MASTER

Location and allocation of Amgen's distribution centers for one centralized, European distribution structure

Benthem, M.

Award date:
2006

Location and Allocation of Amgen's Distribution Centers

For One Centralized, European Distribution Structure

AMGEN®

TU/e

Eindhoven University of Technology

Master's Degree Thesis

Marco Benthem

2006

The importance of Demand Chain Management:

'Anyone who thinks the customer isn't important should try doing without him for a period of time'
-Anonymous-

Location and Allocation of Amgen's Distribution Centers

For One Centralized, European Distribution Structure

September 2005 – June 2006

Master's Degree Thesis by:

Marco Benthem
0496261
Eindhoven University of Technology
Department of Technology Management
Program in Industrial Engineering and Management Science
Sub-department of Operations, Planning, Accounting and Control

University Supervisors
Dr. T. van Woensel
Prof. Dr. A.G. de Kok

Company Supervisors
Drs. T. Kok
Dhr. P. van der Aar

On behalf of:

Amgen Europe B.V.
Minervum 7061
Postbus 3345
4800 DH Breda
The Netherlands

I. Preface

This report presents the results of a research project in order to receive the Master's Degree in Industrial Engineering and Management Science from the Technische Universiteit in Eindhoven (TU/e), the Netherlands. The project was carried out from September 2005 to June 2006 at the biotechnology company Amgen Europe B.V. in Breda, the Netherlands.

The company and the open and informal culture within Amgen interested me immediately after the first introduction interview with Pim van der Aar, and also the problem and the ideas for an initial project. The complexity and the scope of the project, namely supply chain management and distribution strategies, were completely in line with my interests. Therefore I want to express my thanks to Pim van der Aar who give me the opportunity to complete my Master's Degree thesis with Amgen. Also I would like to thank Tineke Kok, my Amgen daily supervisor, who was always willing to free time for me, give explanations and provide me with feedback and suggestions. Amgen gave me the opportunity to determine my own path in this research. During the project I gained experience in applying theory to real-life situations. I had to face the challenge of broadening the scope half-way through the project when the analysis produces a result which was in line with the current situation. Furthermore I want to thank all my colleagues who I worked with for the great working environment and for the enjoyable last nine months. I can say it has been a very meaningful and pleasant experience, to which I can look back with great satisfaction. I am very grateful and thankful for the opportunity and challenge Amgen gave me for this thesis and I am sure that this experience will be of great value in my further career.

I would also like to use this opportunity to express my thanks to my first university supervisor Tom van Woensel for his willingness to be my supervisor and for providing me with very valuable and critical remarks during the meetings we had. It was a very pleasant collaboration in an informal and open way. Next to him, I would like to thank my second supervisor Ton de Kok for his helpful comments and ideas especially on the quantitative analysis of the supply chain and on the supply chain models.

Also in my personal life the effects of carrying out my Master's Degree thesis must have been visible. A full agenda was more a rule rather than an exception. Therefore I want to thank everybody who has in one way or another been involved. Especially my parents and my family, but also my friends, for all their patience, encouragement and continuing support.

Marco Benthem
Eindhoven, June 2006

II. Abstract

The goal of this final thesis project is twofold: Firstly, an in depth analysis has been carried out on Amgen's largest retail market, namely Germany, and different distribution strategies to distribute the German retail market have been discussed. Secondly, this project shows the development of a model, with variable input parameters, that optimizes the transport and facility costs for a one centralized, European distribution structure and discusses the possibility of cross-border land services.

III. Executive Summary

Amgen (*A*pplied *M*olecular *G*enetics) was established in 1980 in Thousand Oaks (California, US) and is currently the largest independent biotechnology organization of the world. Amgen carries out a lot of research and discovers, develops, manufactures and distributes human therapeutics for several medical disciplines (inflammation, nephrology and oncology & hematology). Since 1997 Amgen Europe B.V., the European Logistics Center (ELC), was established in Breda. In the ELC, unlabeled products arrive from the US and Puerto Rico, stored in the warehouse, are packaged and labeled and then finally the medicines are distributed directly or indirectly to the end-customer in the whole of Europe, but also to North Africa and the Middle East. The main reasons for Amgen to look at the possibilities of having one centralized European structure are:

- The lack of space of the ELC and the necessitates to scale up to facilitate future growth;
- The trend of consolidating at European level by competitors;
- The desire to be closer to the customer and having more flexibility;
- The possibility to decrease counterfeiting through having greater supply chain control.

All those developments, together with the expirations of some of Amgen's patents, cause a tremendous change and larger competition pressure that Amgen has to adapt to. To remain competitive Amgen was interested in new and different distribution approaches to cope with those changes. The objective of this final thesis project is twofold and consists of two parts:

Direct distribution out of the ELC to the German retail pharmacies is not a profitable and feasible solution

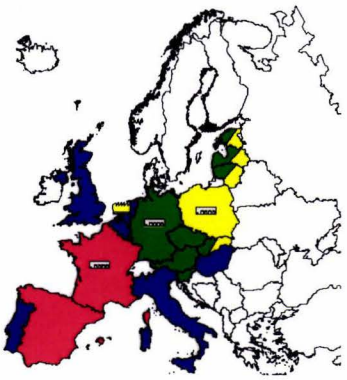
Part I, presents an in depth analysis on the German retail pharmacies to investigate the possibilities to integrate this specific group of end-customers into Amgen's supply chain and to choose the best distribution strategy for Amgen to distribute to the German retail pharmacists. The orders of the retail pharmacies are often orders of only 1 or 2 packages per time which have a tremendous effect on the number of shipments. Different distribution strategies have been discussed and a strong preference was given for the current strategy with the logistic service provider Fresenius; it is the cheapest option and also 4 out of 7 qualitative measurements are positive and last but not least, there are no reasons to question Fresenius and their performances exist. In addition, the direct distribution out of the ELC to the German retail pharmacies is not a profitable and feasible solution and is hard to realize for this specific market. However the main advantage of the direct distribution strategy is to become closer to the customers and therefore greater supply chain control and flexibility can be achieved.

Open a warehouse in France, Poland and Germany

Part II, shows the development of a model, with variable input parameters, that optimizes the transport and facility costs for a one centralized, European distribution structure and discusses the possibility of cross-border land services. So besides the ELC in Breda, where else should Amgen locate warehouses to distribute the hospitals and pharmacists in most of the European countries directly? Regarding the logistical parameters in the model, a difference was made between the demand and the cost variables which are the two main control parameters of the model. The variable:

- Total sold packs per country per market; } Demand
- Ratio Hospitals / Pharmacies of a country; } Demand
- Average packs per order for the group hospitals and pharmacies; } Demand
- Transportation Costs per shipment for both groups; } Costs
- Fixed charge to locate each potential facility site. } Costs

were used to evaluate several scenarios to find robust facility locations solutions and to reflect future trends. The conclusion that can be drawn is that the optimal solution is quite robust and that for a centralized, European distribution structure, Amgen should open distribution centers in France, Poland and eventually one in Germany.



ELC	France	Poland	Germany
The Netherlands	France	Poland	Germany
Belgium	Spain		Austria
Hungary			Czech
Italy		? ←	Estonia
Portugal		? ←	Latvia
United Kingdom		? ←	Lithuania
			Luxembourg
		? ←	Slovakia
			Slovenia

The figure depicts the ELC in the Netherlands and the three warehouses in France, Germany and Poland. When the color of a specific country matches with a color of a country where a warehouse is located, the country is allocated to this warehouse. This is shown in the table.

The results of part II complements the wishes of distributing directly to the German retail Pharmacists; not out of the ELC but out of the new Amgen warehouse located in Germany. The results from the investigation on the German retail pharmacists reveal that the current distribution strategy, so via a LSP, is the best option. It was not profitable to apply another distribution strategy to those pharmacies and the option of a complete new warehouse was not feasible at all. Broadening the scope in part II to an European level, and taking all the different volumes of each country into account with cross border possibilities, results in setting up a German warehouse as part of the optimal solution. Locating a distribution center in Germany is attractive through aggregating the total volume of Germany and other countries instead of concentrating only on a small part of a specific market which leads to sub-optimization. As a result the German retail pharmacists can now be delivered directly from this new warehouse and provide therefore also a desirable answer to part I.

IV. Table of Contents

V. Introduction

This introductive chapter provides an overview of this report. The goal of this final thesis project is twofold: Firstly, an in-depth analysis of Amgen's largest retail market Germany, and different distribution strategies that can be applied for distributing to the German retail market have been discussed. Secondly, this project shows the development of a model, with variable input parameters, that optimizes the transport and facility costs for one centralized, European distribution structure and discusses the possibility of cross-border land services. Part III of this report, gives the general conclusion and recommendations of the project based on the results obtained from both Parts I and II and several ideas are given for future research.

Therefore the outline of the report consists of three main parts:

1. **PART I: Analysis and Optimization of the German Retail Distribution**
   An in depth analysis on the German retail pharmacies to investigate the best distribution strategy for Amgen to distribute the German retail pharmacists (directly, indirectly or maybe a hybrid form)
2. **PART II: Analysis and Optimization of the European Distribution**
   The development of a model, with variable input parameters that optimizes the transport and facility costs for one centralized, European distribution structure and discusses the possibility of cross-border land services
3. **PART III: Conclusions and Recommendations**

and the content of each is as follows:

Chapter 1 gives a short overview of Amgen, including Amgen's products, developments, production and distribution facilities around the world, the Dutch site office and the European Logistics Center. When the environment of Amgen is transparent, the details of this project are the main focus of **Chapter 2**. First some background information is given on Amgen's supply chain before external threats and areas for improvements are given. The positioning of the project has been given attention and the chapter ends with the scope of the project.

PART I: Analysis and Optimization of the German Retail Distribution

Chapter 3 is the first chapter of Part I and gives an in-depth analysis of the German retail pharmacies. The supply chain, the order pattern, costs and the order process are discussed in detail. **Chapter 4** continues with a literature overview of supply chain management to obtain an appropriate model, together with the needed input data, to analyse the different distribution strategies for the German pharmacists. These distribution strategies are discussed in more detail in **Chapter 5**. For each strategy the direct costs of transportation, stock holding and order handling costs are presented after which in **Chapter 6** the feasible strategies are compared with each other. This chapter ends with the results of part I.

PART II: Analysis and Optimization of the European Distribution

Chapter 7 is the first chapter of Part II and starts with an overview and analysis of different distribution and facility location models which are available in the current literature. A specific model is selected to realize the optimization of one centralized, European distribution structure with a few Amgen warehouses to distribute to hospitals and pharmacists in most of the European countries directly. Furthermore the analysis on the European countries served by the ELC is given. The current distribution flows, the group of end-customers and the European regulations for pharmaceutical companies are discussed. Finally the European countries, which will be included in the model, are shown. Next, in **Chapter 8**, the model for a centralized, European structure is described in detail. The goal and the input data needed to minimize the total transportation and facility costs are given. Hereafter the model is developed after which a validation check is performed. Subsequently, **Chapter 9**, provides some scenarios and sensitivity analysis to find a robust facility location solution. Finally, this chapter ends with the results of part II.

PART III: Conclusions and Recommendations

The report ends with **Chapter 10** providing concluding remarks, recommendations and several thoughts for future research.

References, **Abbreviations** (used in this report) can be found at the end of the report. Because certain information is confidential, some figures and numbers are marked blanked and all **Appendices** are detached from this report. These are collected in a separate bundle.

1. Company Description

1.1 Amgen Worldwide

Amgen (*A*pplied *M*olecular *G*enetics) was established in 1980 in Thousand Oaks (California, US) and is currently the largest independent biotechnology organization of the world with sales of more than $ 10 billions in 2004. Amgen carries out a lot of research and discovers, develops, manufactures and distributes human therapeutics for several medical disciplines. Today, Amgen's main research areas are inflammation (for example rheumatoid arthritis), nephrology and oncology & hematology.

Amgen concentrates especially on the development of new medicines based on DNA and human proteins to develop, with biotechnological methods and clinical studies, new and cost-effective medicines which offer great advancements for patients. This objective is translated in the mission of Amgen: 'We aspire to be the best human therapeutics company. We will live the Amgen values and use science and innovation to dramatically improve people's lives'. The mission is also well known by the 14,000 employees who are employed by Amgen worldwide. The figure below shows an overview of the Amgen's facilities worldwide.

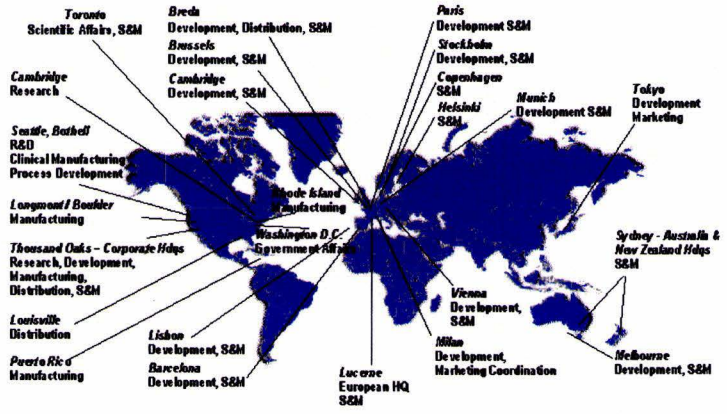


Figure 1 Amgen Worldwide

Since the foundation in 1980 the sales of Amgen's product have shown an upward trend and particularly over the last few years. In 2001 there were 7,000 employees working worldwide for Amgen, which resulted in sales of more than 3 billion dollar. During that period Amgen's success was due to two main products: Epogen and Neupogen, which they introduced more than a decade ago. These were the first biologically derived human therapeutics (see figure 2 for the product sales). Those medicines became the biotechnology industry's first blockbusters, which resulted in a turnover of more than one billion dollars.

Four years ago Amgen introduced a successor of Epogen, called Aranesp, which has experienced an enormous growth over the last few years. Aranesp is an anemia treatment, but has the advantage that it has a longer half-life than Epogen, allowing it to circulate in the body longer. As a result the patients need less frequent dosing. The company has invested, since 1994, at least 20 percent of product sales in research and development each year, with a total of $2 billion in 2004. The result of this is a great product pipeline that ensures a lot of new introductions the next few years.

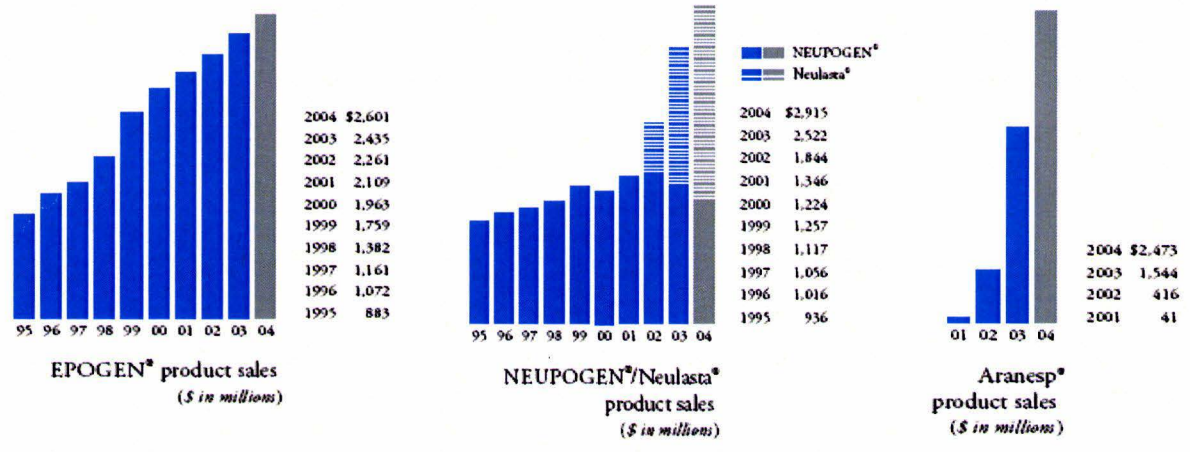


Figure 2 Product Sales of Epogen, Neupogen and Aranesp **Source**: Amgen 2004 Annual Report

At this moment, most of the product sales are in the US. The US product sales have increased 22 percent to $8.3 billion, representing 83 percent of Amgen's total product sales in 2004. Amgen's international product sales have increased 54 percent to $1.7 billion in 2004. This growth was driven primarily by additional market penetration of the products on the European market. In figure 3 it is clear to see that these differences already decreased in the last few years and that the international market (the market outside the US) will get a more prominent role for Amgen.

