaching the topic in a case study method manner because, according to Stake (1995) and Bryman & Bell (2011, pg 59), case study is suitable when examining the complexity of the subject.

Qualitative research methodology is selected for the project by collecting empirical data. The qualitative methodology is appropriate for researches that focus on the context of the investigated topic (Bryman and Bell 2011, pg. 410-411) and thus is appropriate for the subject of clinical trial supply chains. The empirical qualitative data are derived from interviews with people who have key roles in the two parallel supply chains in order to fully comprehend the current situation of AstraZeneca's clinical supply network and investigate its future state after the coordination of the distribution flows.

The vital element in order to answer the research questions by generating solid conclusions is to analyze the empirical data using relevant models as found in literature. Dubois and Gadde (2002) developed the model of systematic combining, in which the literature review, the empirical data and the analysis emerge at the same time. This is the process of matching. The process of direction and redirection takes place after the collection and analysis of the empirical data, in order to better match the findings with the literature review (Figure 9).

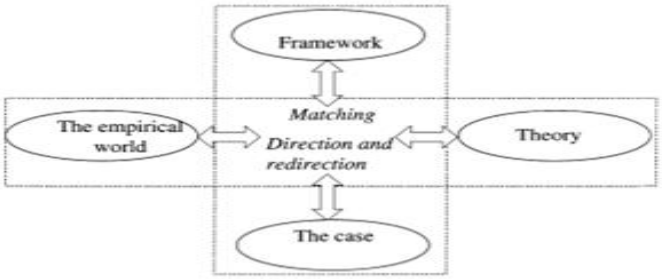


Figure 9: Systematic Combining (Source: Dubois and Gadde, 2002)

The work in this study was performed in three phases. In the Phase one (1) the main issue was to define the scope of the project. The research questions were formed, an initial understanding of the problem was achieved and the headlines in the theoretical framework were defined. Phase two (2) consisted of gathering the empirical data through semi-structured interviews and internal documents. The empirical data are presented according to the steps of value stream mapping. In this way a part of the current-state research question is answered. In Phase three (3) the analysis of the empirical data took place in order to evaluate the current state of the two chains and identify the feasibility, the challenges and the benefits of the proposed solution. In Table 6 the three main phases of the study are summarized.

Table 6: The phases of the project (Source: compiled by authors)

	Phase 1	Phase 2	Phase 3
	Scope of Project	**Case Study- Empirical Data Collection**	**Data Analysis & Conclusions**
GOAL	• Comprehend the problem • Define the scope of the research	Identify the stakeholders in the two chains and map the logistics processes in the material and information flow across the distribution channel to the investigation sites	• Evaluation of the "As-Is" state of the two chains • Implementation of the "To-be" state • Challenges and benefits • The value of the supply chain mapping as a redesign tool
METHOD	Theoretical Framework • Supply chain mapping • Lean principles • Strategic Fit • Triple-A supply chains • Constraints in the clinical supply chains	Case Study Empirical data collected with: • Semi- structured interviews • Internal company documents	Use of the theoretical models to analyze the empirical data.

3.2 Data collection

A wide variety of sources were used to collect data for the needs of the project enhancing its quality. The gathered data are labeled either as primary (empirical) or secondary. The first category of data is collected by the researchers (Management Study Guide, 2011), tailored for the project of the thesis, by interviewing people in key roles in the clinical supply chains of AstraZeneca and from internal documents of the company. The latter category of data, which are generated and gathered by other researchers, were collected after a thorough investigation on literature and related, documents (Management Study Guide, 2011).

3.2.1 Semi-structured interviews

A very common source of primary information in case studies is the conducted interviews. The interviewees can be asked to provide information or their insight for a particular matter. It is crucial to identify the key informants for the specific case study in order to acquire all the data possible and a broad view of the topic. The development of interpersonal influence with the interviewees must be avoided by not solely depending on few ones, but instead having more sources of information on the issues that the key respondents present their point of view. Interviews in qualitative research usually have unstructured or semi-structured form. In contrast to the quantitative research in which structured interviews are more appropriate to extract valid and reliable numerical data, qualitative interviews emphasize on understanding the concept of the scheme and on the interviewee's point of view. There is a high level of flexibility for both sides, since the interviewer can ask questions based on the interviewee's replies departing from the schedule and following the direction the interviewee takes the discussion. In this way the interviewer can extract rich data. (Bryman and Bell, pg 466-467)

For the specific project, the form of semi-structure interviews was judged as the most suitable. The interviewers formed an interview guide, in which the topics of discussion and some key questions had been predefined. The interview guides were highly modified for the different actors of the clinical supply chain that were interviewed. This type of interview provides flexibility to the researcher to deepen the investigation and obtain a clear understanding of the theme from each interviewee's perspective. The interviews were recorded after the interviewees had given their permission. Later, the notes from the interviews were summarized for the mapping of clinical trial supply network and for potential improvement using the related theoretical framework.

3.2.2 Literature Research

Deep literature research was conducted to gather information on the theoretical subjects that were relevant to the project and the research questions. The literature research helped the researchers build a solid theoretical basis regarding the selection of the most appropriate supply chain mapping method and use of it to gather the empirical data, the evaluation of the supply chains by combining the lean principles and the strategic fit model, and the constraints of the pharmaceutical sector that affect the potential coordination. The most valuable sources of information for the literature are public scientific books, articles, reports and web sources. The majority of the articles and reports were collected using the online services of the library of University of Gothenburg and Chalmers Technical University. The Summon database was reached through the website of the library of GU and allowed access to a vast majority of scientific papers. The Scopus and Google Scholar databases were also used in a smaller extend.

The keywords that were used during the search were relevant to the selected topics investigated. The main ones were "pharmaceutical supply chains", "clinical trial supply chain". "clinical research supply chain", "supply chain mapping", "value stream mapping", "lean manufacturing", "waste", "strategic fit", "triple-A supply chain", "R&D

pharmaceutical sector", "regulations in supply chains", "constraints", "distribution", "consolidation".

3.2.3 Internal documents

Apart from sources in the literature, internal documents were also used to collect related data. According to Yin, (2014, pp.106-118) there are various types of internal papers: company reports, events, personal documents and mass media, like newspapers. All of the internal documents used in the thesis were company reports and documents. The documents were used by the researchers after they had been evaluated based on their authenticity, reliability, credibility and representativeness.

3.3 Data analysis

The relationship between the theory and the research findings characterizes the data analysis process for this qualitative project. Based on that, there are three methods of data analysis: the deductive, the inductive and the iterative. In the deductive strategy the relative to the topic theory is used to reach to observations and findings while in the inductive strategy the reverse approach is used, the theory is the outcome of the research findings based on generalizations. In iterative data analysis, both deductive and inductive strategies are used: the researcher is weaving back and forth between data and theory (Bryman and Bell, pg 13).

In the specific project theoretical models are used during the gathering and analysis of the empirical in order to answer the research questions. Using the systematic combing model during the project, additional theoretical models were introduced and used for the analysis of the empirical data. Therefore, the data analysis of the project can be characterized as deductive.

3.4 Reliability and validity of the research

According to Bryman and Bell (2011, pg 41) the evaluation of trustworthiness of a research is formulated by the elements of reliability and validity.

Reliability measures and assesses the coherence and the repeatability of a study. The reliability of the specific project is guaranteed from the use of standardized theoretical models in each step towards the investigation of the current and future state of the clinical logistics network. This means that the process of investigating the specific case study would be the same no matter when or how many times it would be conducted. The coherence of the research is enhanced by saving the processes of the research, like for example the stakeholders of the supply chain that will be interviewed and the recording of the interviews (Bryman and Bell 2011, pp.41-42).

Validity is considered as the main criteria of a research and it evaluates the integrity of the outcomes from a research. Bryman and Bell (2011, pp. 41-44) identify three types of

validity. Construct validity is concerned with the validity of the operational measures. The use of many sources of evidence which have sequential interconnection enhance the construct validity of a research (Yin, 2014, pp.46-48). In the specific project interviews from all the stakeholders of the two supply chains who cooperate for the clinical logistics operations and internal documents with quantitative data guarantee the construct validity of the project. A second type of validity, internal validity, investigates the causal relationship between two (or more) variables. Internal validity in this project is implemented through the process of, meaning that several sources of data were investigated over the same topic (Bryman and Bell 2011, pp. 397). Interviewing both representatives from AstraZeneca and its outsourcing partners in the two supply chains, the authors investigated each topic of the clinical logistics (i.e. lead times) from both participating sides. Moreover, the conducted interviews were recorded so that the researchers could listen to them plenty of times and take notes. Finally, the external validity relates whether and in what extend the findings of the project can be generalized and be applicable to other topics. The methodological approach and analysis of the future-state plan could be applied in coordination projects that the involved supply chains present similarities with the ones of the pharmaceutical sector.

4. EMPIRICAL DATA: AstraZeneca's clinical supply chains

In this chapter, the empirical data which have been gathered from interviews with people representing the stakeholders in the two supply chains and from internal documents are presented. In order to answer to the first part of the "current-state" research question the empirical data are presented according to the steps of the Value Stream Mapping method as shown in paragraph 2.1.3. Therefore, the actors of the drug and lab kits supply chains have been identified, the outbound flow of products through the distribution networks is tracked and traced, and the information systems that support the logistics processes have been recognized. In Table 7 the interviews which have been conducted are presented in chronological order.

Table 7: List of the conducted interviews (Source: compiled by the authors)

Name	Position	Company	Date
Benny Jönsson	Clinical Project Manager of EUCLID	AstraZeneca	Multiple meetings mainly in February
Stefan Berlin	Supply Chain Study Manager	AstraZeneca	Multiple meetings mainly in February
Ulrika Ivarsson	R&D Supply Chain IVRS Leader	AstraZeneca	02/03/2016
Bryan Egner	Functional Planner and Business Analyst	AstraZeneca	03/03//2016
Malin Wikberger	Clinical Studies Sourcing Manager	AstraZeneca	11/03/2016
Chris Jones	Distribution Manager	AstraZeneca	17/03/2016
--	--	Fisher	24/03/2016 (sent questions)
Alex Klim	Head of Business Development & Consulting Manager	DHL Clinical Trial Logistics	29/03/2016
Anna-Lena Ek	Clinical Sample Scientist	AstraZeneca	08//04/2016
--	--	Covance	20/04/2016

4.1 The actors

The development and completion of the third phase of drug development of EUCLID project, is supported by two clinical supply chains: the drug and lab kits. Their aim is the disposal of the two product groups to the investigation sites that cooperate with AstraZeneca in the particular clinical study. In their turn, the investigation sites will recruit patients by examining firstly their liability to participate in the study by using the lab kits to take specimens from them and, depending on the laboratory result, will be given the types of drugs that are used in the clinical research (Jönsson & Stefan, 2016). The interviews which were conducted for the drug and lab kit supply chains revealed the major actors involved in the logistics process of distribution to the sites.

Tables 8 and 9 present the stakeholders in the clinical supply chains of drugs and lab kits respectively. It could be supported that these stakeholders are generally met in clinical R&D pharmaceutical supply chains. In the same tables also, the actors in the investigated case study are being presented.

4.1.1 Actors in drug kit supply chain

As it can be observed in Table 7, AstraZeneca has the leading role in the supply chain of drug kits. The study group that works on the EUCLID project, in cardiovascular sector, focuses on investigating the efficacy and effectiveness of a new drug, Brilinda (Jönsson & Stefan, 2016). The team is responsible for the design of the research, which affects in a great extend the logistics operations and the geographical expansion of the distribution network. (e.g. location of the recruited investigation sites).

Fisher Company is a leading 3PL logistics provider specialized in the clinical logistics operations. The firm is a strategic partner of AstraZeneca having undertaken the logistics operations of packaging, labeling and distribution of the drug kits to the investigation sites for most of clinical studies of the firm. Nowadays, Fisher has undertaken the logistics processes of almost 86% of total operating drugs, while a 14% is operated from AstraZeneca (Wikberger, 2016).

Fisher contracts with courier companies to perform the shipments of drug kits to the sites and therefore they also play a key role in the outbound flow of drug kits. DHL, FedEx and PSI are the major courier companies that cooperate with Fisher and AstraZeneca (Jones, 2016). The settlement of obligations, costs, cargo management and responsibility between the couriers and Fisher (and AstraZeneca) are defined by INCOTERMS commercial terms (Klim, 2016).

Regulation agencies and customs authorities play a notable role in the clinical drug development. The license of importing a new drug for clinical purposes is decided from the regulation agencies of each country. Clinical trial approval entails long lasting processes of auditing and documentation. Additionally import processes at the customs are also time-consuming. These regulations affect the supply chain of drug kits in terms of the performed lead times, the distribution structure and the potential consolidation of the two product groups.

The researchers involved in the clinical study and cooperate with AstraZeneca are called investigators. As investigator can be an individual researcher, a doctor, an organization or a hospital. Investigation sites are the locations where the investigators are and recruit patients dispensing the imported drugs. The lab kits play an important role for the sites, as they are the tools they use to extract results of the efficacy and effectiveness of the studied drug. The actors of the project are presented in Table 8.

Table 8: The actors in the drug kits supply chain (Source: compiled by the authors)

MATERIAL FLOW OF DRUG KITS

Manufacturer and sponsor of the clinical study	The 3PL clinical services providers	The couriers that perform the drug kits shipments to sites	Regulation authorities & customs	Investigation sites (i.e. hospitals)
CASE STUDY				
AstraZeneca Clinical study: • Cardiovascular sector • Phase III • EUCLID program	**Fisher Clinical Services** Outsourced Services: • Secondary Packaging • Labeling • Distribution Network • Documentation	**Contracted couriers with Fisher &AZ** Shipments in Fisher's distribution channel: •Direct to Site (DTS) •Via country depot (VD)	**Drug regulation agencies and customs** 28 importing countries: • Varying legislation framework • Clinical Trial Approvals (CTA) • Import Licenses (IL)	**Sites that recruit patients with the clinical drug of the EUCLID program** •13,500 recruited patients in 28 countries •Drug dispense to patients for the whole study period (3-5 years)

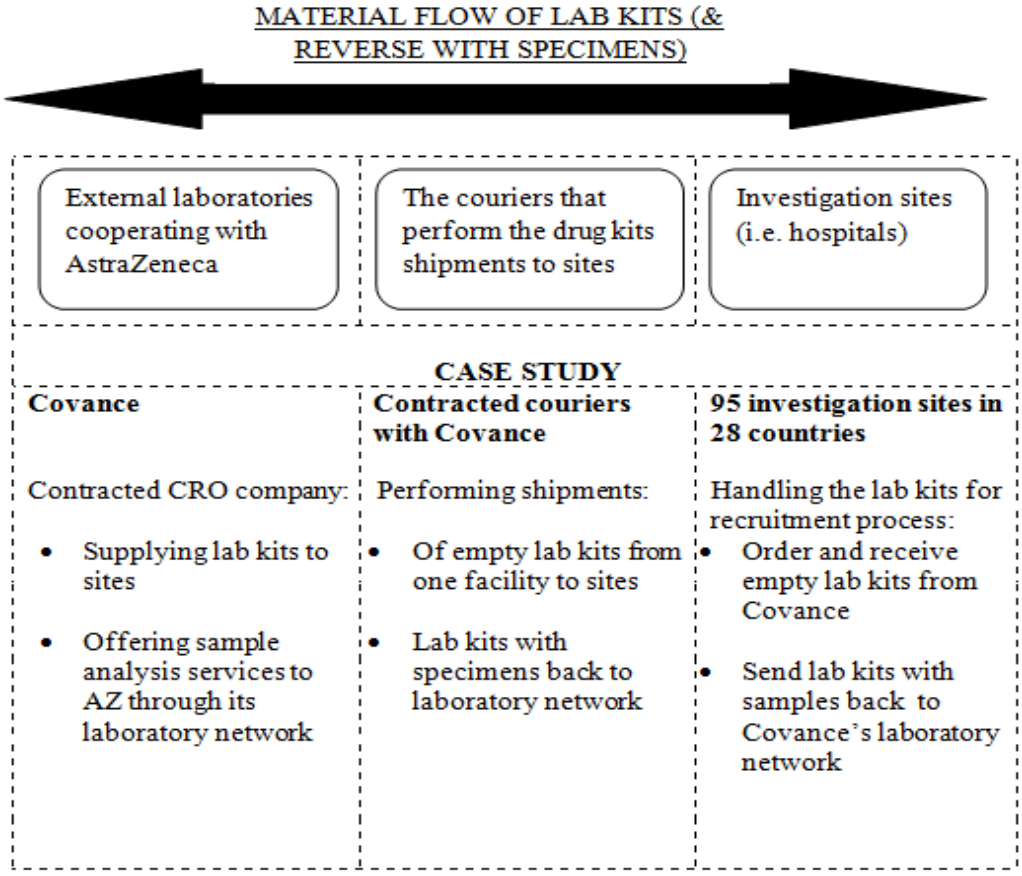
4.1.2 Actors in lab kits supply chain

In the supply chain of lab kits, AstraZeneca cooperates with Covance one of the largest Clinical Research Organization (CRO) companies that provides laboratory services to pharmaceutical companies. Having developed a network of owned and contracted laboratories, Covance provides complete geographical coverage service to its clients (Covance, 2016). Acknowledging that, AstraZeneca has contracted with the firm to provide laboratory services on the last phases of the clinical studies which require a big number of recruited sites and patients globally expanded (Jönsson & Ek, 2016) Under this service, Covance supplies the investigation sites with lab kits and receives them back with patient specimens for laboratory analysis in order to provide information to AstraZeneca about the efficacy and efficiency of the developed drug. Case study's project, EUCLID, is not an exception. The cooperation between AstraZeneca and

Covance is going to expand in clinical studies which are in earlier development phases (Ek, 2016).

Like Fisher, Covance has contracted the shipment of lab kits to the sites and backwards to courier companies. Apart from courier companies with global presence, like DHL and UPS, Covance cooperates with local firms in some countries (Covance, 2016). Finally, the investigation sites are the last actors in the chain, as they receive the empty lab kits they have ordered from Covance for taking samples from the recruited patients and ship them back for analysis. The main actors in the lab kits supply chain are presented in Table 9.

Table 9: The actors in the lab kits supply chain (Source: compiled by the authors)



4.2 The products

4.2.1 The drug kits

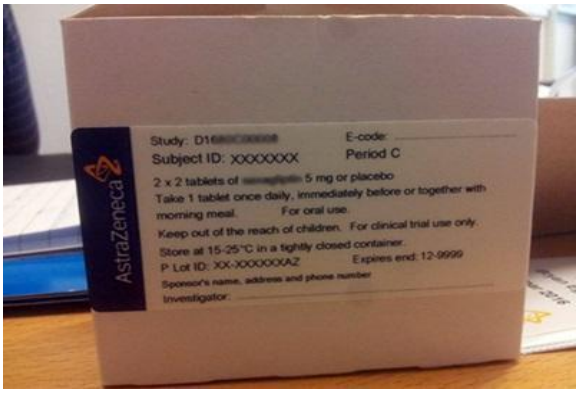
The information regarding the characteristics of the drug kits and the logistics processes of packaging and labeling are provided during the interview with Bryan Egner (2016) accompanied with an observation on the departments of packaging and labeling at AstraZeneca's R&D centre. These logistics processes, that take place in AstraZeneca's headquarters and concern small scale quantities of drug kits, are identical with the processes operated in Fisher's central depot with the difference that the quantities of drug kits there are much bigger. Additional information was sent by Fisher after the authors

had handed them further questions on the clinical logistics operations they perform for AstraZeneca

In the last phase of most of the blinded clinical trials, like EUCLID project, study drugs are packaged into drug kits for their distribution to the investigation sites. The content may be or not homogeneous, including more than one drugs, in different forms (pills, tablets, liquid etc). A drug kits may also include combination of products, namely products composed by a combination of drugs and devices (e.g. inhaler). Brilinda, the studied drug of EUCLID project, has the form of pill. The other types of participating drugs (placebos and competitors' commercialized drugs) have the same form. The drug kits enable investigators to administer study drug to subjects in a blinded manner. (Jönsson & Egner, 2016)

Packaging and labeling processes play a very crucial role in the formation of the drug kits. There are two types of packaging: primary and secondary. Primary is called the first layer of packaging that has direct contact with the dosage (drug) element. An example of primary packaging is vials that contain liquid drug. As secondary, is characterized the additional packaging layer that protects the dosage and primary packaging. Examples of secondary packaging are the carton boxes. The primary and secondary packaging formulate the drug kit or otherwise the container closure system. (Egner & Fisher, 2016)

Picture 1: A packaged and labelled drug kit box (Source: Taken by the authors)



Packaging is one of the main processes Fisher has undertaken for AstraZeneca, both primary and secondary type. The procedure takes place in Fisher's main depot centers in UK, USA and Switzerland where there are the appropriate facilities to support both ambient and refrigerated packaging. What is important for packaging is the compliance of the processes with the current Good Manufacturing Practices (GMP) requirements. (Fisher, 2016)

The labeling of the drug kits is associated with the information which has to be written on the primary and secondary packages. Some examples of information that need to be printed on the labels are: the code of the program, the code of the study, the kitID (IWRS/IVRS number), the expiry date, the name of the investigator, the e-code (code for the patient), the visit number and the sponsor (see Picture 1). The varying regulations which apply to the importing countries complicate the labeling of the kits. For example, while AstraZeneca has outsourced to Fisher the customization of booklets that accompany each drug kit, according to the importing country (i.e. language translation), it

still keeps in- house the printing of the first page of every booklet as it contains information that comply with common legislations in all countries (Egner, 2016).

Compliance with uniformity according to the blinding design of each study is important for the process of labeling of the drug kits. Fisher acknowledges that and has created a specific intra-company body, Clinitrak Clinical Label Services, that focuses on providing customized labels to the study drug kits respecting the blinding design of the clinical study (Fisher, 2016).