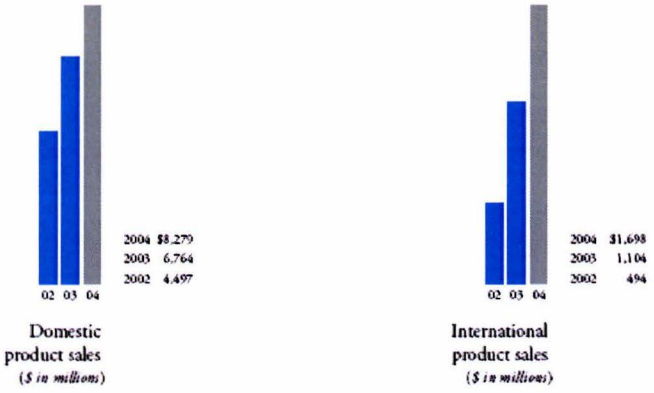


Figure 3 Domestic and International Product Sales **Source**: Amgen 2004 Annual Report

1.2 Amgen Products

As stated earlier, Amgen's products are medicines mainly for oncology, hematology, nephrology and rheumatism. For a long time Amgen had only two main medicines: Epogen and Neupogen. Over the last few years new generations are launched. These two products called Aranesp and Neulasta respectively. These successors have longer-life which means that the patient requires fewer injections. At this moment Amgen has eight products on the market and invest a great part (more than 20 percent) of the annual sales in research and development. The result of this is a promising pipeline with many new potential products. Figure 4 gives an overview of the eight commercial products (the abbreviations of the manufacturing sites are given in paragraph 1.3).

	FDA Approval	Field	Available outside USA	Vial	Syringe	SureClick	Tablet	Strengths	Cold SC needed?	Manufactured
Epogen, treatments of anemia for patients with chronic kidney desease. Stimulates the production of red blood cells	1989	Nephrology	No						Yes	Still ACO Will be AML
Aranesp: "successors" of Epogen. *Advantage*: less frequent dosing	2001 (nephrology) 2002 (oncology)	Nephrology, Hematology / oncology	Ys	X	X	X		12	Yes	ACO Still ATO Will be AML
Neupogen: For prevention and treatment of infection for cancer patients undergoing certain types of chemotherapy. Stimulates the production of one type of white blood cell	1991	Hematology / oncology	Yes	X	X			2	Yes	Still ATO Will be AML
Neulasta: "successors" of Neupogen. *Advantage*: Once-per-cylce injection	2002	Hematology / oncology	Yes		X	X		1	Yes	Still ATO Will be AML
Sensipar / Mimpara: For patients with chronic kidney disease. Acts directly at the calcium-sensing receptor to control parathyroid hormone	2004	Nephrology	Yes				X	3	No	Outsourced
Kepivance: A therapy for mucosites	2004	Hematology / oncology	Yes	X				1	Yes	ACO
Enbrel: A therapy for Rheumatoid Arthrites	2002	Inflammation	No						Yes	ACO, but in Europa distr. by Wyet
Kineret: A therapy for Rheumatoid Arthrites	2001	Inflammation	Yes		X			1	Yes	ACO

Figure 4 Overview of the eight Amgen Commercial Products on the Market

1.3 Amgen Manufacturing & Distribution

Amgen has a number of development, production and distribution facilities around the world where the medicines are developed, manufactured in bulk, packaged and distributed. The process development and/or product manufacturing facilities are in California, Colorado, Rhode Island, Washington and Puerto Rico. Amgen's manufacturing capabilities are further broadened by strategic relationships with a range of contract manufacturers in the United States, Europe, Canada and Japan. Figure 5 shows Amgen's main facilities and a more detailed description is given in appendix 1.

Facilities	
Corporate Headquarters	ATO (Amgen Thousand Oaks)
Manufacturing facilities	ATO (Amgen Thousand Oaks) ACO (Amgen COlorado) ARI (Amgen Rhode Island) AML (Amgen Manufacturing Limited, Puerto Rico)
F&F (Filled & Finished) site	AML (Amgen Manufacturing Limited, Puerto Rico)
Development facilities	ATO (Amgen Thousand Oaks) AWA (Amgen WAshington)
Distribution centers	LCD (North American Distribution center) ELC (European Logistic Center) Melbourne (Australia)

Figure 5 Major Amgen's Productions, R&D's en Distributions Facilities around the World

In addition, Amgen has many brand offices in the world, many of which are in Europe. Finally it is important to mention that Amgen, as a biotechnology supplier and distributor, need to comply with GMP[1] and GDP[2] and is monitored by the FDA[3] for product deliveries in America and by the EMEA[4] for deliveries in Europe.

1.4 Amgen Netherlands B.V.

In 1989, Amgen was established in Europe. In the same year the Dutch site office, Amgen Netherlands B.V., was established in Breda. The most important activities of Amgen B.V. were and still are clinical investigation, marketing and sales. There are currently 60 employees working at Amgen B.V., divided over the following departments: Marketing & Sales, Clinical Investigation, Medical Information, Finances and Registration.

1.5 Amgen Europe B.V.

Since 1997 Amgen Europe B.V., the European Logistics Center (ELC), was established in Breda. In the ELC, unlabeled products arrive from the US and Puerto Rico and stored in the warehouse. All European orders are handled by the ELC. The unlabeled products are packaged, labeled and distributed directly or indirectly to the end-customer. For most of the products a cold supply chain is necessary, which means that the products have to be cooled at all times. As mentioned earlier, the medicines are packaged, labeled and distributed to the whole of Europe, but also to North Africa and the Middle East. However each country is different in terms of customer needs, legislation and compensation rules. Therefore the packages and labels are unique for each country. When countries have similar requirements Amgen clusters countries in groups to reduce the different numbers of SKUs. Amgen Europe B.V also supports the clinical studies and introductions of new products. Furthermore the European IS-department, the Finance Shared Services department, coordinating all European financial operations, and the Customer Service department for order taking and customer contact, are situated within Amgen Europe B.V.

Figure 6 The European Logistics Center

[1] GMP: Good Manufacturing Practice
[2] GDP: Good Distribution Practice
[3] FDA: U.S. Food & Drug Administration
[4] EMEA: The European Agency for the Evaluation of Medicinal Products

This project took place within Amgen Europe B.V., the European Logistics Center (ELC), in the Business Development department. The managing director of the ELC is Hubert Koevoets and the organization chart is shown in figure 7.

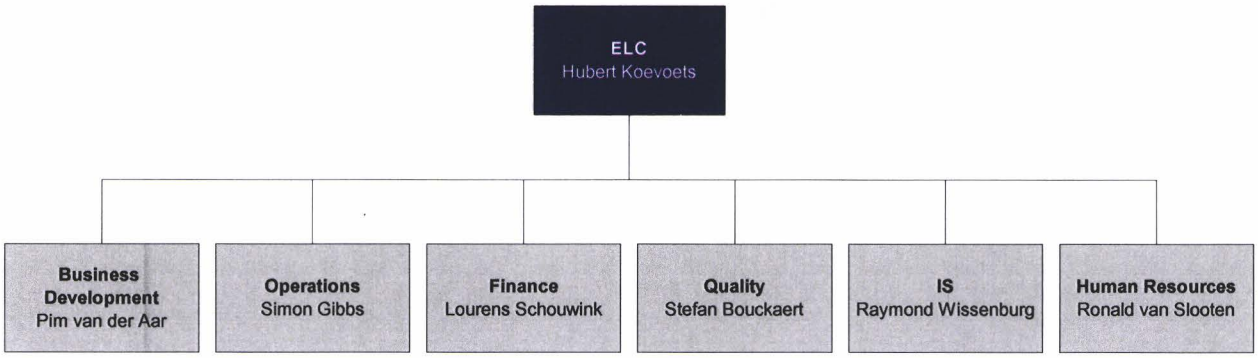


Figure 7 Organization Chart ELC

1.6 Business Development Department

The Business Development department, under leadership of Pim van der Aar, employs 19 people and the mission of the Business Development department is to increase the added value of the ELC for Amgen. It looks for ways to meet or exceed customer expectations and to stay competitive in the best possible way. There are 3 disciplines within this division. Firstly there is the 'PMO' (Program Management Office) division. Within this division, innovative projects are created, supported and executed. The second discipline is 'Commercialization'. This division manages projects to launch new products and maintain and develop markets of current products. In general, they make sure that products are available for distribution from the ELC at the date agreed upon with marketing and the local affiliate. The last discipline is 'Package Development' that manages the design and the specifications of the packages and labels. This can be the case when new products are introduced but also for existing products on the market when a change occurs. The organization chart of Business Development is given in figure 8.

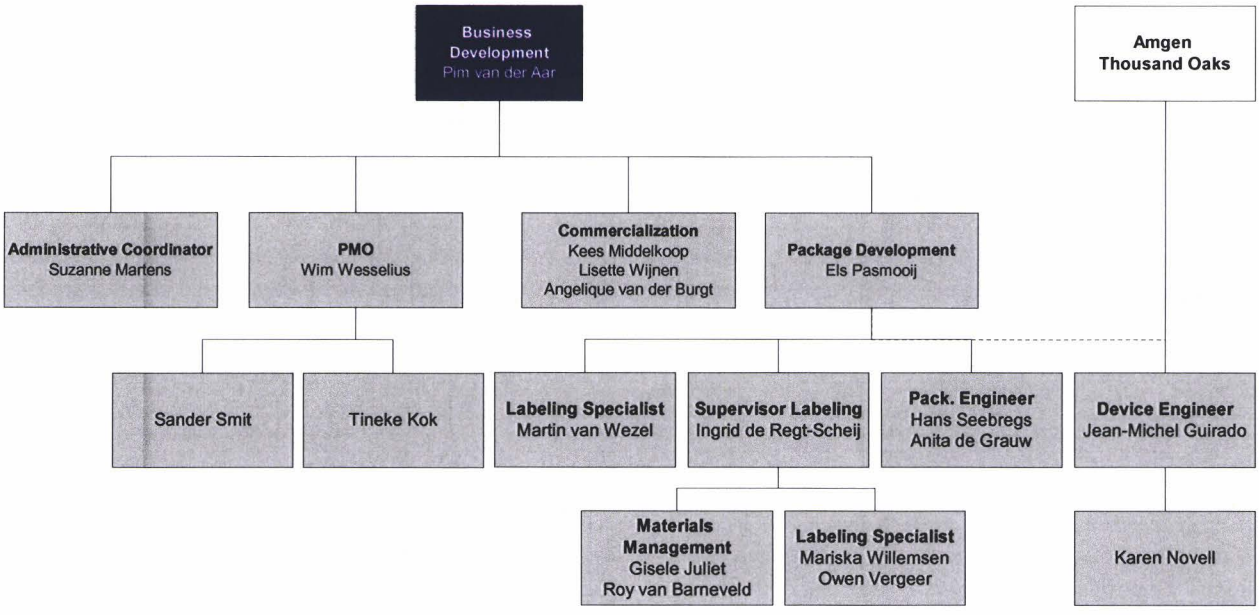


Figure 8 Organization Chart Business Development

2 Research Project

2.1 Background

As stated earlier in the previous chapter, in the ELC, unlabeled products arrive from the US and Puerto Rico and stored in the warehouse. Then the medicines are packaged, labeled and distributed to the whole of Europe, but also to North Africa and the Middle East. The figure below (figure 9) shows the supply chain. Bulk production takes place in Amgen Colorado (ACO) and Amgen Thousand Oaks (ATO). In the future the latter will move the bulk production to Puerto Rico (AML) because the focus of ATO will change from a commercial manufacturer to a clinical manufacturing site for. AML is, at this moment, the only F&F (Fill & Finish) site of Amgen. Here, the bulk products are received from all manufacturing sites and the vials and syringes are filled. After the F&F, the unlabeled vials and syringes are distributed to the ELC where the products will be labeled and packed. The products are all made to stock through forecasting and the Customer Order Decoupling Point (CODP) is located at the end of the chain: at the ELC.

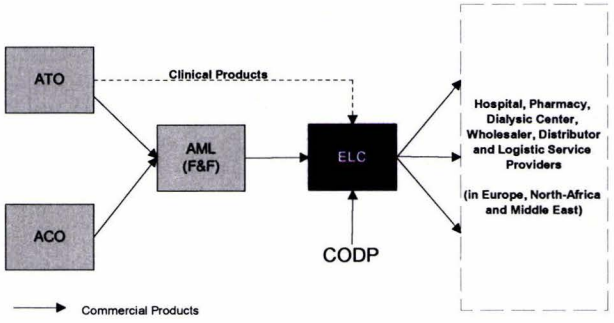


Figure 9 Supply Chain ELC

As shown in figure 9, ELC has different kinds of customers who are being supplied with Amgen's products. The end-customers are patients at home as well as patients in the hospitals. However pharmaceutical companies are not allowed to serve those patients directly and only pharmacists are allowed to deliver these patients on doctors' prescription. Therefore, Amgen's real end-customers are hospital pharmacies, the (smaller) retail pharmacies, large wholesalers or distributors and Logistic Service Providers. The main difference between a large wholesaler (or distributor) and a Logistic Service Provider is the ownership of the inventory: a wholesaler will buy the products and becomes the owner of those medicines, the products at a Logistic Service Provider remains property of Amgen. Amgen has a number of Logistic Service Providers in countries such as France, Switzerland, Germany, Spain, UK and the Czech Republic.

2.2 Problem

In 1997 the ELC was built and extra capacity was added later on to meet future growth. Now, almost 9 years later, the growth Amgen faces is much larger than expected. The yearly growth in dollars is around 20-30 percent and the ELC is now not only serving Europe, Amgen's first intention, but now includes the rest of the world. North Africa, the Middle East and Australia are already supplied through the ELC. South America and China will probably be added in the future and even the US market will be supplied through the ELC for the Aranesp SureClick products. Due to this the supply chain complexities have increased to a large extent: many SKUs, many stock points, and many different local partners. Actually, every country has/needs a different distribution strategy.

One of Amgen's goals of 2005 was 'win in a changing marketplace' because the competitive power become tougher than ever before. Part of this goal is to grow the market size & share and to reach new patients. The supply chain must ensure supply to every patient every time. Amgen wants to be as 'close' as possible to the end-customer. To achieve this, another distribution approach will be necessary because large part of sales volumes is handled by wholesalers and distributors. In addition, Amgen wants to create a distinct profile at the care insurers because those institutes influence which medicines will be reimbursed for specific populations.

The trends of pharmaceutical sector in Europe were presented by Accenture (2005). During April and May in 2005, Accenture consulted people in charge of Supply Chain in Europe's main pharmaceutical companies, to obtain their vision on "key points of the supply chain within the pharmaceutical market in Europe and potential impact that logistic strategies have". This study reflects that companies with a European market can be divided in two groups:

- Those who have already consolidated at European level and obtaining on average 6 DCs, and
- Those who still maintain the local DCs model with a range of 14 to 16 DCs.

According to the study, logistic operations still fall under control of country sales organization in 44% of the respondents, although 19% are already being managed in a centralized way. The rest was still halfway.

In addition, Accenture concluded that many companies are planning to centralize in the mid-term, whilst maintaining some local distribution centers. The three main reasons of changing current logistic networks are (1) to reduce logistic costs, (2) to reduce the complexity and (3) to improve the level of service. The two most common changes are:

- Outsourcing finished products to third parties;
- Migrating local centers to one centralized European structure.

A good example is Pfizer: this large pharmaceutical company eliminates at this moment most of the current wholesalers in their supply chain to apply more and more direct distribution via own private distribution centers.

Furthermore counterfeiting is a hot topic now and this threat is not only affecting the finance business or the music industry but also the pharmaceutical industry where it is becoming a growing problem. In the pharmaceutical world this is a very serious matter because it can effect patients' lives and could have a major financial impact on the manufacturer due to ongoing sales losses, brand switch because patients shift for safety to more reliable products, and expenses of remediation (for example investigation, communication, security systems and even maybe expenses for given damages for compensation). Counterfeit medicine can involve (1) no active ingredients (2) incorrect ingredients and/or (3) incorrect amount, but also (4) repackaging of illegally imported medicines. So although not all forms of counterfeiting have the same dangerous effects, the result always leads to a large decrease in trust for a certain product. An estimate of the World Health Organization (WHO) is that approximate 8 - 10% of the global medicine supply is counterfeited. However, these percentages are higher in some specific areas (for example China and Columbia but also closer to Europe like Russia (12%) and Ukraine). With a growing number of new territories which the ELC will distribute to and the expansion of sales in those countries, counterfeiting is becoming an increasing concern.