4.2.2 The lab kits

Covance owns one central facility where all lab kits are produced. All the investigation sites are supplied with lab kits from this manufacturing facility. What should be clear with the term "production" in the case of lab kits is that Covance does not manufacture the content objects of the lab kits (e.g. tubes) but only composes the lab kits with the appropriate tools that will be used for the sampling and the analysis required for each clinical study.(Covance, 2016)

Different types of lab kits may be used in the same clinical study, depending on the phase each recruited patient is. In the case of EUCLID project, where lab kits are used just once for each candidate patient, the content is the same for all lab kits.(Ek, 2016)

The most usual content inside a lab kit are different types of tubes. Each type is used for different blood sample analysis. Needles and biomarkers also are usually included inside a lab kit. Packaging also plays an important role in the supply chain of lab kits, especially when they contain human specimens. Lab kits without containing samples are, in most cases, ambient products and therefore no temperature controlled packaging and distribution conditions are required. In contrast, their reverse flow back to Covance being filled with samples, special secondary packaging solutions may be needed to protect the human specimens which are sensitive to the conditions of the external environment.

4.3 Mapping of drug kits outbound flow

4.3.1 The distribution channel

With the clinical research network expanding across the globe, a few years ago AstraZeneca decided to outsource a large part of the clinical logistics services to Fisher and in a much lower scale to Almac.

The distribution of drug kits to the participating sites and from there to the recruited patients is performed through a globally widespread network of Fisher depots and, in a smaller scale, from AstraZeneca centers. Fisher has sixteen facilities that comply to the Good Distribution Practices (GDP) regulations for storage and shipments conditions. From those sixteen, three of them are the central ones: in Horsham (UK), Allentown (USA) and in Singapore. All the others are depots that serve investigation sites in

regional and country geographical expansion level. In some countries though, Fisher does not hold own depots and therefore cooperates with local logistics service providers (Fisher and internal documents, 2016)

As aforementioned, the shipments, either from a Fisher depot or AstraZeneca centre, are performed by courier companies. These couriers have been contracted by the firms to perform the transportation of the drug kits until they reach to their final destination. In most cases established firms, like DHL and FedEx, perform the international echelon of the distribution from the Fisher (or AZ) site to the country/regional depot (if there is one), while the transport within a country from the local site to the investigation sites may be also performed by local couriers. The contracts between them set the issues of transport responsibility, cargo safety, costs etc. The documentation accompanying the shipments, like customs clearance, is fully operated by Fisher. In some cases though, AstraZeneca takes full responsibility using its own customs agents. (Jones & Klim, 2016)

Two types of distribution strategies can be recognized in the clinical drug supply chain:

1. Direct to Site (DTS) distribution: These are the shipments where the drug kits are sent directly from the central Fisher depot in UK to the investigation sites (Figure 10).

Figure 10: Fisher's Direct to Site Distribution (Source: compiled by the authors)

2. Via Depot (VD) distribution: These are the shipments where the distribution is comprised of two legs: the first leg is the transport of the drug kits in bulk quantities to country/regional depots of Fisher from the central Horsham depot and the second one, which takes place inside the importing country from the country depot to the investigation site (Figure 11).

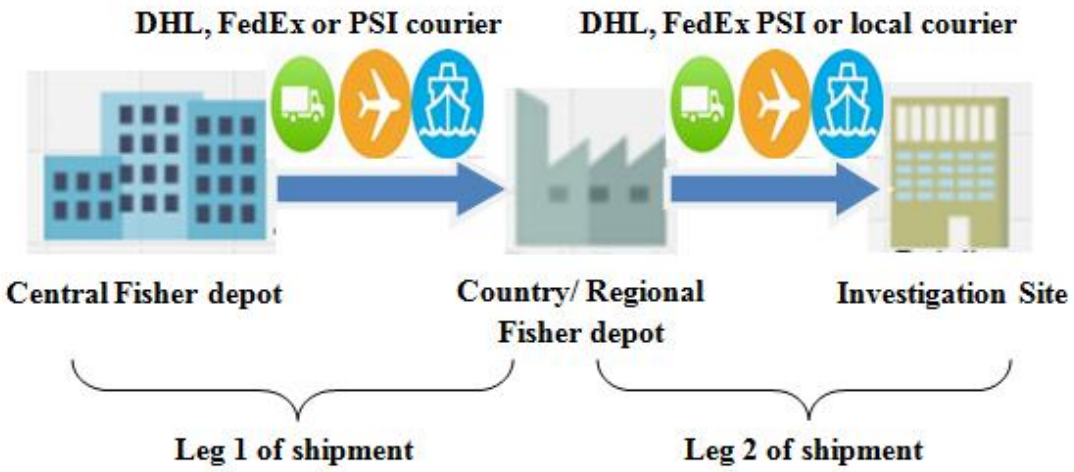


Figure 11: Fisher's Via Depot Distribution (Source: compiled by the authors)

The type of the distribution strategy that is selected for each destination is formulated based on various factors. The design of the clinical study, the distance of the importing countries from the central depots and the regulations that apply to those countries are the most crucial factors (Fisher, 2016).These factors are interrelated and therefore their influence towards the formulation of the distribution network by DTS and VD shipment routes is complicating.

As the main performance indicator of any distribution process is the shortest possible lead time for each order, the selected strategy must serve this goal taking into account the aforementioned factors. In general, Direct To Site shipments are performed to countries which are rather close to the central depot, have a rather simple regulatory framework for the importing drugs and therefore present rather short lead times. On the other hand, in the importing countries where the regulatory agencies have imposed a rather strict framework regarding the import licensing and customs clearance, indirect shipments through Fisher's owned country depots are performed. In many of these countries, there are laws that require from the pharmaceutical companies to hold a country depot in order to import study drug (Chris, Klim and Fisher, 2016).

4.3.2 Physical locations and lead times

As aforementioned, Fisher owns a central depot in Horsham (UK), two regional depots: one in Allentown, USA that serves US and Canada and one in Singapore which serves Southeast Asia and many smaller depots, serving the investigation sites at the countries in which they are located. Additional to the depot network of Fisher, AstraZeneca also sends small consignments of drug kits from its R&D centre in Gothenburg, Sweden. In the case of EUCLID study, investigation sites from 29 countries participate and receive drug kits that include the study drug of Brilinda and placebos. The shipments to those countries are performed in DTS or VD way (Table 10).

Table 10: The list of participating countries in EUCLID clinical program, separated by the method of distribution they are supplied (Source: compiled by the authors)

DIRECT TO SITE SHIPMENTS	VIA DEPOT SHIPMENTS
Bulgaria	USA
Czech Republic	Canada
France	Brazil
Germany	Argentina
Hungary	Mexico
Italy	Chile
Netherlands	Russia
Poland	Ukraine
Romania	Turkey
Slovakia	Japan
Spain	Philippines
UK	China
	Singapore
	South Korea
	Thailand
	Vietnam

As it can be observed from Table 10, the shipments of drug kits to the EU member states are sent directly from the Fisher central depot in Horsham, UK while for the rest counties regional depots of Fisher intervene at the distribution channel. The inventory in the first case is hold in the central depot, as the lead times are rather short. On the other hand, for the VD countries of the second column, inventory is positioned at the country depots in order to be close to investigations sites and avoid the risk of shortages due to the high lead times to these countries. (Internal document, 2016)

The expiry dates and the high cost of potential shortages of drug kits at the sites, make lead times to be a very crucial factor in the pharmaceutical supply chains. Lead times are mainly affected by the importing regulations and the documentation processes which accompany clinical drugs. These elements vary from one country to another and therefore their lead times can be quite different. The provided internal documents calculate the lead times of the importing countries, summing the completion time of the processes on the outbound flow of the drug kits to the sites. These processes are: License Timeline, Order Receive, Invoice Approval, Transit, Delivery and Depot Receipt time (Tables 11-13). The sequence of these processes is the same for both DTS and VD shipments, which have one and two leg of shipments respectively (Internal document, 2016).

The role of regulation agencies and customs in lead times is prominent in the element of License Timeline explaining also why the lead time of the initial shipment is usually much longer than the following re-supplying shipments to the same country. After the regulatory agency of the importing country gives the Clinical Trial Approval (CTA) to the pharmaceutical company, the drugs kits must be the soonest available to the investigation sites. The initial shipment though of the drug kit can be a quite challenging

task. Any minor error or omission in the documentation of shipment, like translation of the language, delays the import of the drugs increasing lead times. (Klim & Jones, 2016)

In many importing countries, especially the developing ones, the initial shipment is followed by an "Umbrella" import license (IL) which is a draft of the processes that took place in the first shipment, and that will cover the following re-supplying shipments. Thanks to the Umbrella IL next shipments for the same clinical study will record shorter lead times as the license is partially obtained automatically. This method though is not applied in all the importing countries. In countries with the "Individual" label on licensing, each importing shipment of drugs of the same clinical study, requires a separate license. There are also some countries where the import licensing for clinical study shipments is arranged along with the clinical trial approval and therefore the lead time for import license is zero ("Not applicable" label). (Internal document, 2016)

The following tables show some examples of the performed lead times for DTS and VD countries.

Table 11: "Direct to Site" outbound lead times in France and Germany (Source: Internal document)

Country	Type	License Timeline	Order Receive	Invoice Approval	Transit	Delivery	Depot Receipt Time	Overall Time including License	Overall Time excluding License
France	Umbrella	10	2	0	1	1	0	14	4
Germany	Non Applicable	0	2	0	1	1	0	4	N/A

Table 12: Leg 1 "Via Depot" outbound lead times in Turkey and Argentina (Source: Internal document)

Country	Type	License Timeline	Order Receive	Invoice Approval	Transit	Delivery	Depot Receipt Time	Overall Time including License	Overall Time excluding License
Turkey	Umbrella	15	2	5	2	3	3	30	15
Argentina	Individual	15	2	4	3	25	3	52	N/A

Table 13: Leg 2 "Via Depot" outbound lead times in Turkey and Argentina (Source: Internal document)

Country	Type	License Timeline	Order Receive	Invoice Approval	Transit	Delivery	Overall Time including License	Overall Time excluding License
Turkey	Umbrella	0	2	0	0	2	4	N/A
Argentina	Individual	0	2	0	0	3	5	N/A

In Table 11 where the lead times of DTS EU countries of France and Germany are analyzed and calculated, the overall lead times are quite short. The difference between the two countries lies in the label regarding import licensing. The "umbrella" licensing in France, takes 10 days, while in "non applicable" Germany zero. Thus, the overall lead time in the last column is four days for France, excluding import licensing duration. This is the lead time of re-supply shipments, while the previous column that includes the ten days of import licensing is referred to the initial shipment. In the case of Germany, the overall lead time is four days both in initial and the following shipments of the same clinical study as no import licensing is applied.

Tables 12 and 13 analyze and calculate the lead times of VD countries of Turkey and Argentina. Each table calculates the lead times of each leg. The first table shows the lead times of the first leg from central Fisher depot in Horsham to each country depot and the second table the lead times from the country depots to the participating sites. In the case of Turkey which its regulation framework adopts the umbrella IL, the lead time of the first leg of the initial shipment is 30 days, while in re-supplying 15 days. In the second leg of inland distribution from the depot to the sites is 4 days. In the case of Argentina, where for every shipment of the same study a new import license is required, the overall lead time is 57 days, 52 from the international (first) leg and 5 days from the inland distribution to the site.