At last but not least the coming years patents of particular products will expire whether it is possible to introduce new biosimilars by competitors on the market All those events will cause a tremendous change and larger competition pressure where Amgen has to deal with.

2.3 Positioning the Project

To investigate the structure of an industry, to give the strengths and weaknesses of a company's strategy and to support the project, the competitive forces model of Porter (1980), see figure 10, is a suitable tool. It can be used to position the company and to relate the company to its external environment. In the competitive forces model, five industry forces determine the profit potential of an industry.

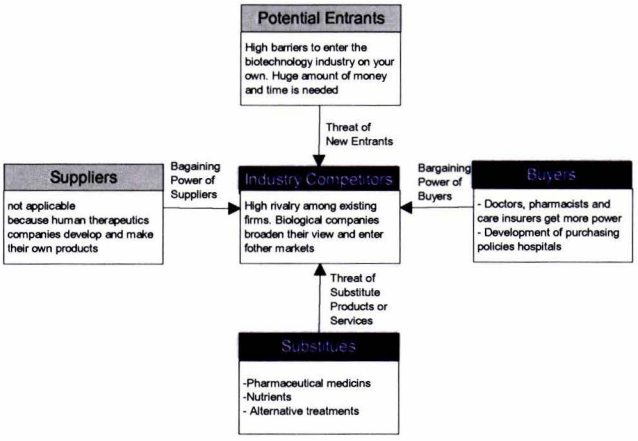


Figure 10 Competitive Forces Model of Porter

In the biotechnology industry the bargaining power of suppliers is not applicable because human therapeutics companies develop and make most of the products they bring to the market within their own company. Secondly, the barriers of potential new entrants are very high for the biotechnology industry. Hugh amount of money is needed to make biological medicines and to go through all phases and tests before receiving approval. It is common for larger companies to acquire (smaller) companies reducing the number of new companies entering the market (see for example Amgen and Immunex). However, if the biotechnology industry is analyzed in specific areas, for example oncology or nephrology market, the barriers are much lower and are more competitive. Over the last few years, more companies are trying to enter other markets where they are not yet active. So instead of focusing on only the nephrology market they broaden their view to enter for example the oncology market. Biological companies who, at first, offered no competition to the company are suddenly competitors. Further, the threat of substitute products also exists and not only biological medicines, but also pharmaceutical medicines, transfuse nutrients and other alternative treatments may be chosen by the patient.

Finally the bargaining power of the buyers is increasing enormously. The doctors and pharmacies have the possibility to choose medicines from several suppliers, the care insurers have greater influence in deciding which medicines will be reimbursed and there are a many rules and government regulations which may give the buyers more power (for example fixed prices). A larger amount of hospitals are trying to set up new purchasing policies to combine orders of several hospitals in order to negotiate better prices.

All these developments, together with the expirations of some of Amgen's patents, will cause a tremendous change and larger competition pressure that Amgen has to adapt to. So to remain competitive Amgen must focus on:

- Demand Chain Management: Focusing on the (end)customer will be tremendously important. Understanding the customer's situation and needs (patients / doctors / pharmacies) together with the right offering will give a competitive advantage.
- Costs: The costs have always been taken into account when different strategies have to be compared with each other. It is an important goal of Amgen because delivering financially is critical every year. In the pharmaceutical industry investing in R&D is enormously important because this offers competitive advantages and ensures the continuation of the company.
- Risk: Amgen is focusing more on the risk aspects within their own company to prevent any situation in which Amgen is unable to deliver to patients on time. Therefore the risks, associated with different distribution strategies, have to be taken into account.

According to Heikkilä (2002), understanding the customer's need together with the right demand chain structure results in good co-operation in improving the joint demand chain, which further leads to superior demand chain efficiency and customer satisfaction. This means that the distribution strategy must have the ability to deal with customer's needs and expectations and have the flexibility customers require.

2.4 Scope of Project

In the previous paragraphs several threats and the weaknesses of a company's strategy were mentioned briefly. The capacity of the ELC which may become an issue in the next few years through distribution to more and more countries, the increase of the supply chain complexity by the introduction of new products, devices, SKUs and regions, the need for flexibility, the integration of the customer in Amgen's supply chain, the trend of consolidation at an European level and taking the most effective anti-counterfeit activity into account which is to control the supply chain from beginning to end demand another type of supply chain. A different distribution approach will be necessary to cope with those changes:

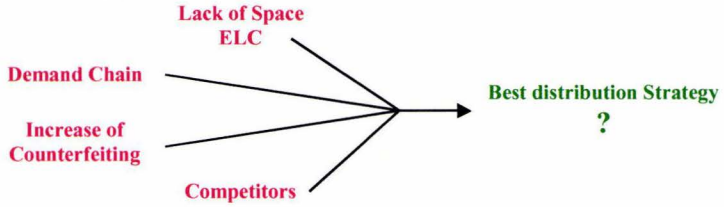


Figure 11 Threats that Influence the Type of the Distribution Strategy

The objective of this final thesis project is twofold:

PART I: Analysis and Optimization of the German Retail Distribution

An in depth analysis on the German retail pharmacies to investigate the best distribution strategy for Amgen to distribute the German retail pharmacists (directly, indirectly or maybe a hybrid form)

First, an in depth analysis has been carried out on Amgen's largest retail market, namely Germany. The German retail pharmacies take almost 68 percent of the total deliveries to European pharmacies for their account and are distributed by Amgen's Logistic Service Provider 'Fresenius Medical Care'. However to do the deliveries in own management and distribute the retail pharmacists directly to integrate this type of group more in Amgen's supply chain, an in depth analysis on the order characteristics is needed. Hereafter different distribution strategies to distribute the German retail market will be discussed. For each distribution strategy the network shall be given, or in other words, the way the supply chain is organized. The pros and cons of each strategy will be given, looking at the differences in fill rates, the size of the safety stock, the costs, flexibility of the strategy and finally the impact on the ELC of each of the strategies shall be analyzed.

PART II: Analysis and Optimization of the European Distribution

The development of a model, with variable input parameters, that optimizes the transport and facility costs for one centralized, European distribution structure and discusses the possibility of cross-border land services

Secondly the distribution strategy consolidating at an European level through migrating local centers to a centralized, European structure with a few Amgen distribution centers in Europe has been investigated. So, how many satellite warehouses are needed to distribute the European countries at minimal costs? This is a good opportunity to check the possibility of cross-border land services (so whether (smaller) markets can be served by truck cross-border from an own warehouse or of a LSP-location outside the country). This part shows the development of a model, with

variable input parameters, that optimizes the transport and facility costs and different scenarios are evaluated and the results are discussed.

PART III: Conclusion and Recommendations

The report ends with part III, presenting concluding remarks and recommendations of both part I and II and provides several thoughts for future research.

PART I

Analysis and Optimization of the German Retail Distribution

An in depth analysis on the German retail pharmacies to investigate the best distribution strategy for Amgen to distribute the German retail pharmacists (directly, indirectly or maybe a hybrid form)

3 Analysis of the German Retail Distribution

3.1 Introduction

One of the largest European market for Amgen is Germany. In Germany, Amgen directly distributes the hospitals and Amgen Munich handles the customer service and orders. These orders consist of many (different) packages and different SKU's. There is also a large retail, consisting of city pharmacies which take almost 68 percent of the total deliveries to European pharmacies. Those German retail pharmacists are distributed by Amgen's German Logistic Service Provider 'Fresenius Medical Care'. The stock situated at Fresenius remains property of Amgen. When a retail pharmacist places an order at Fresenius, Fresenius will deliver those orders through the carrier 'Transoflex'. The orders of the retail pharmacies are often orders of only 1 or 2 packages per time. 'Fresenius Medical Care' has around 15.000 shipments per month, the ELC has 'only' 7.500 shipments of Amgen products to European customers per month. It is predicted that this distributor will become larger and therefore gain more power in the future. This together with the fact Amgen wants to integrate the customer more in their own supply chain, the question arose: Is it possible to manage the deliveries in own management and distribute the retail pharmacists directly from the ELC?

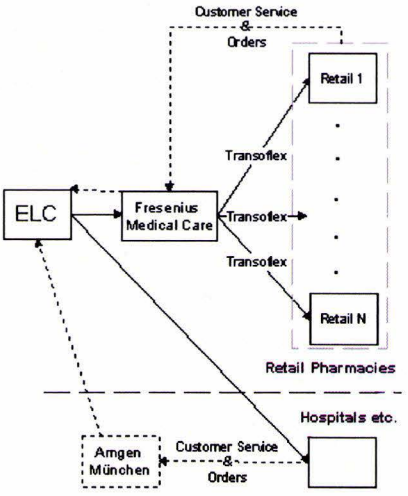


Figure 12 Supply Chain Germany

3.2 Europe

The ELC is the European Logistic Center for serving Europe, North-Africa and the Middle-East. In the first few years Amgen ELC was only serving the 15 major European countries (the West-European countries including Scandinavia) which have a population of 380 million people. In 2004 they started to distribute their products to 8 new East-European countries including Czech Republic, Hungary, Turkey, Poland, and Slovenia. As a result of the expansion the potential customers grew with 73 million people to 453 million (a growth of 16 percent). In 2005 the ELC was serving 27 countries in total and the prognosis is that this number will only grow in the future.

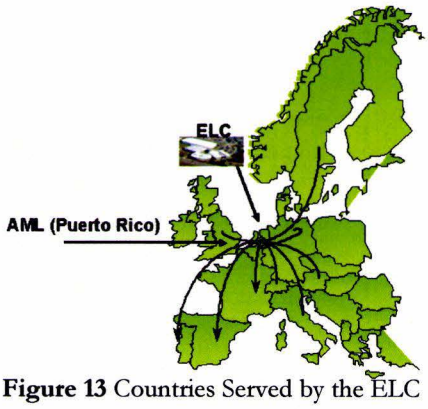


Figure 13 Countries Served by the ELC

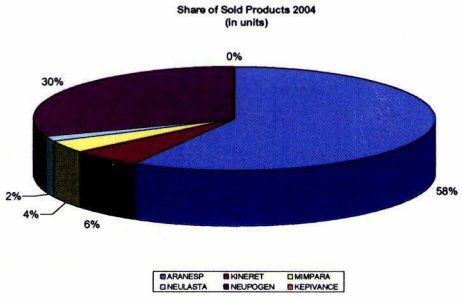


Figure 14 Share of Sold Products 2004

Looking at the total sold units (syringes, vials, the SureClicks and tablets) shipped in 2004, France was the biggest customer and Germany was second place with 1.592.234 sold units. Looking at the data of 2005, up to 09-10-05 are incorporated, Germany will probably become the largest purchasing country. Figure 15 on the next page shows, for most of the countries, that the previous year sold units has already been reached in the first three quarters of 2005. The growth percentages for the ELC are between 20 and 30 percent per year and the expectations are that this will continue in the coming years.

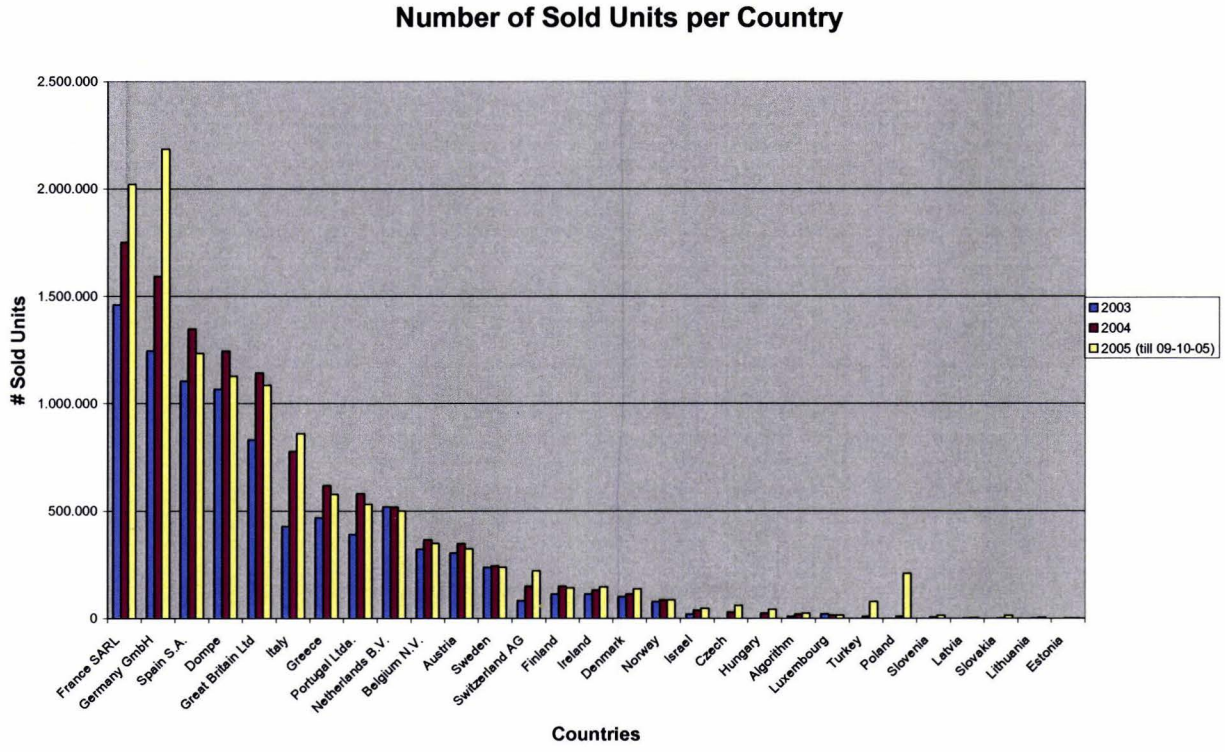


Figure 15 Number of Sold Units per Country (2003 to Sept 2005)

Appendix 2 shows the distribution flows in 2004 for Europe and for Germany. It distinguishes three flows, namely the ELC direct flow, ELC local flow (the flow to the local service providers) and the non-ELC flow (the flow behind the logistics service providers to the end-customers). The first table in appendix 2 clearly shows that most of the pharmacies in Europe are distributed to indirectly via logistic service providers. It is possible that the differences are even bigger because the flows behind the distributors and wholesalers, who are served directly by the ELC, are unknown. Looking at the flows to Germany, and then especially the flows to the pharmacies, it can be concluded that out of the 650 thousand sold units to the pharmacies a large part is dealt by the local service provider Fresenius. Only a minor part of the sold units is sold via direct shipments. In addition it can be noticed that the German retail pharmacies take an substantial part, almost 68 percent, of the total deliveries to European pharmacies. This is an important reason for focusing on Germany and that the result of this project may be an input for the ELC to distribute to the retail pharmacies in other European countries.

3.3 Germany

3.3.1 Fresenius

Fresenius Medical Care

Fresenius Medical Care is not only a logistic service provider for other companies but is the world's leading provider of products and services for individuals with chronic kidney failure. They obtained a net revenue of more than $ 6 billion in 2004 and more than 44.000 employees are active for Fresenius Medical Care. Fresenius Medical Care is one of three business units of the Fresenius group. Through its network of approximately 1,670 dialysis clinics in the United States, Europe, Latin America and Asia Pacific, Fresenius Medical Care treats approximately 130,400 patients around the globe. One of the main reasons Amgen partnered with Fresenius for supply to the retail market was Fresenius' extensive network of dialysis centers in Germany. Besides the role of a logistic service provider for Amgen, Fresenius will also do promotional activities, as part of the contract. Finally Fresenius Medical Care uses the road carrier Transoflex which ensures that the medicines will be delivered to the German retail pharmacies the next day (most of the deliveries are even delivered before noon the next day).

3.3.2 Distribution Flows October 2004 – September 2005

Appendix 2 shows the distribution flows for Germany from October 2004 to September 2005 for the measurements 'shipped units', 'shipped packs', 'orderlines', 'orders' and 'customers'. The most noticeable point is the huge difference in the number of shipments out of the ELC and out of Fresenius. As the number of orders is a good approximation to the number of shipments, it can be observed that the total shipments out the ELC are for

Germany 21.000 per year. This is, in contrast with Fresenius, a small part because Fresenius deals with 150.000 shipments a year. Furthermore appendix 2 shows that only Aranesp and Mimpara are distributed to Fresenius and the retail pharmacies. Before any conclusions can be drawn the flows to the retail pharmacies have to be investigated. This will be done in the next section.

3.4 Pharmacies Germany

3.4.1 General

Figure 16 presents the supply chain to the German retail pharmacies and identifies the different steps needed to distribute the medicines to the pharmacies. It also indicates the CODP (Customer Order Decoupling Point).

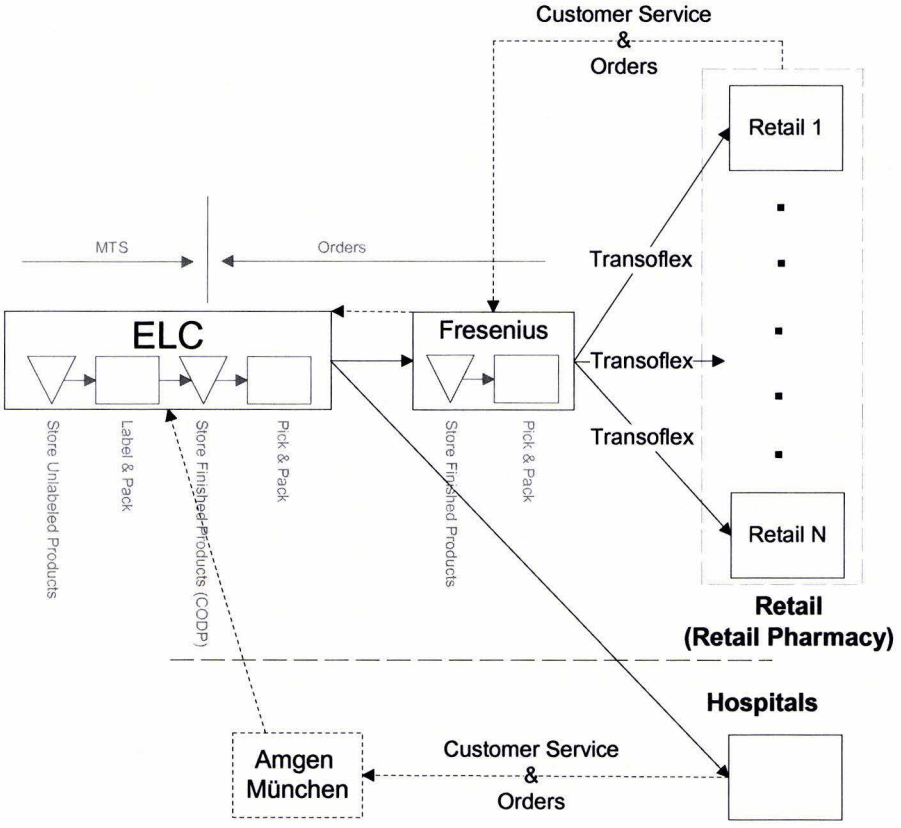


Figure 16 Supply Chain German Retail Pharmacies

As already mentioned in the last paragraph, the products which are sold to the pharmacies are Aranesp and Mimpara. Aranesp exist in two forms, namely the syringe, on the market for a couple of years now and the SureClick[5], which was launched the second half of September 2005. Both products need a cold supply chain. The second product, Mimpara, was launched the end of December 2004 and does not need to be cooled. For both products different strengths exist. Appendix 2 shows all the SKUs that are being distributed to Fresenius at this moment.

3.4.2 Order Pattern

This section will investigate the order pattern of the German retail pharmacies: how many retail pharmacies exist, how often do they order, what is the average size of an order and is there a minority who are accountable for a large part of all placed orders. The data is extracted for the period October 2004 to September 2005.

[5] SureClick is a new device for simple and secure subcutaneous administration of the medicines Aranesp and Neulasta. The greatest advantages are the patient independency, the ease of handling and is safer because of the hidden needle (reduce chance of needle stick injury to Health Care Professionals).

Facts	
Period	Oct 04 - Sep 05
# Shipments day	254
# Number of pharmacies	18.250
# Orders	150.656
# Shipped packs	223.096

Figure 17 Facts of the German Retail

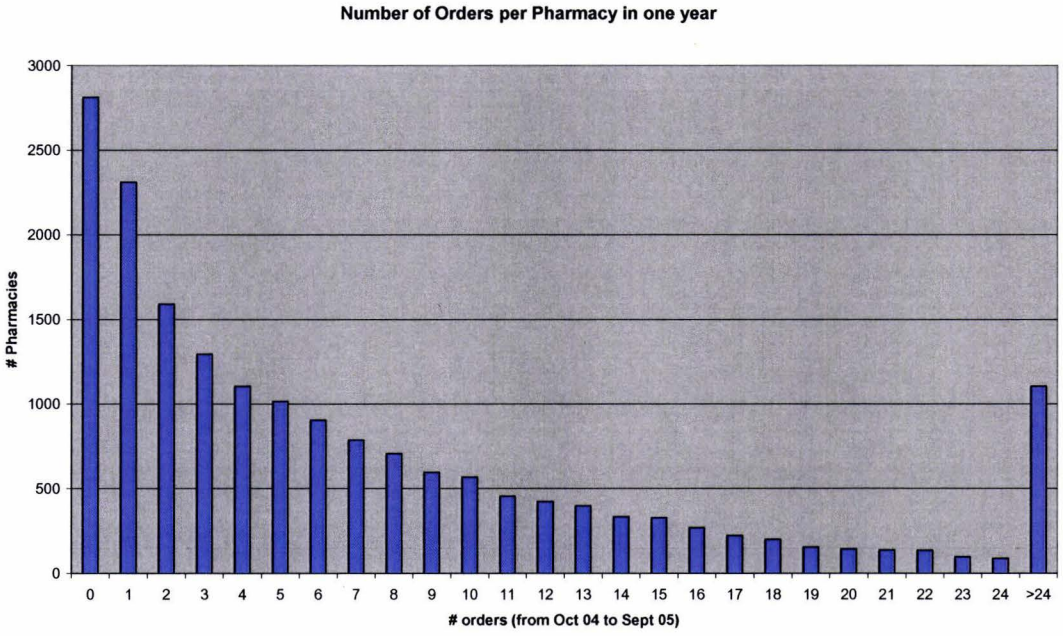


Figure 18 Number of Orders per Pharmacy in the Period Oct 04 to Sept 05

From the data provided before it can be noticed that each order contains on average of only 1,48 packs (223.096/150.656). Furthermore almost 3000 retail pharmacies did not order at all last year, 14 thousand pharmacies ordered (on average) maximum once a month and just over a 1000 of the 18.000 pharmacies ordered more than twice a month (this is the last bar in figure 18). The last figure in appendix 2 shows that the majority of the placed orders just contain 1 SKU.

Previous figure gives a good overview of some of the characteristics of an order but one aspect is missing: the variety of the number of packages in an order. This will be important for the order handling and the size of an Insulated Shipping Container (ISC, see figure 19). It is shown that this will be an average of 1.5 packages, but there is a chance that this gives an unrealistic view: it is possible that a small number of pharmacies order many packs at a time and it is important to take this into account when a distribution strategy has to be developed. The following figures will show the orders and the average packs per order per pharmacy.

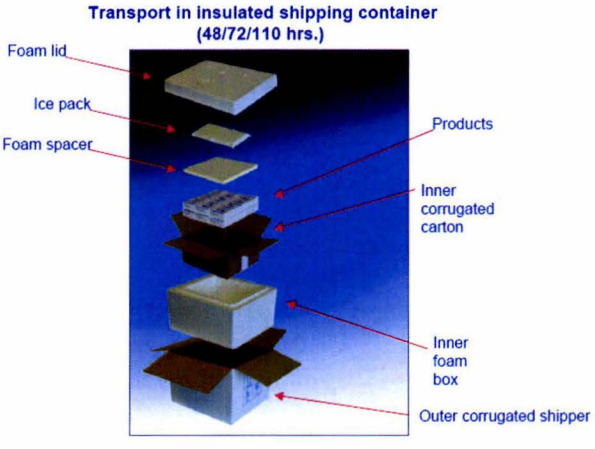


Figure 19 Insulated Shipping Container (ISC)

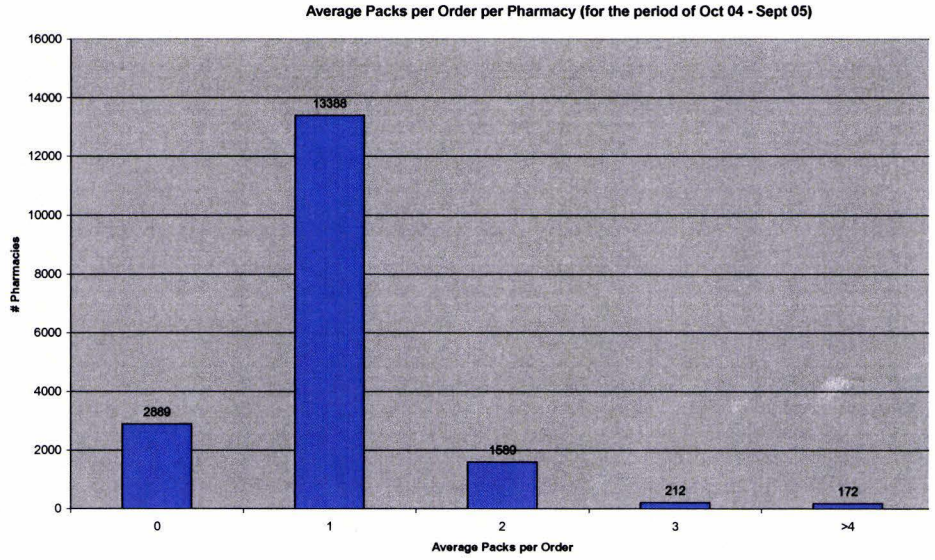


Figure 20 Average Packs per Order per Pharmacy for the period of Oct 04 - Sept 05

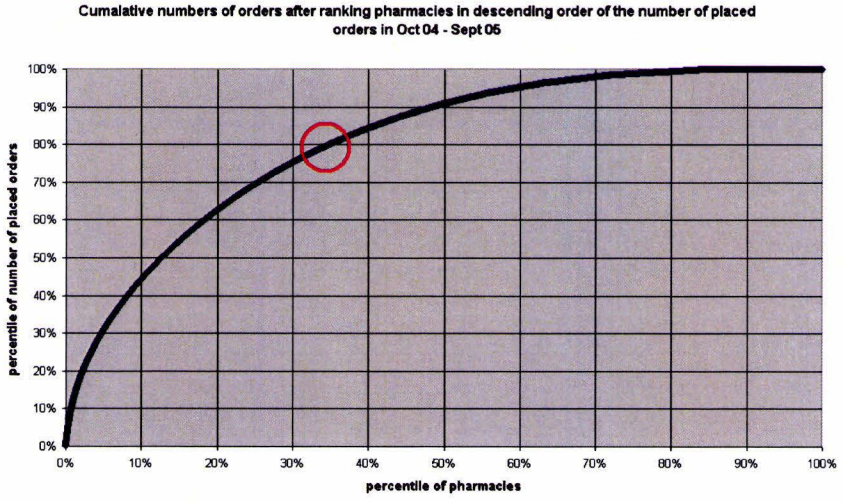


Figure 21 Orders versus Pharmacies

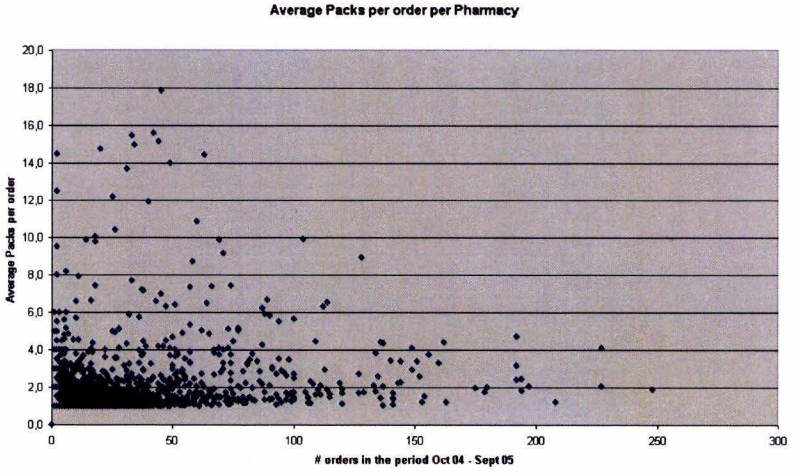


Figure 22 Average Packs per Order for all Pharmacies

The three figures show that a small number of pharmacies are accountable for a great part of orders placed in a year (about 20 pharmacies ordered more than 150 times a year) but it can be seen that the average order size of those pharmacies does not significantly differ from the small pharmacies. In figure 22 it can be noticed that most of the orders contain only 1 or 2 packages and that for only 172 pharmacies the average packages per order is more than 3.

3.4.3 Costs

In appendix 3 the direct distribution costs for products distributed by Fresenius to the German retail pharmacies are given. The quantities, which are used to determine those costs are based on the average figures of the third quarter of 2005.

The stock holding costs are calculated with the formula $\bar{I} \times v \times r$, with '$\bar{I}$' the average inventory in packages, 'v' the variable cost of the item (this is not the selling price) and 'r' Amgen's internal interest rate for investments. It is important to note that, because of the fact that Amgen is the owner of the inventory situated at Fresenius, the total stockholding costs at the ELC and Fresenius is not dependent on the number of shipments carried out from the ELC to Fresenius (only the proportion is changing). Those costs will only change when the production runs (input) and/or the demand of the end customer (output) changes. Appendix 3 presents also the average cost per package to distribute a medicine from the ELC to the retail pharmacies for the third quarter of 2005. Some conclusions can be drawn. Firstly, the average cost of distributing a package to the German retail pharmacies is almost X Euros. It should be noted that this will be different for every other country and even for the same country when you distribute to another group, for example the hospital market. Secondly the transportation cost is the biggest part of the total costs.

3.4.4 Order Process

As mentioned before the orders of the German retail pharmacies are placed at Fresenius who will deliver those goods through the carrier Transoflex. Because of the fact the inventory at Fresenius is consignment stock and is owned by Amgen, Amgen will determine the size and the time of the replenishments. Part of the excel-replenishment order form is presented below for the SKU Aranesp Syringes, 30mg, 4pk.

	1	2	3	4	5	6	7	8		
item	Inventory at 3-okt-05	Current inventory 6-okt-05	Usage over # days 3	Usage over 31 days	Sep LE for Oct	Short (-) on inventory		Replenish advise 2-nov-05	Actual replenish 2-nov-05	Inv. after replenish 6-okt-05
1110-E02 4-pk 30 µg	2328	1662	666	6882	3593	-9722	72	9792	0	1662

Column 1: Stock level at Fresenius begin of the month;
Column 2: Stock level at Fresenius on the check day;
Column 3: Sold packages between the beginning of the month and the check day (column 1 – column 2);
Column 4: Expectation of sold packages this month when columns 3 will be extrapolated (column 3 / 3 days (in this case) * 31 days);
Column 5: The expected sales, the Latest Estimate (LE) value;
Column 6: Expected shortage. The norm for the Safety Stock is 0.5 times the LE (LE * 1.5) + (# days to go till next replenishment * average demand per day of that month) – stock level check day;
Column 7: Number of packages in one box;
Column 8: Advice of the total number of packages for next replenishment (rounded off on full boxes).

In principle there is one replenishment per month and for Fresenius this is always the beginning of each month. The figure on the next page shows schematically the replenishment process.

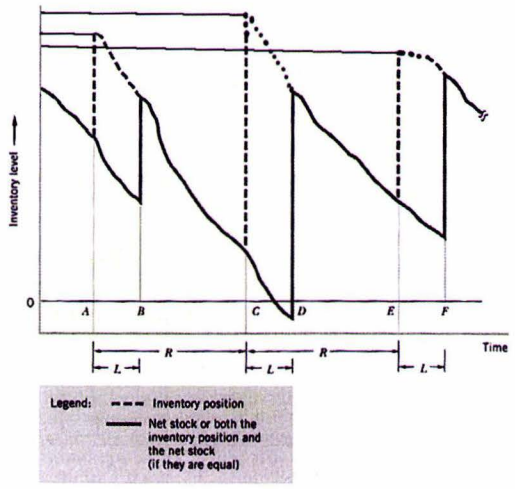


Figure 23 Replenishment Process Fresenius

The control procedure is that every 'R' units of time enough packages are ordered to raise the inventory position to level 'S'. This means every 'R' periods a replenishment will be sent to Fresenius. The replenishments always take place at the beginning of each month and the size of the replenishment depends on the forecast (Latest Estimate) and the demand that will occur during the lead time. Therefore there is not a fixed order-up-to-level 'S' but one which will vary each month (see figure 23). Furthermore 'L' stands for the lead-time which is one day. The department PPIC (Production Planning & Inventory Control) takes care of packaging and labeling the products and determines for each SKU the time between two production runs and the safety stock in time units.