4.3.3 Information Flow

Acknowledging that the administration of globalized clinical researches is crucial for the company's strategic goals, AstraZeneca has implemented the technology of Interactive Response System (IRT) which is widely adopted in the field of clinical researches. The technology is used for the remote access to a system, supporting the completion of transactions and surpassing the locational constraints. The phone or fax services (Interactive Voice Response System- IVRS) and Web (Interactive Web Response System-IWRS) are the two means of accessing and updating information in the system. The system allows the study administrators and investigators to interact with the study database enhancing the efficiency and effectiveness of the study deployment. (Internal document, 2016)

For the stakeholders in the drug kits supply chain, IVRS/IWRS system has different role as they perform different transactions when accessing the system. Specifically, the study team of AstraZeneca has the qualification to activate or/and deactivate the access to the database of the sites that participate in the specific clinical research. The supply chain study manager (SCSM) uses the IRT system mainly for the needs of inventory management handling information regarding the drug batches, the delivery scheduling in accordance with expiry dates of the drugs and emergency shipments. On the other side of the drug kits supply chain, the site investigators access the IRT system for various operations. Some of them are daily tasks, like confirming the receipt of the drug shipments. The most important task though, is the randomization and enrollment of the patients to the clinical study. The real time feedback from the centralized database allows the investigators to recruit patients to different treatment arms of the clinical study in order to acquire better statistical results. Additionally, investigators inform the database about the drug dispensing to the recruited patients. (Ivarsson, 2016)

Additionally, the IRT system runs a sweep inventory algorithm, called ConsGen0 (Consignment Generator), which assesses continuously the inventory levels at the sites and determines if there is a need for re-supplying according to the study design. If so, it automatically triggers shipments with the needed drug kits to the site. Each site triggers re-supplying in different inventory levels. This is an element which is determined from configurable parameters, like the study design of the research, the site capacity and its recruitment rate. Moreover, the system stores information regarding patient and kit randomization in its database. For each patient, who gets a unique code in the database information regarding his treatment are stored in tables. The same is the case for the drug kits for which information regarding their content, expiry date, packaging and manufacturing batch is stored. (Internal document, 2016)

Fisher has partially access to the IVRS/IWRS system. Each Fisher depot accesses the database and confirms the receipt of the shipment of each drug kit from another depot or from the manufacturing centers of AstraZeneca. In this way and through the kitID code database, the system tracks the drug kits across the whole distribution pipeline to the sites. (Ivarsson & Fisher, 2016)

4.4 Mapping of lab kits outbound flow

4.4.1 The distribution channel

The supply chain of lab kits has two reverse flows. The first flow is the distribution of the lab kits from the Covance's central production facility to the participating investigation sites across the world. The reverse flow is the shipment of the lab kits that include samples from the sites back to Covance's laboratory network. The firm contracts with couriers to perform the shipments of lab kits, both from labs to sites and vice versa (Covance, 2016). They cooperate with big courier companies, like DHL and UPS, but also with local couriers in some countries. The selection of the appropriate courier depends on the offers being received from the candidates. In countries where the available sites are rather few, Covance is pressed to pay more for the transport services in order to reach all the available sites as required from the pharmaceutical company (Ek, 2016).

Customs import regulations play an important role in the supply chain of lab kits too. Covance takes full responsibility on managing issues regarding the customs clearance processes. The globalized laboratory network is accustomed to this factor. For example, Japan's regulatory agency has imposed strict regulations on the importing lab kits, which have to be customized in order to acquire import license. For that reason, Covance has contracted with local lab kit suppliers to overcome this obstacle. The customs brokers are supported from Covance, providing them with all the appropriate information and documentation they need in order to perform the fastest possible, the customs clearance processes for the shipments. (Ek, 2016)

As aforementioned, Covance has developed a global network of laboratory centers, owned and contracted. This laboratory network has also distributional character, as the shipment of lab kits to/from the investigation sites is performed through its nodes and channels.

The supplying of all sites starts from the manufacturing site of Covance in Indianapolis, USA. This centre works also as a distribution centre. From there, lab kits are firstly shipped to the four distribution/laboratory centers which Covance owns (five with Indianapolis centre). Each of those centers is responsible in supplying investigation sites to four groups of regions/continents (Figure 12).

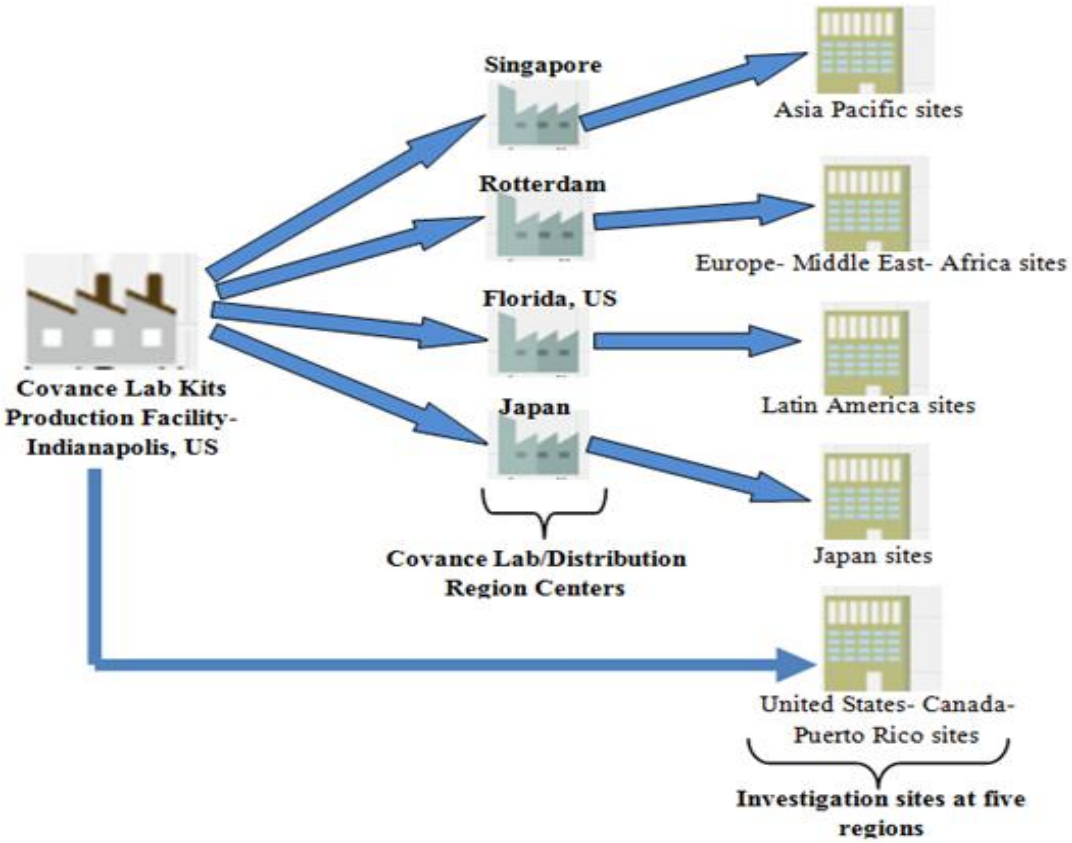


Figure 12: The distribution flow of the lab kits to the investigation sites through Covance's laboratory network (Source: compiled by the authors)

4.4.2 Physical location and lead times

As aforementioned, Covance owns a central manufacturing site in Indianapolis (USA) where lab kits are produced. This site supplies all the other four regional depots located across the world, while the same site supplies investigation sites located in USA and Canada. The other four depots are in Florida, Rotterdam, Singapore and Japan and supply investigation sites located in different continents (Figure 12).

Like in the case of drug kits, the lead times of the initial and re-supply shipments differs a lot. Before the initial shipment is performed time consuming documentation processes precede, especially the statement of work which is signed between Covance and the investigation site under the guidance and supervision of AstraZeneca. This document defines in details various operational aspects of the clinical research like the number of shipments that should be performed, what type of analysis the study design requires and what kind of reports should be sent out from Covance to investigators. The initiation and shipment of the first lab kits to sites cannot start before details, like those ones, have been settled. The shipment lead times vary depending from one country to another. Apart from the geographical distance, regulations regarding the customs clearance processes affect the performed lead times. Covance offers expedited and standard delivery of the lab kits to the sites in a higher price. For the 29 countries of the EUCLID study it can be observed

that the lead times do not vary a lot for countries in North America, Europe, Middle East and Asia, but the lead times for South America are longer (See Appendix). In Table 14 some examples of lead times can be seen.

Table 14: Examples of shipping lead times to sites (Source: Covance)

Country	Region	Expedited Request (days)	Standard Request (days)
Netherlands	Europe	6-8	10-14
Spain	Europe	6-8	11-15
Russia	Europe	N/A	19-23
Philippines	Asia	5-7	10-14
USA	North America	3-5	9-13
Argentina	South America	20-24	25-29
Mexico	South America	9-11	14-18

4.4.3 Information flow

Like IRS system in drug kits supply chain, Covance has developed an online platform, LabLink+, for managing the information flow regarding the distribution of lab kits to the sites and backwards. The platform provides access to Covance on viewing the inventory level of lab kits at the sites. Additionally, the platform tracks for each kit type the number of those which have been shipped to each site, returned to Covance and those who have pending shipment status. It also displays the expiration dates of the kits which have not been received by Covance.

In contrast to IRS system though, the LabLink+ system does not have an automatically triggered inventory mechanism and therefore the inventory management is totally dependent on the orders the sites give to Covance. Furthermore, site investigators do not have access to LabLink+ so far due to an issue of filtering. The system as it is now, would allow investigators to have a view of all participating sites in a clinical study, while they should only be allowed to have access to their own site's data. Therefore, sites order lab kits in the traditional and rather inefficient way of phone calls and faxes.

AstraZeneca's role in this information channel is very confined. IRS and LabLink+ platforms do not communicate or exchange any data that would coordinate the information of the allocated drug and lab kits to each patient. The firm can have an overview of the available inventory of lab kits at the sites through the visits of the study monitor performing audits to check the readiness of the site before the study starts (Ek, 2016)

4.5 Summary of findings of the empirical data

Having gathered data from the interviews and the internal documents following the steps of the value stream mapping tool, some important findings have been revealed which consist valuable elements in developing the empirical analysis.

Firstly, the relationships between the actors that participate in the two supply chains are multileveled. The two supply chains are managed by a network of outsourcing and contracting partners. Specifically, AstraZeneca has outsourced the distribution and other logistics processes to two key partners, who in their turn have contracted with courier companies to transport the two product groups. These dual relationships interact at their final destination which is the investigation sites. The basic difference between the two supply chains under the scope of relationship is that AstraZeneca has partial control over the operations of drug kits chain, while on the lab kits supply chain the firm is totally absent. This fact confirms the argument that until recently, pharmaceutical companies underestimated the ancillary supply chains and their contribution to the clinical projects considering that the lab kits management is a separate budget from the rest clinical operations (Klim, 2016). Investigation sites seem to be the problematic actor, especially in the lab kits supply chain, as it generates demand uncertainty due to the recruitment process and therefore Varying regulations in the importing countries set obstacles in the improvement of the performed lead times, especially in the developing economies which are critical markets in the clinical R&D sector.

The distribution networks that are used in the two supply chains present differences. The distribution network of Fisher is based on direct shipments to European countries and on shipments via depots in rest countries. It is significant to note that Fisher uses local depots in most countries that the importing regulations are complicated. On the other hand, Covance ships straight to the sites only in USA and Canada. For all the other sites, five central depots are used and then the shipments are shipped straight to the sites. Therefore, the distribution networks have different levels of geographical proximity to the investigation sites and consequently, the two outbound flows are not equally responsive to the uncertain demand from the investigation sites. Thus, it is obvious that the potential coordination of the flows is challenging.