The products Aranesp SureClick & Mimpara are grouped in a specific country group. Therefore those SKUs are not only for the German market but also for the countries the Netherlands, Austria, United Kingdom and Ireland. The syringes are labeled and packed specific for the German market only.

The situation of Amgen can be approached by a (R, $S_{variable}$) policy. Also a (R,s,nQ) policy is suitable where the parameters 'R' is 1 month, 's' the short on inventory and the last parameter, the size of the replenishment, is determined by 'nQ'. The 'Q' is in this case 72 (packs per box) and ensures that it will be rounded up on full boxes.

4 Supply Chain Models for the German Distribution Strategies

4.1 Research in Supply Chain Management

During the last decade a lot of research has been done in Supply Chain Management and in quantitative Supply Chain models. From mathematical programming point of view Linear Programming approaches can be used to optimize the supply chain. However a great drawback is that those approaches are based on deterministic demand that do not take the stochastic of the demand into account.

Silver Pike and Peterson (SPP, 1998) give several quantitative stock control models, which deals with the stochastic for one product in one stock location for policies like (s,Q)[6] and (R,S). However the formulas, described in SPP have a limited validity because the authors made several assumptions about the behavior of the demand process and distribution, order process and the delivery process. Because of changing conditions, in particular smaller order quantities and higher demand variability, the assumptions lose their validity. In the handout of De Kok (2000) the assumptions are removed one after the other, in order to obtain results with a broader validity than those of SPP. As mentioned before, these formulas have the one stock location limitation.

De Kok en Fransoo (2003) did a lot of research in the supply chain planning and in this article they describe another approach namely the Supply Chain Operation Planning or the SCOP. The objective of SCOP is to coordinate the release of materials and resources in the supply network under consideration such that customer service constraints are met at minimal cost. The SCOP function is responsible for the coordination of activities along the supply chain, by making decisions on the quantities and timing of material and resource releases. The SCOP problem thus relates to the integration of the Master Production Schedule (MPS), Rough Cut Capacity Planning (RCCP), Material Requirements Planning (MRP-I), and Capacity Requirements Planning (CRP) functions in the well-known MRP-II framework (Spitter et al, 2005).

In the article, the SCOP is positioned in the hierarchy and after describing the basic notions that enable to define the SCOP problem in the form of generic SCOP constraints the authors are describing two ways of solving the SCOP problem to minimize the supply chain inventory capital:

1) **Mathematical programming models**: using the generic SCOP constraints to derive an LP formulation for the SCOP problem based on deterministic exogenous demand in a rolling schedule approach.

2) **Stochastic models that incorporate random demand**: Pure base stock[7] policies were discussed and in the case of pure assembly systems Rosling (1989) developed an optimal policy. The article of Diks and De Kok (1998) shows an optimal control of a divergent multi-echelon inventory system under the balanced assumption (which assumes that the policy always allocates non-negative stock quantities). But in general supply networks the pure base stock policies is infeasible because the policy generate material orders without checking availability of upstream orders and therefore it violates the material orders constraint. In De Kok and Visschers (1999) a method, the *concept of synchronized base stock policies*, is developed to translate a general assembly network into a set of divergent systems. Through this it will become possible to use the algorithms proposed by Diks and De Kok (1999), which using linear allocation functions in order to determine order-up-to-levels and rationing fractions that satisfy the service level constraints to derive close-to-optimal policies even for large-scale systems. De Kok and Fransoo worked out a numerical example which shows that the SBS concept considerably outperforms the LP-based concept and is closed to the optimal solution. A few years ago a tool SCOE, the Supply Chain Optimizer and Evaluator, was developed which used the SBS method to easily optimize supply chains.

In conclusion the formulas mentioned in SPP (1998) and De Kok (2000) can be used for analyzing one stock locations. This is the case if the ELC distribute to the German retail market directly. For broader networks, so networks with more than one echelon, the SBS concept described by De Kok and Fransoo (2003) with the program SCOE is a suitable tool to analyze and optimize networks. Due to the simple and short distribution network of Amgen the formulas for analyzing one stock location will be described before they will be used to analyze the different distribution strategies.

[6] Continuous review system that ordered a fixed quantity Q whenever the inventory position drops to the reorder point s or lower

[7] Base stock policies or S policy: If x<S, order S-x, otherwise do not order. Here x should be interpreted as the on-hand inventory plus on-order inventory minis back order. The term base stock signifies that the inventory position (on-hand plus on-order stock) is always maintained at the base level of S.

4.2 Formulas for Analysis of One Product/One Location Inventory Models

One of the most common inventory control policy is the order point, order-quantity (s,Q) system. This is a continuous review system that orders a fixed quantity Q whenever the inventory position drops to the reorder point s or lower. The inventory position, and not the net stock, is used to trigger an order because the inventory position takes the on-order stock into account. As said stated the formulas, described in SPP (1998) have a limited validity and in the handout of De Kok (2000) the assumptions are removed in order to obtain results with a broader validity than those of SPP.

The situation of Amgen can be approached over the time by a (R, $S_{variable}$) policy. If you will analyze a specific moment in time the S will be fixed and can be approached by a normal periodic review, order-up-to-level system (R,S). Both SPP and De Kok derived different kinds of formulas and expressions for the performance measurements P_1 and P_2 for a (s,Q) model. As there is a rather remarkable, simple analogy between (R,S) and (s,Q) systems (SPP, 1998) the (R,S) can be approached by a (s,Q) situation if the following transformations are made:

(s,Q)	(R,S)
s (reorder point)	**S** (order-up-to level)
Q (order quantity)	**DR** (demand during the review period)
L (delivery time)	**R+L** (review period + delivery time)

Several input variables are needed for the formulas described in SPP and De Kok. Those input variables are given below and in the next few paragraphs these are discussed in detail and applied to the situation of Amgen.

	Input	Explanation	Paragraph
-	**$E[D_i]$**:	The expected demand per period for end-item *i*	4.2.1
-	**$\sigma(D_i)$**:	The standard deviation demand per period for end-item *i*	4.2.1
-	**P_i** :	The target customer service level for end-item *i*	4.2.2
-	**L_i** :	The planned lead time of orders released for end-item *i*	4.2.3

4.2.1 Expected and Standard Deviation Demand

The demand and the standard deviation of each SKU Aranesp Syringes and Mimpara have to be determined. At this moment the Aranesp SureClick is not taken into account because the official launch was September 2005 and therefore not enough historical data was available. The expectations are that the SureClick will substitute the Aranesp syringes in the future because of the ease of handling and the safety improvements (e.g. the hidden needle). In appendix 4 the demand and SD are determined for the SKU Aranesp syringe 30 and it can be noticed that two groups are generated: the demand of the retail pharmacist and the demand of the rest, grouped as the 'others'. The average demand per week is calculated from the data of the period Oct 04 to Sept 05. As noted before the group others for the Aranesp syringes is only the demand of the German market (except the demand of the retail pharmacies) but for the product Mimpara the demand of the countries the Netherlands, Austria, United Kingdom and Ireland are included. To determine the standard deviation of both groups the rise or decline of the demand in that period is taken into account through regression analysis to get a more accurate figure of the standard deviation. Finally, with those figures, the Variation Coefficient can be calculated with the formula $VC = \sigma / D$. In appendix 4 the results of those calculations of all SKUs are given for both groups.

The VC is being calculated with the view to simulate expected future situations and to investigate the robustness of the several distribution strategies. The future demand can be obtained from the Latest Estimate planning or the Long Range Planning made for every country but unfortunately, it is not possible to determine the standard deviation. To be able to say something meaningful about this we assume that the VC will not change throughout the years and remains the same. The assumption of a constant VC is made after some conversations with Van Woensel and De Kok and is based on the idea that high demand level causes a higher standard deviation than a low demand level.

The VCs for the retail pharmacies, calculated in appendix 4, are between the value 0.10 and 0.20. The VC of the group others are higher but the VC of the product Mimpara are conspicuously high. An explanation for this is that those products have been on the market for a few months and shows a very capricious demand. When the product reaches saturation point, the expectations are that the VC of those two products will decrease. For future simulations this will be taken into account.

The average demand of the third quarter of 2005 will be used to model the current situation to give a more reliable result. After determining the average demand per week the standard deviation can be calculated on basis of the VC.

Finally, to use the data for analysis, these values are converted to days, assuming that the demand per day are mutually independent and identically distributed stochastic variables. Appendix 4 shows the input data of the demand and standard deviation needed to model the current situation with the formulas.

4.2.2 The Target Customer Service level

In SPP (1998) and De Kok (2000) the two most used performance measures are discussed, namely the performance measures P_1 and P_2. The P_1 measure is the probability of *no* stock out just before the arrival of an order or in other words the probability of no stock-out per replenishment cycle. The P_2 measure is the fraction of demand satisfied directly from the shelf, known as the fill rate.

The service level used by Amgen is the probability of *no* stock out just before the arrival of an order. Amgen want to serve every patient anywhere, on time, and with the right product. Therefore the aim of Amgen is to obtain a service level of 100% for their products (this is in contrast with other industries where lower service levels are more accepted).

4.2.3 Planned Lead Time of Orders Released

The L_i stands for planned lead-time of orders released and in case of Amgen this will be the expected distribution lead times between several locations. The last figures in appendix 4 give the time between two production runs of all the Aranesp strengths syringes, the number of deliveries per year of the three SKUs Mimpara (this product is not packed and labeled within Amgen but is outsourced to a company in the UK) and the lead times of transportation between the different locations. These results will be needed in the formulas.

It is important to note that those variables are exogenous and therefore cannot be changed. Changing the values of the production runs may not only influence the stock holding costs but has also an impact on the production costs and the production runs of other SKU for other countries. To take those impacts into account is out of the scope of the project and therefore the assumption of independent production runs is made.

4.3 Description of Model to Minimize the Stock Holding Costs of Germany

After determining the demand and the standard deviation per day for the pharmacies and the group 'others' (see paragraph 4.2.1 and appendix 4), and with the restriction of a certain service level, the minimum safety stock and the average inventory can be calculated for all SKUs. The figure below (figure 24) shows a schematic view of the excel file and the formulas used for the calculations are given in appendix 5.

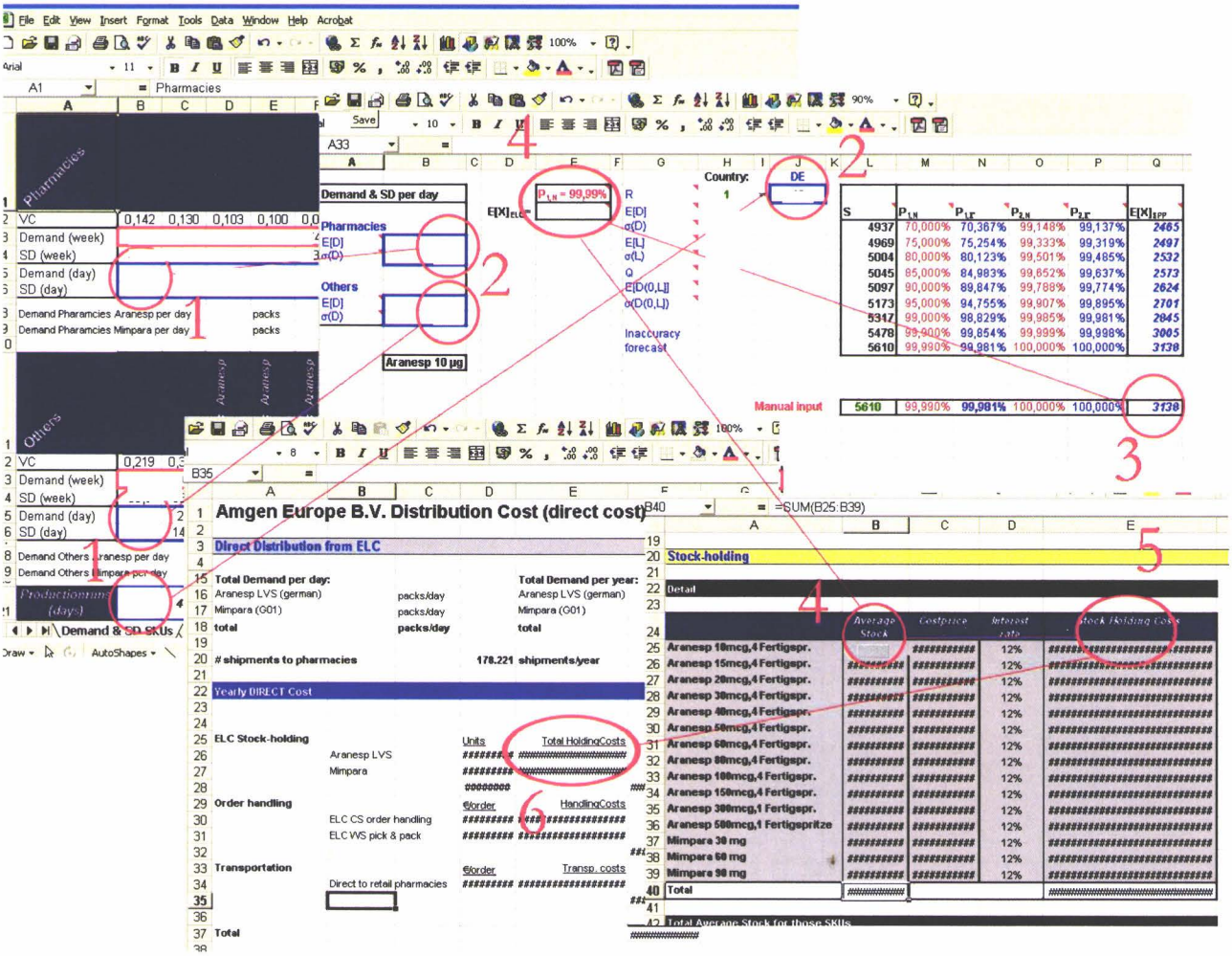


Figure 24 Schematic View of the Excel File to Minimize the Total Stock Holding Costs

In the first worksheet the demand per week for both groups and the time between two production runs have to be filled in and with the variation coefficient, the standard deviation per week will be given. With the assumption that the demand per day are mutually independent and identical distributed stochastic variables, the demand and standard deviation per day will be generated (circles 1 in figure 24). These values are linked to another worksheet (circle 2) and with the formulas, explained in appendix 5, the minimum order-up-to-level and the average stock level will be determined (circle 3). The accuracy of the forecast had to be taken into account because the package and labeling department will plan their production quantity on the basis of the forecast. As there is a difference between the forecast and the actual demand the inaccuracy has to be included in the safety stock. For Germany the forecast accuracy is very high and is in general between the 85 and 90%. This means that it is possible that the actual demand deviates 10 to 15% from the forecast. For this reason the safety stock has to be increased by 15% of the demand during the review period (circle 4). The result appears in the next worksheet and with the formula Īvr the stock holding costs are calculated (circle 5). Finally those results will be linked to the summary worksheet (circle 6) which shows the total costs of the distribution strategy.

5 German Distribution Strategies

The previous chapter has focused on the analysis of the formulas for the one-location inventory control models including the input variables needed to analyze the different distribution strategies. This chapter now continues and presents the different distribution strategies that will be analyzed by those formulas. Those results, together with other quantitative and qualitative measurements will be used to choose the best distribution strategy.

In the pharmaceutical world legal considerations are extremely important because those companies are monitored by the FDA for activities in the US and by the EMEA for activities in Europe. Amgen has to comply with the strict regulations and not every distribution strategy is therefore allowed through the legal boundaries. In Germany it is allowed to distribute directly from the ELC in the Netherlands to German license-holders such as hospitals, pharmacies and wholesalers/distributors. The intension of Amgen is to create a supply chain as short as possible to be as close as possible to the end-customer. Taking this and the legal boundaries into consideration the next four strategies are a possibility for a distribution strategy for Amgen:

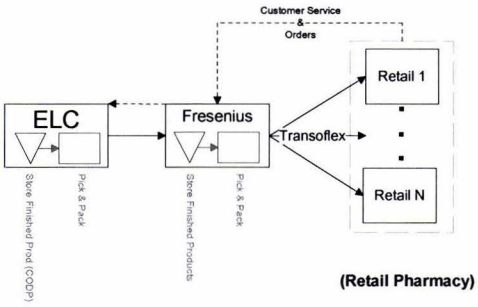
1. **The current situation**: A supply chain with the logistic service provider Fresenius who take care of order handling and who distribute the products to the retail pharmacies.
2. **Direct shipments from the ELC**: A supply chain with no further echelons except the ELC and where the products will be distributed directly from the ELC to the retail pharmacies.
3. **Direct shipments from the ELC with a cross-docking (hub)**: A supply chain with a cross-docking (hub) to distribute the products to the retail pharmacies. The products will be consolidated till the hub and after this hub, somewhere in Germany, the products will be distributed directly to the retail pharmacies.
4. **Direct shipments from the ELC together with the VMI concept**: This is almost the same strategy as 'direct shipments from the ELC'. However in this situation the VMI concept (Vendor-Managed Inventory) is used to hold inventory, controlled by Amgen, at the retail pharmacies to reduce the number of shipments.