Finally, comparing the information flow of the two chains it is obvious that there is a gap in the aspect of efficiency. IRS operations can fully support the logistics processes of the drug kits supply chain, linking AstraZeneca, Fisher and the sites in a common platform. On the other hand, in the information flow of the lab kits which is supported by the LabLink+ platform, the actors (Covance and sites) are not interconnected sufficiently, while AstraZeneca has no access at all.

Having mapped the two parallel supply chains in terms of material, information and distribution flow it is feasible to compare them, identify their weaknesses and finally investigate their potential coordination by this analysis. This ins the process that will be followed in the next chapter.

5. ANALYSIS- Potentials for improvement

In this chapter, the remaining models from the theoretical framework will be combined with the empirical data in order to investigate the redesigned future-state distribution network. Firstly, an evaluation of the current-state supply chains will be performed by identifying their wasteful sources, which are the outcome of the value stream mapping performed in the previous chapter, and using the strategic fit model to detect their position regarding the strategic fit zone assessing their responsiveness to the requirements of the clinical studies. In this way, the second part of the "Current-State" research question will be answered. In the next step the answer of the "Future-state" question is developed. Specifically, the "future-state" plan of the supply chains will be presented in terms of distribution, material and information coordination considering the principles of Triple-A supply chain. Furthermore, the challenges that emerge from the coordination plan are presented, considering the constraints that affect the implementation of the solution. Finally, the benefits that the stakeholders can reap from the co-distribution plan are presented.

5.1 Wastes in the two parallel clinical supply chains

Having acquired a clear overview of the two parallel supply chains by gathering the empirical data in the form of the steps of the value stream mapping, the elements of waste according to the lean principles are identified as presented in 2.3.2 chapter.

5.1.1. Wastes in the drug kits supply chain

Despite the fairly efficient operation of the drug kits supply chain thanks to the integrated logistics operations supported by the IRT systems, waiting time waste has been identified in the form of the prolonged lead times in some importing countries. Specifically, from the presented lead times in the distribution network of EUCLID program, it is obvious that the processes of import licensing and other processes, like invoicing, can increase radically the total number of days a shipment may need to reach to the investigation sites at some countries causing waiting time waste, as the drug kits cannot move down in the supply chain. This is an issue that all interviewees of the chain have underlined.

As it can be observed from the empirical data (See Appendix) the highest lead times are recorded in the developing countries of Latin America and Asia where in most of them individual import licensing type is applied, in some cases for both transport legs (Leg 1 and Leg 2). For most of these markets, the lead times of distribution to the country depots from Fisher's central depot in UK (Leg 1) is consisted mainly from import and clearance time, rather than the actual shipment (transit, delivery time and depot receipt). In Argentina, for example, whose legislative framework requires separate import license for every shipment of the same clinical study ("Individual" IL), it takes 57 days for the drug kits to reach at the investigation sites. Invoice approval time is also significantly high in some countries, due to the long lasting documentation and lack of the technology which supports automation of the process. For example in Philippines, the invoice approval time

is 34 days, and along with import licensing required for both legs, the total lead time is 88 days (See Appendix). The complicated legislative framework in these countries, which are in the same time the most promising for the sector, is a challenging issue for the R&D pharmaceutical firms (like AstraZeneca) and for the clinical logistics managers, as Mr. Klim (2016) has highlighted in his interview.

On the other hand the, the EMEA regulation agency, that sets a common legislative framework for EU countries, does not require lengthy import licensing (with the exception of France) and in combination with the short distance from Fisher's depot in Horsham (UK), drug kits reach to the sites only in 4 days. Similarly, the distribution channel that serves US and Canada, through the Fisher depot in Allentown (US), performs rather short lead times as no import licensing is required for the specific clinical study. In these regions, the clinical trial approval before the initiation of the clinical research covers the import licensing for shipments of the particular study and there is no waiting waste for the products. (See Appendix)

From the interviews with the stakeholders and the VSM no other types of waste have been identified in the outbound flow of the drug kits supply chain. The only other weakness which has been mentioned from most interviewees has to do with the uncertain demand from the investigation sites in the initial period of the clinical study, when the recruitment processes in developing. Thanks to the inventory mechanism of IRS though, the situation gets standardized as soon as each patient is finally recruited and the system checks the inventory level at the sites and triggers (or not) shipments of drug kits. Representative of AstraZeneca are pleased with the performance of the Fisher in the clinical logistics operations, mentioning that only in some importing countries cases the firm intervenes at the customs clearance processes.

5.1.2 Wastes of lab kits supply chain

The main impression the supply chain of lab kits gives, is the lack of coherence in the information flow between the actors. In the material flow of the lab kits, despite the fact that Covance has a well structured distribution laboratory network, which is crucial for the reverse channel of the lab kits with specimens, the flow of the empty lab kits to sites presents wastes due to the weak actor of the chain: the investigation sites.

As in EUCLID project, for each candidate patient only one lab kit is used before he gets recruited or not, the number of the needed lab kits from each investigation site are based on the forecasts of the potential patients a site is going to recruit, something which is very uncertain. This element, in combination with the fact that Covance has no access and management on the inventory level of lab kits at the sites, like IRS has on drug kits, causes inventory waste. In this point it has to be reminded that lab kits have expiration dates too. The problem is intensified by the fact, that in contrast to Fisher's distribution network, Covance does not own country-level depots, but only five regional and therefore the distribution network is less flexible. Consequently, these depots are not

geographically close to the sites they serve in order to hold inventory and perform shorter and quicker shipments to the sites.

The weakness in the information linking between Covance and the investigation sites through the LabLink+ and the complete absence of AstraZeneca in the supplying process of lab kits are the main reasons for the inventory waste (or shortage) of lab kits. The firm's subtle involvement in the lab kits distribution to the sites affirms the perception that pharmaceutical companies encounter ancillary products (like lab kits) as an add-on element to the main clinical operations despite the fact that the acknowledge their importance for the clinical study processes.

From the interviews with the stakeholders of the lab kits supply chain and VSM no other types of waste have been identified in the outbound flow of the lab kits to the investigation sites. The shipments to the importing countries are not as strictly regulated as the drug kits and for that reason Covance has the ability to offer expedited and standard distribution services. On the other hand though, the fact that the distribution network of Covance reaches only up to regional level (and not country) and that the demand from the investigation sites is rather not standard, increases the risk of shortages or oversupplying of the lab kits to the sites.

5.2 Strategic fit of the supply chains

The strategic fit model will be used in order to evaluate whether both the supply chains of drugs and lab kits operate in the zone of strategic fit. As the products of the two supply chains are not commercialized, the factors of the theoretical model are adapted to this fact. For example, a major change is that the end customer as referred in the model, who in the specific case is the recruited patient, does not have any power in selecting a specific product or service neither purchases it, like a retail customer does. Therefore, the "*Price of the product*" and the "*Innovation rate that is required in the product*" aspects of the model, do not apply in the specific project.

5.2.1 Strategic fit of the drug kits supply chain

Taking into account some of the elements in the two steps that compose the strategic fit model presented in paragraph 2.3 and the empirical data the following evaluation will occur.

On the horizontal axis which measures the implied demand uncertainty it can be supported that the drug kits supply chain scores rather high. This uncertainty results mainly from the rather uncertain demand from the investigation sites. The criticality of having available drug kits anytime a patient recruitment takes place and the fact that each site usually runs more than one clinical studies increases the demand uncertainty. On the other hand, the fact that Fisher in most cases delivers the drug kits in time, as stated by AstraZeneca interviewees mitigates the supply uncertainty risk.

On the vertical axis which measures the capability of the drug kits supply chain in terms of the responsiveness spectrum, it can be characterized as quite responsive. This is due to

two elements. Firstly, from the capability of IRS system to trigger automatically shipments to the sites by checking their inventory level and secondly from the Fisher's distribution network which allows to store drug kits at central and country depots adapting to the regulatory standards of each importing country. In the issue of the capability to perform short lead times, AstraZeneca interviewees are satisfied by the performance of Fisher, acknowledging that the import and customs regulations are a main source of delay

In Figure 13 the resultant point from the points in the axes of uncertainty and responsiveness spectrums extracted by the two analyzed steps, shows that the drug kits supply chain performs in the zone of strategic fit. This means that the downstream logistics operations,(and the whole supply chain) aligns with the goals AstraZeneca expects from its 3PL logistics provider, Fisher.

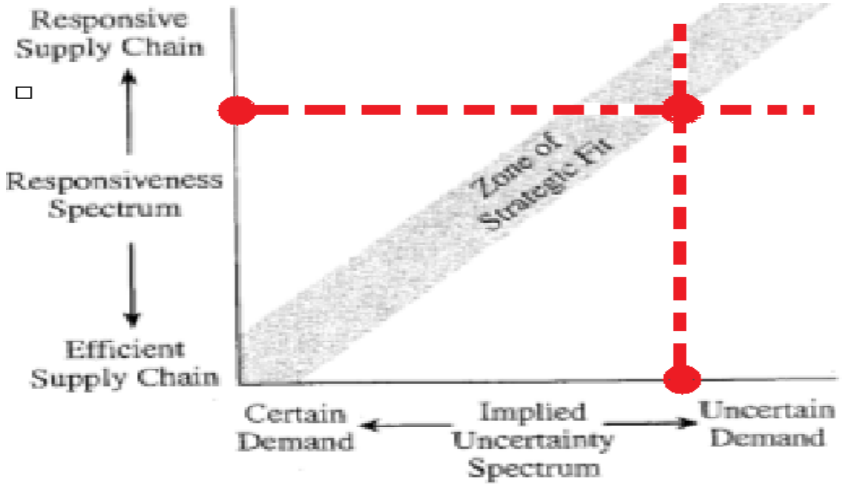


Figure 13: Zone of Strategic Fit for the drug kits supply chain (Source: compiled by the authors)

5.2.2 Strategic Fit of the lab kits supply chain

The lab kits supply chain scores close to the middle in the implied demand uncertainty horizontal axis. As mentioned in the wastes chapter, this uncertainty is stemming from the sites demand instability. Considering that product availability of the lab kits at the sites is as important is for the drug kits and the fact that lab kits variety depends on the different clinical studies that an investigation site runs increase the implied demand uncertainty. On the contrary, the uncertainty of supplying lab kits is rather low. Covance has adapted its distribution network to potential complexities regarding import regulations (i.e. has a separate Japan depot as the country does not allow lab kits importations) AstraZeneca representatives are quite pleased with Covance's performance in supplying the investigation sites.

On the vertical axis which measures the capability of the lab kits in terms of the responsiveness spectrum, it can be supported that the chain balances between responsiveness and efficiency. Considering that Covance offers expedited and standard deliveries, the capability of LabLink+ platform to track the shipments of various types of

lab kits across its distribution channel but its lacking of managing the inventory levels at the sites it supplies it can be argued that the lab kits supply chain operates in a make-to-stock environment that needs to meet short lead times.

In Figure 14 the resultant point from the points in the axes of uncertainty and responsive spectrums extracted by the two analyzed steps, shows that the lab kits supply chain is in the zone of strategic fit. This means that Covance responds, despite some weaknesses, rather effectively to the requirements of AstraZeneca and the cooperating investigation sites in the service of supplying them with lab kits for the needs of the clinical study.