Figure 25 How to distribute Germany?

To see if the strategies are feasible the next few paragraphs present for each strategy the direct costs of transportation, stock holding and order handling. After this, the feasible strategies are compared with each other in the chapter 6.

5.1 The Current Situation

A supply chain with the logistic service provider Fresenius who take care of order handling and who distribute the products to the retail pharmacies.



The cost of the current situation has already been calculated in chapter 3 (see paragraph 3.4.3. and appendix 3) based on historical data (the actual number of orders, shipments etc). In this paragraph the average demand of the third quarter of 2005 together with the determined variation coefficient are used to model the current situation again to compare the four strategies as fair as possible. To calculate the direct costs, the subdivisions transportation, order handling and *total* stockholding costs are made. The reason for this decision to calculate the total stockholding costs is that the average stock depends both on the standard deviation (impact on the safety stock) and on the demand (impact on the productionbatch size). Therefore there is not a division rule to allocate fairly a part of the total average stock to the pharmacies.

5.1.1 Direct Distribution Costs

To calculate the average stock of the current situation Amgen's inventory policy is used. Amgen has 0.7 month safety stock at the ELC for the total demand of the product Aranesp syringe distributed to Germany and for the product Mimpara a safety stock of 1 month. However, for the pharmacy part there is an extra safety stock of 0,5 month at Fresenius for both products. For determining the stock on average the general formula is:

$$E[X] = \frac{1}{2}Q + SS$$

is used but because of the shipments from the ELC to Fresenius a correction has to be made of a half shipment. Therefore the next formula is used for calculating the average stock at the ELC:

$$E[X_{ELC}] = \frac{1}{2}\left((D_{Ph+Oth} * \Pr) - \frac{D_{Ph} * 260}{\#Sh_{ELC-FMC}}\right) + SS$$

D_{Ph+Oth} = Total demand per day for this SKU, so add up the demand of the pharmacies and others;
Pr = Time between two productionruns of this SKU;
260 = 260 Working days per year;
$\#Sh_{ELC-FMC}$ = The number of shipments per year from the ELC to Fresenius.

So the average size of one shipment to FMC is 'Demand Pharmacies (days) * 260 days/ # shipments per year ELC-FMC' and therefore the formula

$$E[X_{FMC}] = \frac{1}{2}\left(\frac{D_{Ph} * 260}{\#Sh_{ELC-FMC}}\right) + SS$$

is used to calculate the average consignment stock at Fresenius.

The direct distribution costs for the indirect distribution, using Fresenius as a service logistic provider, are given In appendix 6, together with the detailed calculations.

5.1.2 Optimizing the Total Stock Holding Costs of the Current Situation

To determine a difference between the current average stock according Amgen's policies and an optimal average stock the formulas for 'Analysis of one product / one location inventory control models' will be used, because one big virtual stockpoint is actually generated.

When using the demand and the standard deviation per day for the 'pharmacies' and the group 'others', and with the restriction of a certain target service level, the minimum safety stock and the average inventory can be calculated for all SKUs. The average inventory can be calculated with the formula:

$$E[X] = \frac{1}{2}Q + k_\alpha \sigma \sqrt{L}$$

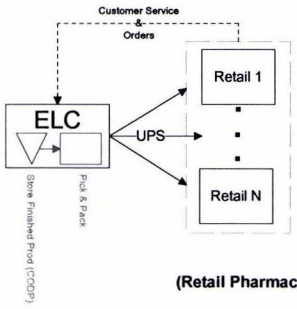
so on average the inventory equals half the production run size plus the safety stock ss, which is $k_\alpha \sigma \sqrt{L}$. This means the ss can be calculated to multiply the standard deviation of the lead time by the safety factor k_α which follows from $P_1 = \alpha = \Phi(k_\alpha)$ (assuming that the demand has a normal distribution). The average inventory derived from on those formulas is given appendix 4.

The aim of Amgen is to obtain a service level of 100% for all their products. It can be seen that for a target customer service level P_1 of 95%, the probability of not being out of stock just before a run from production arrives, the formulas gives almost the same average inventory. However, when a higher service level has to be obtained the average inventory increased.

If the customer service level P_1 is set at 99,99% and if the inaccuracy between the forecast and the actual demand is included in the safety stock, then the result of the minimal average stock needed to achieve the target service level of 99,99% can be found in appendix 4.

5.2 Direct Shipments from the ELC

A supply chain with no further echelons except the ELC and where the products will be distributed directly from the ELC to the retail pharmacies.



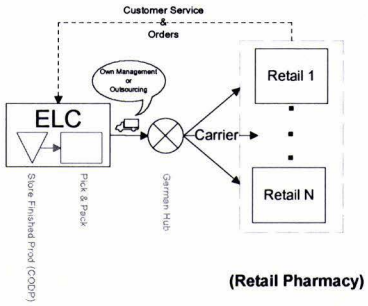
In this distribution strategy the logistic service provider is removed out the supply chain and only one stock location remains. Now Amgen will have to take care of all the order handling and pick & pack activities coming from the German retail pharmacies. When looking at the costs aspect the safety stock determined by Amgen will not be used but the safety stock will now be optimized using the formulas mentioned in paragraph 5.1.2 and calculated in the previous paragraph. The direct costs for direct distribution of the German retail pharmacies are given in are appendix 7 together with the detailed calculations. Some assumptions are made for the time needed for order handling and pick & pack activities are based on several interviews within Amgen and an investigation on how Fresenius dealt with this.

The costs of Insulated Shipping Containers (ISC), which Amgen has to use for the shipments of Aranesp products to the retail pharmacies are added because Fresenius uses their own ISC. For the product Mimpara an ISC is not needed. Some analysis show that none of the placed orders from the pharmacies contained more than one brand or in other words, an order never consists of an unit of Aranesp and an unit of Mimpara. In the analysis on the average packs per order per pharmacy (see figure 18) the conclusion could be drawn that only 178 of the 18.000 pharmacies ordered on average more then 3 packages per order and that almost all other orders contain only one or two packages (the average packs per order ratio is 1,45). Amgen uses different types of ISCs of different sizes. The smallest ISCs are the M11 and the M12. The M11 is suitable for maximal 2 packs of Aranesp 1pk and in a M12 8 packages of Aranesp 4pk can be distributed and therefore the M11 and the M12 can be used for almost all orders received from the pharmacies.

As mentioned before, Fresenius uses their own ISC and reused them. Therefore the boxes have to be returned to Fresenius which imply a cost of € 1,99 per shipment. However if direct distribution is chosen, the ELC has to use his own ISCs and those shipping containers are used once only. Due to strict environment regulations it is now obligatory to either take back the shipping containers and the icepacks delivered to the German retail pharmacies or pay a fixed amount of money per shipment for recycling costs. Unfortunately at this moment it is unknown what the return costs or the recycle costs will be and this has to be further investigated.

UPS is chosen to transport the medicines directly to the retail pharmacies because they have one of the widest networks in Germany (Amgen uses UPS for more than 80% of the total shipments to the German market). As a rule, the medicines have to be delivered before 12 noon. This is not verified yet because it was not possible to involve the retail pharmacies and Amgen Germany but because 'the competitors are doing it' this will be a necessity. UPS is offering an Express Service which means a next morning delivery across Germany (so between 10:30 and 12 noon) and because of the good price agreement between Amgen and UPS (discount of more than 70%) the preference is given to UPS for this strategy. Furthermore it has to be noticed that the price depends on the package's dimensional weight and not on the actual weight because of the large size-to-weight ratio of the ISCs.

5.3 Direct Shipments from the ELC with a Cross-Docking (hub)



A supply chain with a cross-docking (hub) to distribute the products to the retail pharmacies. So the products will be consolidated till the hub and after this hub, somewhere in Germany, the products will be distributed directly to the retail pharmacies.

A supply chain using a cross-docking (hub) to distribute the products to the retail pharmacies shows a lot of similarities with the strategy 'direct distribution'. Like the previous strategy, the ELC has to deal with all order handling and pick & pack activities coming from the retail pharmacies and also the total stock holding costs will remain the same. Actually the only difference is the way of transporting the medicines to the customers. In the strategy, described in the previous paragraph, Amgen outsourced completely the control of product transportation to the end customer to one carrier who pick up the medicines at the ELC and deliver this the next morning to the retail pharmacists (probably this carrier uses internally a cross docking structure to distribute the products but this is their own choice and outside the control/scope of Amgen). To influence the transportation costs a hub somewhere in Germany can be used. To send a package from the ELC to the retail pharmacies costs approximately 11 Euros, but from Fresenius in Germany it is 6,50 euro. If Amgen manage the transportation from the ELC to this hub, so consolidating the products first to a cross-dock center(s), the products can be distributed from this point further to every retail pharmacy in Germany. Sometimes cost advantages can be obtained but this depends on many factors (# shipments per day, (price)agreements, the carrier etc.). Instead of using one large globally active carrier, a domestic specialist can now be chosen. Of vital importance are a fast consolidated line to regional cross-dock center(s), a fast cross-docking at the cross-dock center(s) and a fast domestic distribution by a global or domestic distribution specialist.

A small research on the Internet for potential transport partners resulted in the following but incomplete small list of potential partners:

- UPS

  It is possible to drop off packages on certain locations in Germany provided by UPS. Where and if this brings some costs advantages has to be further investigated.

- Transoflex (also the partner of Fresenius)

  Trans-o-flex wants to meet the customers growing and complex requirements with individual logistic solutions for individual requirements (one solution is that they are now able to deliver medical products at temperatures of between 2 and 8 °C from the pick-up and turnover, to the delivery to the recipient). Furthermore their vision is 'You tell us what you need. We do it'. Last year a customer survey of Transoflex carried out periodically at Expopharm, Europe's largest pharmaceutical trade fair, shows that pharmacists who frequently receive goods from Trans-o-flex were very happy with the provided services.

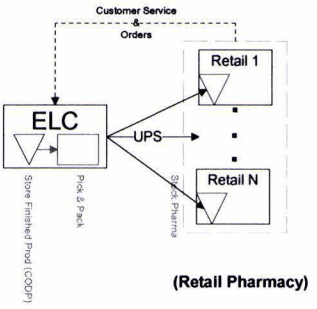
- Birkart Globistics

  Birkart Globistics offers logistics services for almost every requirement. They have several business units for economies of scales, enabling to save time and money. Besides a road cargo business unit they have a special Birkart Pharmalogistics business unit. From acceptance of orders to well-organized stock-keeping they also offer distribution within 24-hour service.

Due to the good price agreement with UPS to transport a product from the ELC directly to Germany it will depend greatly, after a lot of negotiations which cannot be done now in this phase, on the sort of agreement with those (domestic) carriers if some costs advantages can be obtained to make this strategy profitable for Amgen.

Due to the great similarities with the previous strategy it is actually a variant of direct distribution and therefore this option will not be worked out further in detail. More detailed analysis should be carried out in order to determine the best option of transportation and choosing the best carrier partner.

5.4 Direct Shipments from the ELC Together with the VMI Concept



Direct shipments from the ELC to the retail pharmacies and using the VMI concept (Vendor-Managed Inventory) which means that inventory, controlled by Amgen, will be held at the retail pharmacies to reduce the number of shipments.

Again this strategy has a lot of similarities with the strategy 'direct shipments from the ELC'. However in this situation the VMI concept is used to hold inventory at the retail pharmacies to reduce the number of shipments.

VMI is a coordination mechanism in which a supplier manages the inventory on its customer's shelf, deciding when and how much to reorder. In the article of Campbell et al. (2004) several advantages of VMI over conventional inventory management are mentioned. Firstly, VMI can give the suppliers a much clearer picture of the customer's future needs, enabling to plan ahead and manage their own resources better. A more uniform utilization of production resources can lead to a reduction of production and inventory holding costs. Secondly, suppliers can often obtain a more uniform utilization of transportation resources. Less number of transportation is needed and efficient routes by coordinating the replenishment at customers close to each other are possible. But one of the most important advantage of VMI is that both parties must forge a partnership where both sides benefit from the relationship in order to make VMI successfully. From the Demand Chain point of view VMI is a big step forward to get closer to the customers and it helps to retain customers on a long-term basis which give competitive advances.

Using Vendor Managed Inventory in the situation of Amgen, inventory will be held at the retail pharmacies and with electronic data interchange, for example using RFID, Amgen are aware of what is on the retailer's shelf. On the basis of this information Amgen takes responsibility for replenishment of the customer's inventory. No orders are received (so the costs of order handling may decrease), but instead Amgen have to make an indication of the upper and lower limits of stock and it is the responsibility of Amgen to maintain the customer's inventory within the specified stock bands. However, in the pharmacy world, the retail pharmacies demand a shelf life of the supplied medicines of at least one year so infinite amount of medicines at the retail pharmacies is not possible. The advantage of this strategy is to keep inventory at the retail pharmacies to reduce the number of shipments and the related transportation costs. For this reason VMI is only profitable for pharmacists who orders many times per year. If a pharmacy is only asking a certain SKU a few times a year the reduction of transportation costs will be minimal and does not weigh up to the increase in costs of implementing and using the VMI concept. In addition the smaller pharmacies are probably not interested in keeping those products on stock and from the restriction of the shelf life point of view it will also not be feasible.

Amgen (2005) made a business case for dispensing machines in hospitals. For the products Aranesp a cold supply chain is needed and to implement VMI a fridge will be needed at the pharmacies. The dispensing machine concept focused on benefits, costs and risks and a framework was defined on 6 key aspects (commercial, legal, financial, logistics, managerial, technical). Using this concept, Amgen owns inventory held at hospital and the ownership is changed at the moment of dispensing products from the machine.

Three types of dispensers have been investigated in this business case, namely high-tech, medium-tech and low-tech machines. The results show that a high-tech machine was too expensive and did not cover the requirements well enough and a low-tech machine was too complicated to adapt. The best option was the medium-tech. They concluded that a medium-tech solution is best supported by RFID (however there is no FDA/EMEA statement yet that RFID will have no impact on biologicals but within studies which have been started, preliminary data shows no impact on the biologicals. If RFID will not be possible a barcode can be used).

The cost of a medium-tech dispenser machine is 13.5K per machine (for hardware and locking of fridge). This is only the investment cost and the additional transportation costs, additional local inventory costs, tag costs and production costs (tagging) are not included.

The VMI concept is certainly not profitable for the complete retail market

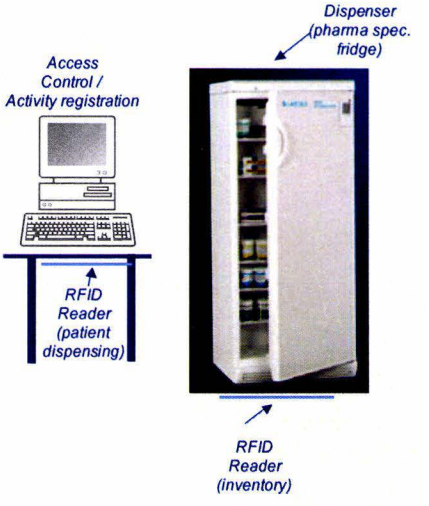


Figure 26 Medium -tech Dispenser Machine

because more than 10.000 pharmacies did not order more than 10 packages per year in total. VMI will only be profitable for large retail pharmacies ordering a certain amount of packages per year. The last bar of figure 18 shows that 1000 of the 18.000 pharmacies ordered more than twice a month and figure 22 shows that about 80 pharmacies ordered more than 100 times a year.