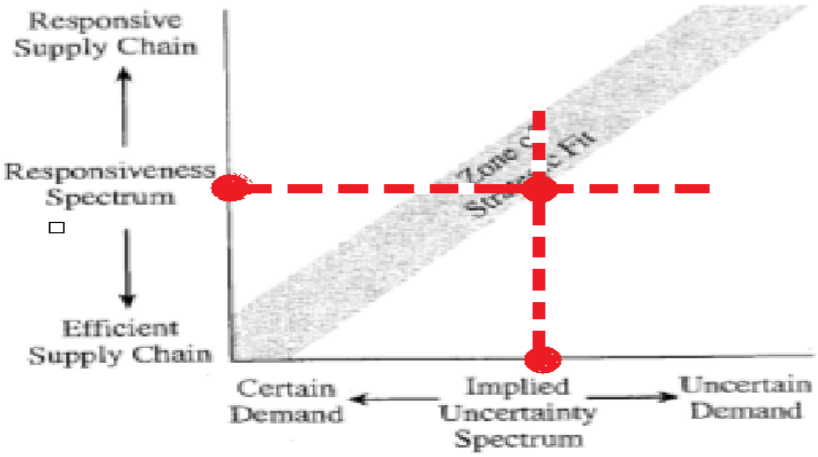


Figure 14: Zone of Strategic Fit for the lab kits supply chain (Source: compiled by the authors)

Despite that both supply chains are in the areas of strategic fit, meaning that the services from the two outsourcing partners meet the goals and the standards of AstraZeneca, they are in different areas with drug kits chain being more responsive than the lab kits. This is due mainly to the fact that as the drugs are more sensitive products with strict regulations that cause lead time waste, AstraZeneca and Fisher have a very close cooperation under a common IT platform. On the other hand, the empty lab kits that are shipped to the sites are handled as typical ambient products being less responsive to the uncertain demand from the investigation sites. The plan of the firm to integrate the distribution flow of the lab kits into Fisher's channel requires from Covance to become more responsive. Despite that the distribution service will be performed by Fisher, Covance will still have to ship the lab kits from its manufacturing centre to Fisher's central or country depots. Therefore, Covance has to align these distributions to the Fisher's distribution flow and rhythm becoming more responsive.

The Triple-A supply chain model (See chapter 2.5) gives guidelines to render a more responsive supply chain. Table 15 shows how some of the Triple-A supply chain methods linked to the model's principles (see Table 3) can be implemented in the coordination of the two parallel supply chains. The coordination processes is developed in the following chapter.

Table 15: Implementation of Triple A model in the coordination of drug and lab kits (Source: compiled by the authors)

Triple A Values (Table 3)	Coordination actions for the project
Alignment: Lay down roles, tasks, responsibilities clearly for suppliers and customers	Applied in the designing of the future distribution network
Agility: Build inventory buffers	Material flow coordination of drug and lab kits
Alignment: Co- exchange information and knowledge freely with vendors and customers	Information flow coordination of IRS and LabLink+ software platforms
Agility: Create a more dependable logistics system	Outcome of the future distribution network

5.3 Coordination of the drug and lab kits supply chains

Having tracked the processes and the wasteful sources in the parallel clinical supply chains and evaluated their performance in terms of their strategic fitting to the high uncertainty clinical studies present, the investigated coordination plan as it depicted in the "To-be" state map can be analyzed in detail.

According to the proposed solution the distribution of the lab kits, which is currently performed by Covance, will be undertaken by Fisher distributing them in the same channel with the drug kits. Therefore the shipments of the two product groups to the investigation sites will be consolidated. The reverse flow of the lab kits, from the sites to Covance's laboratory network will remain as it is.

5.3.1 Integration of the distribution

Having mapped the distribution networks of Fisher and Covance, the comparison between them justifies the selection of Fisher's network as the one that will remain as it is and Covance's that will be integrated. As availability of both products at the sites is crucial for the proper recruitment of patients in the clinical study, the distribution structure must support the closest geographical proximity of those products to the investigation sites. Fisher distribution network of central and country depots is more capable to serve this element in contrast to Covance's network where the five distribution centers supply the investigation sites in a regional (and not a country) level.

The critical point in the co-distribution is the decision at which point of the channel the consolidation will take place. There are two ways of coordinating the separate distribution networks depending at which point of Fisher's outbound channel the consolidation will take place.

The first case is to consolidate the drug and lab kits from the starting point of Fisher's distribution channel, in Horsham, UK. According to Fisher, the central depot has the capability and the capacity to undertake the storing and consolidation of drug and lab

kits, having experience in clinical ancillary management.. This is the only applicable choice for the EU importing countries where no country depots exist. In this solution, the lab kits which are addressed to US and Canada sites do not need to be shipped in Horsham but instead they will be sent to Fisher's depot in Allentown, US. All the other shipments will be integrated with the drugs supply chain in Horsham and will be shipped to the importing countries by the drugs flow.

In the second solution the lab and drug kits share the common distribution network at the called "last mile" as the shipments consolidate in Fisher's country depots. The major benefits of this solution are that it mitigates the risk of delays at the customs for shipments which would include two types of products with varying expiration dates. This is crucial for the importing countries of Latin America and Asia where customs clearance operations are strict and complicating and thus performed lead times are long for both products. The solution though cannot be implemented for DTS countries and therefore Fisher has to implement both solutions.

As the regulations in most of the "Via Depot" countries are complicating and the lead times are rather long, the stakeholders (Covance, Fisher and AstraZeneca) should investigate for each of these countries of EUCLID project, which of the two solutions is the most preferable. The investigation on the legislative framework and a comparison of import tariffs in the cases of separate and consolidated drug and lab kits should be applied.

5.3.2 Material and information flow coordination

The integration of the two distribution channels affects the logistics processes taking place in the material flow of the products. Additionally the coordinated distribution of the drug and lab kits requires an integrated information flow to support the modified distribution channel, which will render the lab kits' supply chain more responsive according to the Triple-A model. The potential changes the distribution redesign brings to these processes will be further analyzed:

Storage: Fisher supports that it has the capacity both at its central and country depots to store both lab and drug kits, something which is also supported by AstraZeneca's representative who works at the Horsham centre. Another element which is important is whether the products have the same storing requirements. For the case of EUCLID project, both lab kits and the two types of drugs which are the content of the drug kits are ambient. Thus, no temperature controlled conditions are required for their storage across the distribution channel. If the drug kits required temperature controlled environment, there would be an issue of inefficiency as the ambient lab kits would occupy storage and cargo space in a refrigerated supply chain.

Packaging-Labeling: Packaging and labeling are critical logistics processes for drug kits as they have to support the design characteristics of the study in terms of the blinding and to comply with the regulations of Good Clinical Practices, that requires the protection of the product (and consequently of the patient). On the other hand, uniformity of the

packaging and labeling of the lab kits is not an issue, at least when they are sent empty to the sites. Therefore, it is crucial that the introduction of the lab kits to the distribution channel will not affect these processes which are crucial for the other product group. Covance can retain these processes as part of its manufacturing service without affected the same processes for the drug kits being performed by AstraZeneca and Fisher.

Information flow coordination: What is important for the coordinated information flow is the tracking of the products across the distribution channel until they reach the final destination. Fisher can trace the drug kits through the IRS system of AstraZeneca. Similarly Covance, through LabLink+ software platform, tracks the shipments of the lab kits to the sites and stores information regarding their reverse flow from the sites back to the laboratory network of the firm for analysis. In the new co-distribution state, Fisher will have to track both product groups along its distribution network. Covance must retain this ability too, despite that the distribution service will not be its responsibility anymore. This is because the lab kits will "carry" information regarding the recruited patients since they get used at the investigation sites. This information, which is managed and stored in the LabLink+ platform, is crucial in the reverse flow of the lab kits (filled with specimens) back to the laboratory network of Covance. It is obvious from the above that the two separate information systems must be interconnected, so that all actors will have the ability to track and trace the two product groups.

5.4 Challenges of coordinating the drug and lab kits

The coordination of the two supply chains entails constraints and challenges stemming from the regulations in the pharmaceutical sector. The main challenge in the coordinated distribution channel is to overcome the inventory and the lead time wastes the two separate supply chains face.

Investigation sites are the actors which are responsible for the inventory waste in the two supply chains because of the uncertain during the recruitment process. The coordinated distribution channel has to retain the on- site availability of the products. As the lab kits chain is less responsive than of the drug kits, according to the strategic fit, their coordination in a common distribution flow is a challenging task. Closer integration of the information flow between Covance and the sites and both of them with the AstraZeneca will mitigate the inventory waste in the new coordinated chain.

As it has been mentioned previously, waiting time waste is a critical weakness for the drug kits supply chain stemming mainly from the delays in the import and customs clearance regulations. What is challenging in the case of co-distribution from the central Fisher depot, are the potential legislative obstacles and complexities of each importing country regarding the shipments that contain diverse product groups. The diversity of the country regulations has to be considered in the scheduling of deliveries of the co-distributed shipments. In the second distribution proposal, the scheduling of the

consolidated shipment to the sites will be challenging as the arrival times of the two separate products at the depots may vary a lot.

Apart from facing the challenges inherited from the two wastes of the formerly separated supply chains, additional challenges stemming from the relationship between the actors in the new coordinated logistics operations arise. In the information flow segment the cost of coordinating the LabLink+ and IRS systems can be quite high and therefore has to be considered from the stakeholders. Another challenging issue is the preservation of confidentiality. The coordination of information flow has to comply with the blinding design of the clinical study which defines different levels of access to information to the actors of the clinical study.

The role of the courier companies in this ambitious project is critical, as they are the actors that actually will execute the shipment of the consolidated products. Both Covance and Fisher cooperate with the same courier companies in the international haulage of the distribution flow (DHL, UPS, FedEx, etc). It will be challenging though, for some local couriers, to transport the consolidated cargo from the Fisher country depots to the investigation sites as the vehicles' (usually lorry) capacity may not be able to support the shipments within one route.

5.5 Benefits of coordinating the drug and lab kits

The awareness that all the involved stakeholders will reap benefits from the potential coordination of the supply chains is critical for the success of the project.

AstraZeneca is the actor who mostly expects to get benefited from the redesign project. The improvement of the clinical logistics operations will enhance the performance of the EUCLID project, while there are promising cost benefits. The consolidation of the two products will allow the shipping of bulk quantities, especially in the first proposed distribution solution. Additionally, AstraZeneca will gain a holistic overview of the clinical logistics operations, as the firm has much closer cooperation with Fisher, who undertakes now the logistics processes, than with Covance. With the redesign of the clinical distribution network, AstraZeneca redesigns partially the strategy of the running studies as they become geographically oriented. In this way, the varying clinical studies acquire a cost effective logistics approach, while the geographical expansion in some developing markets becomes the cornerstone of AstraZeneca's growth strategy.

As far as the strategic partners, Covance and Fisher is concerned, they can expect that the project will enhance even further the cooperation with a key client, like AstraZeneca is. The creation of the new interdependable logistics system will help towards this direction. Movements towards this goal have already been planned, as Covance will undertake to offer its laboratory services in AstraZeneca's clinical project which are at an earlier development stage and Fisher will undertake the logistics processes for even bigger proportion of the manufactured drug kits (Jonsson, 2016). Furthermore, Covance will be able to focus on its laboratory services to AstraZeneca as the distribution of the empty lab kits to sites will be undertaken by a 3PL logistics expert, Fisher.

6. CONCLUSIONS

In this chapter the final answers to the research questions of the problem are demonstrated. Furthermore, recommendations to AstraZeneca for the further development of the project are presented and the application of the findings to other areas is discussed.

6.1 Answers to the research questions

The purpose of this study was to investigate the potential co-distribution of two vital for the clinical studies products, drug and lab kits to the investigation sites that cooperate with AstraZeneca in the EUCLID project. The investigation included two stages: first to provide the study managers of AstraZeneca a clear overview over the current clinical logistics network composed by the two parallel supply chains and secondly present the future state distribution network, the challenges, the constraints and the potential benefits the stakeholders can expect to have. Thus, two research questions were formed and answered:

Current- state research question:

Who are the actors, the logistics operations and distribution links in the two parallel supply chains? In what extent do the two supply chains correspond to the requirements and complexities of the clinical R&D sector?

Having the value stream mapping method as a guide, interviews with people in key positions in the two parallel supply chains in and out of AstraZeneca helped the authors answer the current-state research questions. The network of actors intersecting in the two chains is mainly composed by outsourcing and contracting relationships. This element justifies the rather complicated character of clinical logistics operations driving the pharmaceutical firms and even 3PL companies to outsource the services to specialized actors. The same is the case for AstraZeneca which has outsourced the majority of its clinical logistics operations to Fisher, in the chain of drug kits, and to Covance the distribution of the lab kits to investigation sites. Both outsourcing firms though, have contracted with courier companies the shipping of the products to the sites. Regulation agencies have a critical role affecting the logistics operations and the distribution network along with the performed lead times.

The processes of packaging and labeling are very crucial for the drug kits as they carry important information regarding the design of the clinical study (i.e. blinding) and have to comply with the GCP and GDP regulatory framework. This is not the same case for lab kits which are handled as commodity products, at least until they are used at the investigation sites for taking patient specimens. These differences between the two products groups are reflected to the distribution networks that support them. Specifically, Fisher's network is expanding up to country level so that there will be available inventory close to the sites and mitigating the shortage risk, which can be high in some importing countries with high lead times. Covance's network is less responsive as it reaches to a

regional level performing consolidated shipments to the serving countries from its five centers.

The on- site availability of the two products groups is of ultimate importance, as potential lacking prolongs the duration of the clinical study and increases the costs. Obstacles towards that are the recognized wastes of waiting time and inventory waste in the drug and lab kits chain respectively. Despite that, both partners of AstraZeneca, meet the requirements of the clinical studies being in the strategic fit zone. The potential coordination though, requires from the lab kits supply chain to become more responsive. This implicates that AstraZeneca has to change its perception towards the ancillary products and acknowledge that the lab kits supply chain is as important as the drug kits supply chain is.

Future- state research question:

How will the logistics processes be modified and which are the main challenges and constraints in coordinating the two supply chain flows? Which are the potential benefits that the stakeholders can reap from the implementation of the project?

Having a clear overview of the current state of the clinical logistics network and assessed the two parallel supply chains, the implications on the material, information flow and the coordinated distribution network were developed. In the material flow, it is important that the packaging and labeling processes of the drug kits will not be affected by the addition of the lab kits to the shipments as they are regulated and correlated with the design of the clinical studies. As in the specific case there is no need of labeling connection between the drug and lab kits, Covance can retain these logistics processes in its manufacturing site without needing Fisher to modify them further more. Moreover, in the specific clinical study, the consolidation of the two product groups does not requires any special storing and shipping conditions as both products are ambient. In the coordinated information flow, it is crucial that all stakeholders have access in an integrated common platform preserving the varying levels of confidentiality each stakeholder has so that the efficacy and quality of the study won't be affected. The co-distribution of the consolidated products will be performed through Fisher's distribution network which is more responsive and expands to importing countries. Additionally, Fisher as a logistics service provider specialized in clinical trials has way more capacity and experience to handle the coordinated outbound flow. The point where Covance's and Fisher's consolidation of the products will take place is a matter which is highly correlated to the regulatory framework of the importing countries and the performed lead times of the drug kits shipments in the current state. The most suitable strategy is the implementation of the first solution (consolidation from the start of the Fisher's distribution channel) in the importing countries where there are no country depots (EU countries) or have rather simple importing regulations (i.e. Umbrella IL). The alternative choice is more suitable for importing countries with relative high lead times and complicated import regulations.

The main challenges emerge from the constraints on the importing regulations which, as aforementioned, will affect the coordination of the two distribution channels in terms of aligning the varying lead times. Additionally, the rather problematic cooperation between Covance and the investigation sites raises the challenge of inventory management in the new co-distributing channel. The coordination between the IT platforms of the two chains is challenging in terms of cost and confidentiality. Finally, the capacity of some courier companies to perform the consolidated shipments may be questionable. Despite the obstacles, all stakeholders can reap important benefits from the investigated project. The main benefit for AstraZeneca is the designing of a more dependable logistics network, with enhanced control over it that will allow the firm to control and reduce efficiently the costs, while improving the performance by mitigating the wastes. Fisher undertakes all the clinical logistics operations creating a closer bond with its main customer while Covance, that gives away the distribution service, can focus on its core activity of laboratory service.

6.2 Recommendations for further research to AstraZeneca

For the further progress of the project AstraZeneca should consider various aspects. A deeper investigation in the regulatory framework of countries, which operate under complex importing regulations, could be of first priority. AstraZeneca, Fisher and Covance will have to collaborate closely on this matter as it will formulate the distribution strategy of the unified outbound channel. As cost data were to accessible to the investigators, due to reasons of confidentiality, it is crucial for all stakeholders of the project to perform a financial analysis of the planned project before its implementation. It is obvious that there are cost benefits for AstraZeneca, but those should be calculated in detail. The formulation of KPIs is also very important in order to measure the performance of the new distribution network. Finally, AstraZeneca could also investigate the potential implementation of a similar project in clinical studies that are in an earlier phase of drug development.

6.3 The value of the findings in other areas

The used of the theoretical models to investigate the current and future state of a coordination project could be implemented as a methodology to projects where the supply chains have similar characteristics with the clinical supply chains. The main characteristic is the role of regulation agencies which is of high importance in the clinical R&D sector. Chemical industry is considered as the origin of pharmaceutical sector and thus a potential supply chain coordination plan presents similar challenges. Food industry is a sector that also is highly correlated with the health of the end customers presents complicated import regulations and this is the reason that most regulatory agencies focus on these two sectors (i.e. FDA). Supply chain food networks are composed of parallel supply chains spread across the world and therefore, similar coordination plans can be applicable.

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APPENDIX

A. Tables with the shipment lead times of drug kits to the countries in EUCLID program

EU Member States

Origin	Destination	Supply	Leg1 Courier	Import License (IL) Type Leg1	Leg1 Licence Timeline	Leg1 Order Receive	Leg1 Invoice Approval	Leg1 Transit	Leg1 Delivery	Depot Receipt Time	TOTAL Lead Time with IL (if applicable)	TOTAL Lead Time excluding IL (if applicable)
FCS Horsham (UK)	Bulgaria (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Czech Republic (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	France (Site)	Direct to Site	DHL	Umbrella	10	2	0	1	1	0	14	14
FCS Horsham (UK)	Germany (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Hungary (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Italy (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Netherlands (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Poland (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Romania (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Slovakia (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	Spain (Site)	Direct to Site	DHL	N/A	0	2	0	1	1	0	4	4
FCS Horsham (UK)	United Kingdom (Site)	Direct to Site	DHL	N/A	0	2	0	0	1	0	3	3

USA- Canada

LEG 1

Origin	Destination	Supply	Leg1 Courier	IL Type Leg1	Leg1 Licence Timeline	Leg1 Order Receive	Leg1 Invoice Approval	Leg1 Transit	Leg1 Delivery	Depot Receipt Time	TOTAL LeadTime Leg 1
FCS Horsham (UK)	Canada (Site)	Via Depot	PSI	N/A	0	2	2	2	5	3	**14**
FCS Horsham (UK)	Canada (Site)	Via Depot	PSI	N/A	0	2	2	2	5	0	**11**
FCS Horsham (UK)	USA (Site)	Via Depot	PSI	N/A	0	2	2	2	5	3	**14**

LEG 2

Origin	Destination	Supply	Leg2 Courier	Leg2 IL Type	Leg2 Licence Timeline	Leg2 Order Receive	Leg2 Invoice Approval	Leg2 Transit	Leg2 Delivery	TOTAL LeadTime Leg 2
FCS Horsham (UK)	Canada (Site)	Via Depot	FedEx	N/A	0	2	0	2	1	**5**
FCS Horsham (UK)	Canada (Site)	Via Depot		N/A	0	0	0	0	0	**0**
FCS Horsham (UK)	USA (Site)	Via Depot	FedEx	N/A	0	2	0	0	2	**4**

TOTAL LEAD TIME

Origin	Destination	TOTAL LeadTime including IL Umbrella Licence (if applicable)	TOTAL Lead Time excluding Umbrella Licence (if applicable)
FCS Horsham (UK)	Canada (Site)	19	19
FCS Horsham (UK)	Canada (Site)	11	11
FCS Horsham (UK)	USA (Site)	18	18

Latin America

LEG 1

Origin	Destination	Supply	Leg1 Incoterms	IL Type Leg1	Leg1 Licence Timeline	Leg1 Order Receive	Leg1 Invoice Approval	Leg1 Transit	Leg1 Delivery	Depot Receipt Time	TOTAL LeadTime Leg 1
FCS Horsham (UK)	Argentina (Site)	Via Depot	PSI	Individual	15	2	4	3	25	3	**52**
FCS Horsham (UK)	Brazil (Site)	Via Depot	PSI	Individual	7	2	13	3	10	3	**38**
FCS Horsham (UK)	Chile (Site)	Via Depot	PSI	Umbrella	5	2	5	2	7	3	**24**
FCS Horsham (UK)	Mexico (Site)	Via Depot	PSI	Umbrella	20	2	8	2	5	3	**40**

LEG 2

Origin	Destination	Supply	Leg2 Courier	Leg2 IL Type	Leg2 Licence Timeline	Leg2 Order Receive	Leg2 Invoice Approval	Leg2 Transit	Leg2 Delivery	TOTAL LeadTime Leg 2
FCS Horsham (UK)	Argentina (Site)	Via Depot	Local Courier	Individual	0	2	0	0	3	**5**
FCS Horsham (UK)	Brazil (Site)	Via Depot	Local Courier	Individual	0	2	0	0	3	**5**
FCS Horsham (UK)	Chile (Site)	Via Depot	Local Courier	Umbrella	0	2	0	0	1	**3**
FCS Horsham (UK)	Mexico (Site)	Via Depot	Local Courier	Umbrella	0	2	0	0	3	**5**

TOTAL LEAD TIME

Origin	Destination	Supply	TOTAL LeadTime including IL Umbrella Licence (if applicable)	TOTAL Lead Time excluding Umbrella Licence (if applicable)
FCS Horsham (UK)	Argentina (Site)	Via Depot	**57**	**57**
FCS Horsham (UK)	Brazil (Site)	Via Depot	**43**	**43**
FCS Horsham (UK)	Chile (Site)	Via Depot	**27**	**22**
FCS Horsham (UK)	Mexico (Site)	Via Depot	**45**	**25**