Next a rough break-even calculation is given to investigate the profitability of using VMI for some of the pharmacies. The most important saving costs when using VMI in the situation of direct distribution are the transportation costs. The transportation cost of one order to distribute the product directly from the ELC to the pharmacies is approximately 11 euros (this means a decrease of one order is a saving of 11 euros):

Rough break-even calculation

Savings	=	Investment
$X_{\#orders} \times 11$ euro	=	13.500 euro*
$X_{\#orders}$	=	1227 orders

**) Note this is only the investment cost of a dispenser machine and other costs are not included*

The break-even analysis shows that after saving 1.227 orders/shipments only the investment cost of the machine is recovered. For the largest retail pharmacy this means an earn back time of more than 6 years for only the machine. However the total costs to use the VMI concept are much larger so the conclusion can be drawn that VMI will not be feasible and profitable for the German retail market.

When VMI is applied in the situation of indirect shipments, that is with Fresenius as logistic service provider, the arguments will be slightly different. The costs Fresenius charged ELC depends on the total number of shipments/orders to/of the German retail pharmacies. For each order, Fresenius charge ELC 5 euro for handling and warehousing costs and approximately 6 euros to transport the medicines to the retail pharmacies. If VMI will be implemented for only the biggest pharmacies, controlled by Amgen, and the other pharmacies are still distributed by Fresenius, a decrease of 1 order results in a saving of 11 euros for Amgen. This confirms the previous conclusion that implementing VMI for only the biggest pharmacies is indeed not feasible and profitable for the current situation. Furthermore implementing VMI for the 80 largest pharmacies of a total of 18.000 will not make sense either.

6. Summary of the German Retail Distribution

From the four initial distribution strategies described in the previous chapters, two strategies are finally feasible: 'indirect shipment with a local service provider' and 'direct shipments from the ELC'. The strategy cross-docking or hub is actually a structure and a solution of the strategy 'direct shipment' and the VMI concept is not profitable at all for the German retail market, due to the small and few orders of a single pharmacy. In this chapter the two strategies will be compared with each other.

6.1 Indirect versus Direct Distribution

The figure below shows a summary of the direct costs, calculated in the previous chapter, and the impact on several qualitative measurements. Due to confidential information the costs figures are given in appendices 6 and 7 and figure 27 depicts only a green and a red mark to indicate the lowest and highest value respectively. The explanations why a measurement is positive or negative are given below.

Figure 27 Indirect versus Direct Distribution

[1] As said before Fresenius uses their own ISC and reused them. Therefore the boxes have to be returned to Fresenius which impose a cost of € 1,99 per shipment. However if direct distribution is chosen the ELC has to use his own ISCs and those shipping containers are used once only. Due to strict environment regulations it is now obligatory to take back the shipping containers and the icepacks delivered to the German retail pharmacies or pay a fixed amount of money per shipment for recycling costs. Unfortunately at this moment it is unknown what the return costs or the recycle costs will be and this has to be further investigated.

Qualitative Measurements

- **Space Cold Store**:
When changing from indirect to direct shipments inventory will no longer be held at Fresenius. Therefore the stock located at Fresenius first has to be relocated to the ELC which will increase the average inventory size. In the case of indirect distribution on average X packs were located at the ELC and X thousand packs were situated at Fresenius. In contrast what might be expected, and already explained in paragraph 5.1.2, the average stock in the direct situation will not be increased by X thousand packs but by only X packs due to optimization. The difference of X packs can be explained because of the of the dead safety stock located at Fresenius. Therefore for the direct strategy X extra packs (X pallets), will need to be stored in the cold store. At this moment the utilization grade of the cold store is approximately X percent and therefore keeping X extra pallets on stock in the cold store will not be problematic. For these reason both strategies are marked green.

- Space Warehouse (ISC):
All components which do not have to be cooled, such as cartons, leaflets, parts of the SureClick devices, insulated shipping containers etc., are stored in the ambient warehouse. The free space in the warehouse is limited and with the many new product introductions, especially the launch of the US SureClick mid 2006, the space in the warehouse will become more and more of an issue. For the direct distribution, Amgen needs a lot of extra M11 and M12 ISCs to transport the medicines to the German retail pharmacies directly. To store all those ISCs much extra space in the warehouse is required because it is not possible to fold the boxes. Amgen received three replenishments every two weeks from the ISC supplier but in 2006 this will be four times every three weeks. An increase of 178 thousand direct shipments to the retail pharmacies means an extra of approximately X shipping containers per ISC replenishment. At this moment no extra ISCs can be stored without changing the fixed stock policy. However Amgen is renting depot space of 'van Egeraat', the cooled transport carrier of Amgen, to store ISCs if necessary. Due to the tight space in Amgen's warehouse and because it will not be possible to store X extra ISCs without occurring cost the direct distribution strategy is marked red.

- **Space Pick & Pack**:
At this moment almost X shipments are handled by Amgen each month which requires the pick & pack department to work in two shifts. The end time of the shift is fixed at 7 pm because this is the pick up time of the carriers. Utilization grade of the pick and pack department is hard to give due to the capricious progress of order entry from each country. For the direct distribution of the German pharmacists almost X extra shipments per month have to be handled (almost tripled) which cannot be handled by the current resources. The space available for pick and pack is insufficient and therefore the direct distribution strategy is marked red.

- **Closeness End-Customer**:
In case of direct shipments Fresenius will be eliminated and a supply chain with no further echelons will be created where the products will be distributed directly from the ELC to the German retail pharmacies. As Fresenius will be eliminated from the chain with the direct distribution strategy, Amgen will be closer to the customers. Therefore the strategy with the logistic service provider Fresenius is marked red and the direct distribution strategy is marked green.

- **Risk**:
Amgen is focusing more on the risk aspects within their own company to prevent any situation in which Amgen is unable to deliver the patients on time. Situations where a type of process is only available on one location (for example Amgen Puerto Rico is at this moment the only Fill & Finish site of Amgen) or specific stock is located at only one single stock location will especially cause extra risk. When eliminating Fresenius all the stock for the German market will have to move to one single location, the ELC (risk). For this reason the direct distribution strategy is marked red.

- **# Take over Points**:
For most of the products (except Mimpara) a cold supply chain is necessary, which means that the products have to be cooled at all times. Too many stock points can cause cold chain exposure risks on quality. So a decrease of the number of stockpoints results in a lower quality risk. For this reason the strategy with Fresenius is marked red and the direct distribution strategy is marked green.

- Amgen Supply Chain Control:
A decrease of the number of partners / players in the supply chain of Amgen results in an increase of supply chain control of Amgen. Therefore the strategy with Fresenius, even if this is a logistic service provider, is marked red and the direct strategy is marked green.

6.2 Results Part I

The current strategy with the logistic service provider Fresenius is the cheapest option and 4 out of 7 qualitative measurements are positive. At this moment there are no reasons to question Fresenius and their performance. No critical problems have aroused and Fresenius and the carrier Transoflex are offering good services and customer service levels to the German retail pharmacies. The servicelevel of deliveries of Transoflex within 24 hours has been 99,55% over the last 8 month (this figure is only based on complaints and not on actual lead times of all the shipments).

The main advantage of the direct distribution strategy is to become closer to the customers and therefore greater supply chain control and flexibility can be achieved. Nevertheless this strategy is hard to realize for this market. The costs are higher and the limited space available in the warehouse and pick & pack department may be a problem. Still there are some possibilities to lower the transportation costs:

- **Using the 'Express Saver Service' from UPS**
  In addition to the 'Express Service', UPS is also offering an 'Express Saver Service'. Instead of next morning delivery across Germany (so between 10:30 and 12 noon) the package will be delivered the next day. This service is one euro cheaper per shipment and will result in a yearly saving of almost 200 thousand euro.

- **Reusing the ISCs (like Fresenius)**
  Due to strict environment regulations it is now obligatory to take back the shipping containers and the icepacks delivered to the German retail pharmacies or pay a fixed amount of money per shipment for recycling costs. If, after weighing those costs against each other, taking back the shipping containers will be the cheapest solution, reusing the ISC than may result in some costs advantages. However Amgen's current ISCs cannot be used because those ISCs are not approved to be used more than once. To weigh the return costs and the costs of reusable ISCs against the recycle costs and disposable ISCs, further investigation is needed before any recommendations can be made.

- **Using a hub structure to transport the pharmacies directly**
  Through using a hub structure the total transportation costs may decrease, but this depends on many more factors which have to be further investigated.

The problem of the warehouse can be solved to store the ISCs in the depot of 'van Egeraat'. However the shortage of space in the pick and pack department is a bigger problem. This cannot be solved easily and realistically the only way to cope with this problem, which involves considerable costs, is to expand the building to increase the capacity of the pick and pack department.

To say anything meaningful about the impact of the future on the two different distribution strategies, the forecast for each month till September 2007 for the three products distributed to Fresenius is given in appendix 7. The strategies, described in previous chapters, were analyzed with a total volume per month, so the demand of the German pharmacies plus the group 'others', of X packages Aranesp LVS and almost X packs Mimpara. Appendix 7 shows a slight increase of those two products over the next two years and the Aranesp PFP will grow to a volume of X per month. Therefore the conclusion can be drawn that the packs per order will not change significantly and the gap between the costs of both strategies will only become larger. So despite the decrease of the distance between Amgen and their customers, the increase of the supply chain control & flexibility and the decrease of the number of take over point, the advantages will simply not weigh up against the disadvantages of direct distribution.

Finally, It should be noted that extra information is needed to make a well-considered decision because during this part I some assumptions have been made. For example, Fresenius is also doing some promotional activities. What is the impact of this activity on the sales and what is the share of voice of Fresenius? What are the real requirements of the German retail pharmacists? Are they accepting a delivery after noon? And what are the trends of the German retail pharmacies? Part I was more like a desk study to investigate the feasibility of several distribution strategies and was not intended to involve the outside world immediately. Therefore it was not necessary to involve Amgen Germany and the German pharmacies and as a result the strategies have been worked based on current customer requirements and the information available within the ELC.

PART II

Analysis and Optimization of the European Distribution

The development of a model, with variable input parameters, that optimizes the transport and facility costs for a one centralized, European distribution structure and discusses the possibility of cross-border land services

7 Analysis of the European Distribution

7.1 Introduction

The ELC is the European Logistic Center for Europe, North-Africa and the Middle-East. In the first few years Amgen ELC was only serving the 15 major European countries (the west-European countries including Scandinavia) with a population of 380 million people. In 2004 they started to distribute their products to eight new East-European countries including Czech Republic, Hungary, Turkey, Poland and Slovenia, the so-called ECC countries. As a result of the expansion the potential customers grew with 73 million people to 453 million (a growth of 16 percent). In 2005 the ELC was serving 27 countries in total and the prognosis is that this number will only grow in the future. Nowadays every country in Europe has its own distribution channel and even within a country there are several flows possible. To deal with all the events and changes described in paragraph 2.2, which cause a tremendous change and larger competition pressure, the question arose: optimizes the transport and facility costs for a one centralized, European distribution structure and discusses the possibility of cross-border land services.

In the next paragraph an overview and an analysis of different distribution and facility location models, available in the literature, are described.

7.2 Literature

7.2.1 Overview

In the field of facilities location and customers allocation, model formulations and solution algorithms vary widely in terms of fundamental assumptions, mathematical complexity and computational performance. The study of location theory formally began in 1909 when Alfred Weber considered how to position a single warehouse to minimize the total distance between it and several customers (Mirchandani and Francis, 1991; Owen and Daskin, 1998; Klose and Drexl, 2005). In the beginning of the sixties location theory renewed interest. This was done through some publications about more general problems of locating one or more facilities on a network and to minimize the total distance between the customers and their closest facility or to minimize the maximum distance. During the last decades a lot of research is done in location-allocation techniques which resulted in various model formulations which range in complexity from simple linear, single-stage, single-product, uncapacitated, deterministic models to stochastic models. Roughly there are 3 main subclasses in facility location (Daskin, 1995; Klose and Drexl, 2005):

- **Continuous location models (models in the plane)**

The objective is to minimize the sum of distances between the facilities and a set of given demand points. Continuous location models are characterized through two essential attributes: (a) The solution space is continuous which mean that it is feasible to locate facilities on every point in the plane and (b) Distance is measured with a suitable metric (for example the Manhattan (right-angle) distance metric or the Euclidean (straight-line) distance metric).

- **Network location models**

  The key difference between continuous models and network location models is that in the latter the demands and travels between demand sites and facilities are assumed to occur only on a network or graph composed of nodes and links. In network location models, distances are computed as shortest paths in a graph. Nodes represent demand points and potential facility sites correspond to a subset of the nodes. The article of Hakimi (1964) has shown according Owen and Daskin (1998) and Klose and Drexl (2005) that it is sufficient to restrict the set of potential sites to the set of nodes in the case of concave distance functions (concave means that no line segment lies above the graph at any point so this includes also linear functions). The proof of this theorem is also given in Daskin (1995). Therefore the simplified formulation includes only nodes as potential facility sites and yet does not penalize the objective function value. Several types of network location problems are:

  - *The P-median problem* (introduced by Hakimi (1964)): Measure of effectiveness, find the location of P facilities and minimize the total demand-weighted travel distance between demands and facilities.
  - *Covering problem*: The objective is to minimize the cost of facility location such that a specified level of coverage is obtained. Covering problems are mainly divided into two major segments: situations where coverage is required (location set covering problem) and in which it is optimized (maximal covering problem).
  - *P-center*: Locate a given number of facilities in such a way that minimizes coverage distance and with the restriction to cover all demands (so to minimize the maximum distance between any demand and its nearest facility).

- **Mixed Integer programming**

Starting with a given set of potential facility sites many location problems can be modeled as mixed-integer programming models. However network location models differ only from mixed-integer programming models

because network location models explicitly take the structure of the set of potential facilities and the distance metric into account while mixed-integer programming models just use input parameters which is collected. Those problems can be varied from simple to more complex mixed-integer problems when more level of detail will be added. Therefore several classification exist of discrete facility location models (Aikens, 1985; Daskin, 1995; Klose and Drexl, 2005):

- Single- vs. multistage models,
- Uncapacitated vs. capacitated models,
- Multiple- vs. single-sourcing,
- Single- vs. multi-product models,
- Static vs. dynamic models,
- Deterministic vs. probabilistic models,
- Models without and with routing options included.

As said before one important way to measure the effectiveness of a facility location is by determining the average distance traveled by those who visit it: the P-median problems. So the focus is on minimizing only the travel distance or time for operating costs *once* a facility is located. A close relative to the P-median problem is the set of 'fixed charge facility location problems' that includes problems which have a fixed charge to locate each potential facility site and the costs to run the warehouse. One model in this set is the 'Uncapacitated fixed charge Facility Location problem' (UFL problem, but the abbreviation SUFL (Simple Uncapacitated Facility Location model) is found in the literature too). The UFLP is formulated by adding a fixed cost to the P-median objective function and removing the constraint that dictates the number of facilities to be located. This result in a problem that determines endogenously the number of facilities to locate and sites them so to minimize the *total costs* (so travel, construction and running costs).

Through facility location several questions should be answered:

- How should demand be allocated to the facilities?
- Is it allowed to split the demand of a single point between several facilities?
- How many facilities should be sited?
- Where should each facility be located?
- Which customers will be served by which facility (which result in the size and a certain capacity for each allocated facility)

The most simple model is the uncapacitated, single-stage model (or UFLP, Uncapacitated Facility Location Problem). As mentioned in the previous paragraph, this model considers the trade-off between fixed operating and variable delivery costs. The formulation of this problem mathematically is

Minimize $$\sum_{i\in I}\sum_{j\in J} c_{ij}x_{ij} + \sum_{i\in I} f_i z_i$$

Subject to

$$\sum_{i\in I} x_{ij} = 1, \qquad \forall j \in J \qquad (1)$$

$$x_{ij} - z_i \le 0 \qquad \forall i \in I,\ j \in J \qquad (2)$$

$$x_{ij} \in \{0,1\} \qquad (3a)$$

or

$$x_{ij} \in [0,1] \qquad (3b)$$

$$z_i \in \{0,1\} \qquad (4)$$

where

x_{ij} = The proportion of customer j's demand satisfied by facility i
z_i = 1 if facility i is established, 0 otherwise
c_{ij} = The total production and distribution costs for supplying all of customer j's demand from facility i
f_i = Fixed costs of establishing facility i
I, J = The sets of candidate facility sites I and the set of customers J respectively

The UFL problem is to open a subset of facilities in order to minimize the total costs (transportation costs and fixed costs of the facilities). Constraint set 1 requires that all demand will be satisfied and constraint 2 insures that customers are only served from open facilities. Furthermore constraint 3a or 3b can be chosen. Constraint 3a ensures that a customer can only be supplied by only one facility and when constraint 3b is chosen a customer can be supplied by several facilities. Finally constraint set 4 insures that the z value is binary, so a facility is or open or closed.