Asia

LEG 1

Origin	Destination	Supply	Leg1 Courier	IL Type Leg1	Leg1 Licence Timeline	Leg1 Order Receive	Leg1 Invoice Approval	Leg1 Transit	Leg1 Delivery	Depot Receipt Time	LeadTime Leg 1
FCS Horsham (UK)	Japan (Site)	Via Depot	PSI	Individual	3	2	2	2	7	3	19
FCS Horsham (UK)	South Korea (Site)	Via Depot	PSI	Individual	4	2	4	2	3	3	18
FCS Horsham (UK)	Philippines (Site)	Via Depot	PSI	Individual	4	2	4	2	3	3	18
FCS Horsham (UK)	Singapore (Site)	Via Depot	PSI	Individual	4	2	4	2	3	3	18
FCS Horsham (UK)	Thailand (Site)	Via Depot	PSI	Individual	4	2	4	2	3	3	18
FCS Horsham (UK)	Vietnam (Site)	Via Depot	PSI	Individual	4	2	4	2	3	3	18

LEG 2

Origin	Destination	Supply	Leg2 Courier	Leg2 IL Type	Leg2 Licence Timeline	Leg2 Order Receive	Leg2 Invoice Approval	Leg2 Transit	Leg2 Delivery	LeadTime Leg 2
FCS Horsham (UK)	Japan (Site)	Via Depot	Local Courie	Individual	0	2	5	0	2	**9**
FCS Horsham (UK)	South Korea (Site)	Via Depot	DHL	Umbrella	10	2	10	1	2	**25**
FCS Horsham (UK)	Philippines (Site)	Via Depot	PSI	Individual	30	2	34	1	3	**70**
FCS Horsham (UK)	Singapore (Site)	Via Depot	Local Courie	Individual	0	2	0	0	2	**4**
FCS Horsham (UK)	Thailand (Site)	Via Depot	DHL	Individual	10	2	7	2	2	**23**
FCS Horsham (UK)	Vietnam (Site)	Via Depot	PSI	Umbrella	30	2	2	1	3	**38**

TOTAL LEAD TIME

Origin	Destination	Supply	TOTAL Lead Time including IL Umbrella Licence (if applicable)	TOTAL Lead Time excluding Umbrella Licence (if applicable)
FCS Horsham (UK)	Japan (Site)	Via Depot	28	28
FCS Horsham (UK)	South Korea (Site)	Via Depot	43	33
FCS Horsham (UK)	Philippines (Site)	Via Depot	88	88
FCS Horsham (UK)	Singapore (Site)	Via Depot	22	22
FCS Horsham (UK)	Thailand (Site)	Via Depot	41	41
FCS Horsham (UK)	Vietnam (Site)	Via Depot	56	26

Turkey-Ukraine- China- Russia

LEG 1

Origin	Destination	Supply	Leg1 Courier	IL Type Leg 1	Leg1 Licence Timeline	Leg1 Order Receive	Leg1 Invoice Approval	Leg1 Transit	Leg1 Delivery	Depot Receipt Time	LeadTime Leg 1
FCS Horsham (UK)	Turkey (Site)	Via Depot	PSI	Umbrella	15	2	5	2	3	3	30
FCS Horsham (UK)	Ukraine (Site)	Via Depot	PSI	Individual	35	2	3	2	8	3	53
FCS Horsham (UK)	China (Site)	Via Depot	PSI	Individual	10	2	3	2	6	3	26
FCS Horsham (UK)	Russia (Site)	Via Depot	PSI	Umbrella	17	2	3	2	5	3	32

LEG 2

Origin	Destination	Supply	Leg2 Courier	Leg2 Incoterms	Leg2 Licence Timeline	Leg2 Order Receive	Leg2 Invoice Approval	Leg2 Transit	Leg2 Delivery	LeadTime Leg 2
FCS Horsham (UK)	Turkey (Site)	Via Depot		Umbrella	0	2	0	0	2	4
FCS Horsham (UK)	Ukraine (Site)	Via Depot		Individual	0	2	0	0	2	4
FCS Horsham (UK)	China (Site)	Via Depot	Local Courier	Individual	0	5	0	0	3	8
FCS Horsham (UK)	Russia (Site)	Via Depot	Local Courier	Umbrella	0	2	0	0	3	5

TOTAL LEAD TIME

Origin	Destination	Supply	TOTAL LeadTime including IL Umbrella Licence (if applicable)	TOTAL Lead Time excluding Umbrella Licence (if applicable)
FCS Horsham (UK)	Turkey (Site)	Via Depot	34	19
FCS Horsham (UK)	Ukraine (Site)	Via Depot	57	57
FCS Horsham (UK)	China (Site)	Via Depot	34	34
FCS Horsham (UK)	Russia (Site)	Via Depot	37	20

B.Tables with the shipment lead times of the lab kits to the countries of EUCLID program

Europe

		Expected Delivery Date (in days)	
Origin	Country sites	Expedited	Standard
Indianapolis-->Covance (Rotterdam)	Bulgaria	6--8	10--13
Indianapolis-->Covance (Rotterdam)	Czech Republic	6--8	10--15
Indianapolis-->Covance (Rotterdam)	France	6--8	10--14
Indianapolis-->Covance (Rotterdam)	Germany	6--8	10--14
Indianapolis-->Covance (Rotterdam)	Hungary	6--8	11--15
Indianapolis-->Covance (Rotterdam)	Italy	6--8	10--14
Indianapolis-->Covance (Rotterdam)	Netherlands	6--8	10--14
Indianapolis-->Covance (Rotterdam)	Poland	6--8	11--15
Indianapolis-->Covance (Rotterdam)	Romania	6--8	10--14
Indianapolis-->Covance (Rotterdam)	Slovakia	6--8	11--15
Indianapolis-->Covance (Rotterdam)	Spain	6--8	11--15
Indianapolis-->Covance (Rotterdam)	UK	6--8	10--14

USA-Canada

Origin	Country sites	Expected Delivery Date (in days) Expedited	Standard
Covance (Indianapolis)	USA	3--5	9--13
Covance (Indianapolis)	Canada	3--5	9--13

Latin America

Origin	Country sites	Expected Delivery Date (in days) Expedited	Standard
Indianapolis-->Covance (Florida)	Argentina	20--24	25--29
Indianapolis-->Covance (Florida)	Brazil	18--20	23--27
Indianapolis-->Covance (Florida)	Chile	6--8	9--13
Indianapolis-->Covance (Florida)	Mexico	9--11	14--18

Asia

Origin	Country sites	Expected Delivery Date (in days) Expedited	Standard
Indianapolis--> Covance (Singapore)	China	7--9	11--15
Indianapolis--> Covance (Singapore)	Philipinnes	5--7	10--14
Indianapolis--> Covance (Singapore)	Singapore	5--7	10--14
Indianapolis--> Covance (Singapore)	South Korea	5--7	10--14
Indianapolis--> Covance (Singapore)	Thailand	5--7	10--14
Indianapolis--> Covance (Singapore)	Vietnam	5--7	10--14
Indianapolis--> Covance (Japan) (built in US)	Japan	5--7	10--14
Indianapolis--> Covance (Japan) (built in Japan)	Japan	-	17

C. Interview Guide

Interview with Ulrika Ivarsson

1. Which are the functions of the software that supports the outbound flow of the drug kits to the sites?
2. Are there any potential of further improvements on the standardized operations of the IVRS system? Do you identify any wasteful sources?

3. How would you characterize the clinical supply chain of drug kits? (Lean-Agile)
4. Which are the features of the study design that are closely related to the supply chain operations?
5. Is there any specific relationship between the drug kits and lab kits for the needs of the clinical study?
6. Have you encountered any problems in your distribution strategy from the regulatory agencies in the countries you operate?
7. How does the 3PL provider, Fisher, integrate in the information flow of the IVRS system?

Interview with Bryan Egner

1. Can you describe the processes of packaging and labeling?
2. What information regarding the drug kits does the labeling carry?
3. Can you talk about the regulations when it comes to the packaging?
4. What type of content a drug kit may include? Any temperature control or other storing requirement?

Interview with Malin Wikberger

1. Can you describe the cooperation of AstraZeneca with Fisher?
2. Do you identify any weakness in the performance of Fisher?
3. What do you think about Fisher undertaking the distribution of the lab kits?
4. Which are Fisher's responsibilities as mentioned in the contract?
5. Which could be the role of IVRS/IWRS system in coordinating the distribution of the drug and lab kits?

Interview with Chris Jones

1. Can you describe the distribution channel of Fisher?
2. What about the inventory positioning in the drug kits supply chain?
3. Can you describe the shipping costs and the regulations that concern the shipments?
4. How do they affect the performed lead times?
5. Can you identify any wastes, any potentials of improvement in the drug kit distribution?

Interview with Alex Klim

1. How does DHL operate the distribution of drug and lab kits? What differences do you recognize?
2. What do you think is the necessary information that we need to take into account in order to investigate the feasibility and effectiveness of the project?
3. Does DHL consolidate the clinical trials with other products?
4. Have you experienced any similar project in your career? If yes, can you talk about it?
5. Describe the contracting relationship with 3PL companies, like Fisher.

Interview with Anna-Lena Ek

1. Can you describe the logistics processes related to the the lab kits?
2. Can you describe us what does a lab kit contain? Is it customized for each study and patient? Any packaging, storing particularities?
3. Can you describe the cooperation between Covance and AstraZeneca?
4. Can you describe the information flow between investigation sites and Covance? What is the role of AstraZeneca in this?
5. Can you identify any wastes in the procedures?
6. What do you think about the integration of the two chains?

Questions to Fisher

1. As stated in the company website Fisher offers a service of management of ancillary products. Are lab kits considered as ancillary products or is it a different group which requires different product management? If no, please give a short description of the products that compose a lab kit according to Fisher.

2. Describe the relationship with AstraZeneca? How would you evaluate the coordination between Fisher and AstraZeneca achieved in the material and information flows?

3. Do you think that regulations in some countries would block the integration of the physical distribution of pharmaceuticals and lab kits? If yes, can you give us an example?

4. What would be the benefits of the potential integration of the physical distribution of pharmaceutical and lab kits could be achieved?

5. How does Fisher evaluate the feasibility of undertaking the distribution of lab kits and consolidate their shipments with the ones of the drug kits to sites? How effectively Fisher's country depots could respond to this project in terms of storage capacity and delivery times? Which could be the implications of coordinating the information related to the two separate product groups in the operations of labeling and packaging?

6. Which criteria does Fisher use when choosing the appropriate courier for the distribution of the drug kits to the sites? Which transport mode is mostly used for the first transport leg from Horsham central depot directly to sites (EU countries) and/or to country depots (mainly developing countries) and which ones for the second transport leg inside the importing country, from depots to the sites? Which would be the implications for the couriers in transporting drug and lab kits together in one shipment?

Questions to Covance

1. Can you describe the distribution channel of the lab kits and the procedures within it? How the two reverse supply chains are interconnected?
2. How is the collaboration with the investigation sites and with AstraZeneca?
3. Are there any special regulations regarding the storing and distribution of the lab kits?
4. Can you describe the information flow linking Covance with the investigation sites? Any role for AstraZeneca?
5. Can you identify any wastes in the procedures?