7.2.2 Solution Methods

Linear Programming (LP) problems can be solved extremely efficiently with methods and techniques available today (Hillier and Lieberman, 2001). A LP problem with a bounded feasible region guarantee that a corner-point feasible solution exists that is optimal for the overall problem. This guarantee is the key to the efficiency of the well-known simplex method. However the UFL and the Single-Source Facility Location (SSFL) problems (is a special case of the capacitated facility location problem in which each customer can only be supplied from one facility) are generally more difficult to solve because some or all decision variables are integers or binary. Therefore for IP problems (Integer Problems) and BIP problems (binary variables, so only 0-1 variables) the ease of solving will decrease enormously because the guarantee that a corner-point feasible solution exists that is optimal for the overall problem does not exist anymore. You might think that a pure IP or BIP problem with a bounded feasible region has just a finite number of feasible solutions and therefore may seem to be solved relatively easily, but those finite numbers can be astronomically large. For BIP problems with n-variables, there are only two choices for each decision variable: 1 or yes and 0 or no. Therefore for a BIP problem with n-variables there are 2^n solutions to be considered ($2^n = \sum_{k=0}^{N} \binom{N}{k}$, with k the number of warehouses (Daskin, 1995)). Thus each time n is increased by 1, the number of solutions is doubled (called an exponential growth). So facility location problems requires exponential computation time $O(2^N)$ but when the number of facilities k will be fixed the problem reduces to $\binom{N}{k}$ possibilities (Owen and Daskin, 1998; Daskin, 1995) and will become solvable in polynomial time (this number is $O(N^k)$ for $P << N$). Nevertheless this still requires high computation time for reasonable values of N and P. Such complexity issues have led to the development of sophisticated algorithms for solving this problem.

The solution methods to solve facility problems fall roughly into two broad classes, namely:

1. **Approximations based on exact methods**
2. **Heuristics**

The last five decades many researchers have worked both on exact algorithms and heuristic solutions problems. In the sixties and seventies especially for the simple problems, and the last decade solution methods for the more complex and dynamic problems with a high level of detail, were developed. The problems UFLP and the capacitated CFLP problems (which have an extra capacity restriction for each warehouse) can be solved by exact algorithms and Branch and Bound methods but in some situations the exact methods may not be computationally feasible (especially large scale problems). In such cases heuristics provide most of the time acceptable trade-off between computing effort and solution quality. In the next two paragraphs an overview of the exact methods to solve UFLP (and CFPL) will be given as the most important heuristics to solve easily and fast small problems or to solve large complex problems.

7.2.2.1 Exact Methods

Linear programming problems can be solved extremely efficiently with certain methods and techniques (Hillier and Lieberman, 2001) but for UFL and CPL problems it concerns most of the time integer or mixed integer problems, which are much harder to solve. An exact solution for UFLP can be obtained by using an enumeration tree. In a *total enumeration tree* all possible solutions in a combinatorial problem will be systematically generated, but as the number of locations gets larger, the total number of alternatives grows exponentially and making total enumeration computationally infeasible even for the fastest computers. When the UFL problem will be relaxed (means that the integers constraints are relaxed/deleted) and the solution meets the constraints of the problem, the UFL problem is solved, otherwise a lower bound is obtained. In order to find the optimal solution, without exhaustively searching the entire tree branch-and-bound approaches (means a repeated solution of continuous problems) are developed which only need to examine a small fraction of the feasible solutions through a special enumeration procedure. The basic concept underlying the branch and bound technique is dividing the original large problem into smaller subproblems (branching) to be able to set a bound (how good the best solution in the subset can be, at a particular node when the subproblem is relaxed) to determine if the subset will be discarded. This will be done when the bound indicates that it cannot contain an optimal solution of the original problem. Two such relaxations are (1) linear programming relaxations and (2) Lagrangian relaxations (Sridharan, 1997; Hillier and Lieberman, 2001).

Linear programming relaxation

For solving BIP problems an LP relaxation means that the integers constraints are relaxed to reduce the problem to a 'normal' LP problem. Hereafter the original problem is divided into two subproblems fixing the value of one of the variable at open or closed. (so a warehouse will be selected from the set of free warehouses constrained closed and open respectively at the node from which further branching is done). The best of the relaxed solutions of the two subproblems will be chosen and the other subproblem will be dismissed together with all the sub-subproblems after this node (Khumawala, 1972; Hillier and Lieberman, 2001).

Rather than arbitrary selecting the warehouse to be constrained at each node judicious selections can be used in the hope to reduce the size of the branch & bound. Khumawala (1972) proposed four criteria of branch selection (Aikens, 1985) and each involving a pair of rules:

1. Largest and Smallest Delta rules;
2. Largest and Smallest Omega rules;
3. Largest and Smallest Z rules;
4. Largest and Smallest Demand rules.

For more details concerning how to operate these rules see Khumawala (1972) and Aikens (1985).

One important discovery of linear programming was the concept of duality. This discovery revealed that every linear programming problem has associated with another linear programming problem called the Dual. The dual problem is important for a number of reasons but the two most important ones are that in many cases it is easier to solve the dual problem than to solve the primal problem and secondly, the dual variables give information about how the object function will change as a result of small changes in the constraint values (Daskin, 1995; Hillier and Lieberman, 2001).

Erlenkotter (1978) embroidered this idea and developed the dual-based approach method to solve UFL problems (Aikens, 1985; Sridharan, 1995). Instead of solving the UFLP directly Erlenkotter solved a dual in which the dual of UFLP is reduced to a form involving only multipliers corresponding to constraint 1. The dual ascent procedure starts with some initial dual and hereafter the multipliers have to be adjusted incrementally in such way that complementary slackness violations are reduced. The algorithm stops when no further adjustment can be made without violating one or more of the dual constraints through increasing of the dual variables. A numerical example is worked out in Daskin (1995) and a more formal treatment of the dual-based algorithm is given in Cornuejols et al. (1990).

Lagrangian relaxation

Another form of relaxation is the Lagrangian relaxation. In a Lagrangian relaxation the first step is to relax one constraint by multiplying the constraints by Lagrange multipliers and bringing the constraint into the object function. Hereafter three main tasks are needed (Daskin, 1995, Sridharan, 1995; Christofides and Beasley, 1983):

(1) Solve the relaxed problem easily for fixed values of the Lagrange multipliers. With these Lagrange multipliers the Lagrangian objective function provide a lower bound on the objective function.
(2) Find primal feasible solutions from the relaxed solution. This because the results from solving the sub problems (so the relaxed problems) are not likely to be feasible for the original problems. In particular, it is likely that some demand nodes will not be assigned to any facility and others will be assigned by two or more facilities. A primal feasible solution can be construct by simple locating facilities at the nodes for which $z_i=1$ and assigning demands to the nearest facility. The primal objective function evaluated with this set of location and demand allocations will provide an upper bound in this iteration
(3) Find improve Lagrange multipliers through using for example the subgradient optimization method.

The Lagrangian procedure converges after a number of iterations and decrease the gap between the lower and the upper bound after every iteration. The smallest value between the lower and upper bound over all Lagrangian iterations is the best solution to use (a numerical example using the Lagrangian algorithm is worked out in Daskin (1995)). For UFLP there are two Lagrangian relaxation possible: relaxing the demand constraint (constraint set 1) or relaxing the constraint that insures customer are served only from open facilities (constraint set 2). For CPLP another relaxation is also possible namely relaxing the capacity constraints and include this in the objective function.

7.2.2.2 Heuristics

The heuristics can be subdivided into two groups: *construction* algorithms and *improvement* algorithms. A construction algorithm attempt to build a good solution from scratch and an improvement algorithm tries to improve an initial solution again and again till no more improvements will be achieved.

There are two improvement heuristics that can be used for solving UFLP problems, namely the *neighborhood search* heuristic and the *exchange* heuristic (e.g. the exchange heuristic begin with any set of facility sites and then search the best possible substitution before making any exchange (Daskin, 1995)). Those heuristics are used to solve efficiently P-median problems but for 'fixed charge facility location problems' those improvement algorithms will be less effective. The reason for this is that the improvement heuristic take an initial solution and therefore also the number of facilities as given. If the number of facilities is sub-optimal it is possible to stuck in a local optimum (in the P-medium this could not happen because the number of facilities to locate was an input to the problem and not an output, this in contrast with UFL problems).

For UFLP problems better results can be can be obtained through using *construction* algorithms. One of the earliest approaches (Aikens, 1985; Jacobsen, 1982; Sridharan, 1995) to solve UFLP problems is the heuristic developed by

Kuehn and Hamburger (1963). This approach consists of two parts: (1) the main program, which locates warehouses once at a time until no additional warehouses can be added to the distribution network without increasing total costs and (2) the 'bump and shift routine', entered after processing in the main program is complete, which attempts to modify solutions arrived at the main program by evaluation the profit implications of dropping individual warehouses or of shifting them from one location to the other. This algorithm employed the following three heuristics:

1. The best candidate locations will be near demand concentrations;
2. Near optimum results can be archived by opening warehouses one-at-a-time which produce the greatest cost savings for the entire system;
3. Only a mall subset of all candidate locations need to be investigated in order to determine the next warehouse to open.

So the idea behind the procedure of Kuehn and Hamburger is to locate warehouses one-at-a-time until no more warehouses can be opened without increasing total system costs. This resulted, and a few years later another heuristic was developed by Feldman et al. (1966) which works actually on the same method, in the two most well-known construction heuristics for facility problems:

- The ADD procedure (Kuehn and Hamburger, 1963) and
- The DROP procedure (Feldman, Lehrer and Ray, 1966)

Although the method to solve UFLP is a few decades old it still provides a strong foundation for much of the location theory research done to date. The only changes are that the complexity of the mixed-integer problems increased to add more and more level of detail in the models.

7.2.3 Amgen's Situation

The objective of most models found in the facility locations literature is to minimize the total demand-weighted distance between customers and facilities. However, this is not the driver for Amgen. The (global) carriers used to transport the medicines to the end-customer are not making any distinction in costs between the distance of the place of collection and the place of delivery. They only use the country borders and the weight of the package to determine the price of the shipment. Therefore it is not needed to know the exact location of each Amgen end-customer to optimize the European structure and it will be possible to use an *aggregation* value on country level. The transportation costs will then only depend on the number of shipments between countries or within a country. As a result the total transportation costs and facility costs need to be minimized. So instead of minimizing the total distance, the transportation costs together with the facility costs have to be optimized for Europe.

7.2.4 Summary

To realize the optimization of a centralized, European structure for the situation of Amgen a model is constructed which uses the ADD heuristic. The ADD heuristic is one of the most widely known heuristic and is still a strong foundation for much of the location theory research done to date. Although in case of heuristics no guarantee exists that it would find an optimal solution, using exact methods is not a feasible option either. First, exact solution methods require more knowledge of linear programming and more sophisticated programs to solve those problems. Secondly when the problem becomes too large exact methods may not be computationally feasible.

For the situation of Amgen the ADD heuristic will be a strong and usable tool to solve easily location problems if there are relatively few possible locations. The prognosis is that not many warehouses are needed through Europe to meet the European demand. It is expected that between 2 and 5 warehouses are needed (including the ELC) where the savings on transportation costs to locate a warehouse in a specific country will be larger than the fixed costs of the extra warehouses. It is clear that in an optimal situation the second DC, so the next DC after the ELC, the warehouse with the largest savings will be chosen first. In contrast, the situation will be radically different if 50 warehouse should be located over more than thousand locations through a greedy heuristic, where once a decision is made, it will not be changed anymore. This is not the case and through the possibility to validate the ADD heuristic performances through checking whether the results of the ADD heuristic will be optimal or not the ADD procedure will be a suitable tool to use.

The ADD heuristic together with the widely known Excel program will be used to optimize the centralized, European structure for the situation of Amgen. Several reasons lay the foundation for this choice:

1. **The ease and extensive range of possibilities within Excel**

   With Excel single and separate information can be converted and linked in coherent information that interacts with each other. So input data can be stored, linked and converted through different processes

towards desired output results. Furthermore Excel has several powerful aids to analyze and transfer information, has an extensive range of functions and standard formulas, macro functions to execute an action or standard procedure automatically (on basis of Visual Basic language) and several add-ins such as the solver tool to minimize or maximize object functions.

2. **The ADD Heuristic can be implemented in Excel**

   The steps of the ADD heuristics are rather straightforward and follow an established pattern of repeating iterations of the steps. Whenever a task has to be performed repeatedly in Microsoft Excel a macro function can be used. A macro is a series of commands and functions that are stored in a Visual Basic module which can be run whenever is needed to perform the task. The macro will be a suitable tool to perform the standard steps of the ADD heuristic automatically and can be easily implemented in Excel.

3. **Possibilities to simulate different scenario's**

   Facility location involves most of the time incredible high costs and are long-lasting decisions which will have an impact on numerous operational and logistical processes. Therefore it is important to find robust facility locations and to carry out a sensitivity analysis that addresses the problem of input data uncertainty. So in other words, the selected locations must not only perform well according to the current system state, but also to perform well and continue to be profitable for the facility lifetime, even as environmental factors change, populations shifts and market trends evolve. Therefore the model must have some control variables that can be varied to simulate different scenarios to find out the robustness of the optimal solution. This is possible in Excel where information can be linked to coherent information that interacts with each other.

4. **Almost Everyone is Familiar with Excel**

   The Excel program is widely known and most people are familiar with this program. The intension is to make a model to optimize the current situation and several future scenarios but also a model which can be used in the future by other people within Amgen who are interested in the issue facility location and who wants to update the data, test new situations/scenarios and add new countries and locations to extend the model. The Excel model together with a guide makes it suitable to easily pass on the model and information to anyone who is interested.

Both ADD and DROP procedures are greedy heuristics that generate feasible solutions fast. The ADD algorithm greedily[8] adds facilities to the solution until the algorithm fails to find a facility whose addition will result in a decrease of the total costs. The exact steps of the ADD method in a mathematically way are given in appendix 8. Before a model in Excel can be developed an analysis of all the European countries served by the ELC will be carried out to determine the countries which are suitable to include in the model and to see what the restrictions are for example enforced through legal boundaries.

7.3 European Countries served by the ELC

One of Amgen's goals for 2005 was to 'win in a changing marketplace' because the competitive power will be tougher than ever. Part of this goal was to grow the market size & share and to reach new patients who are in need of Amgen's medicines. Therefore the supply chain needs to ensure the supply to every patient, everywhere and every time. This goal requires and set some restrictions on the maximum distribution time to transport the medicines to the patients. A distribution time *within 24 hours* will be needed to be competitive with the competitors and to meet the requirements of the customers. The results of an earlier internal research project on the minimum number of locations in Europe which are able to cover their patients within a 'normal' reach of a 24h truck distribution is given in figure 28. However, freight carriers are offering special express services to shorten the normal transportation time and guarantee a delivery before noon or nine o'clock next morning in the EU. In the next paragraph the current distribution flows are analyzed.

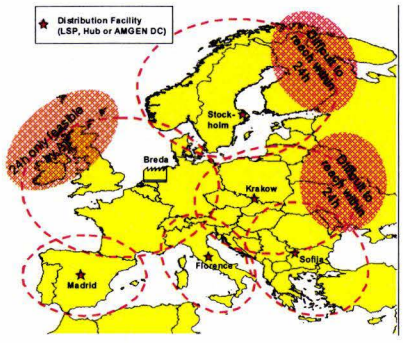


Figure 28 24h Truck Distribution
Source: Presentation Miebach (2006)

7.3.1 Current Distribution Flows

Each distribution flow to a European country is unique and differs from each other through differences in demand and desires of the customers, regulations & legislations, the most 'accepted way' of distribution in the respective

[8] Means that each node/facility that is added to the solution reduces the costs as much as possible and which holds the previously selected sites fixed in the solution

country and the way competitors are doing it. Amgen uses the next four main distribution channels to distribute their products to the end customer (hospitals, pharmacies and dialysis centers):

- **Direct distribution**:

  Direct distribution means that the medicines will be shipped directly from the ELC to Amgen's end-customers via a global express carrier (e.g. UPS or DHL). The orders are picked & packed in the ELC and shipped without any other parties in-between to the hospitals, (retail)pharmacies or dialysis centers;

- **Logistics Service Providers (LSP)**:

  LSPs have their own distribution centers, often as a multi-user site. However the most important characteristic of a LSP is that Amgen owns the inventory which is situated at the LSP and has complete sales information. Physical distribution is done either by the LSP himself or by another subcontracted carrier;

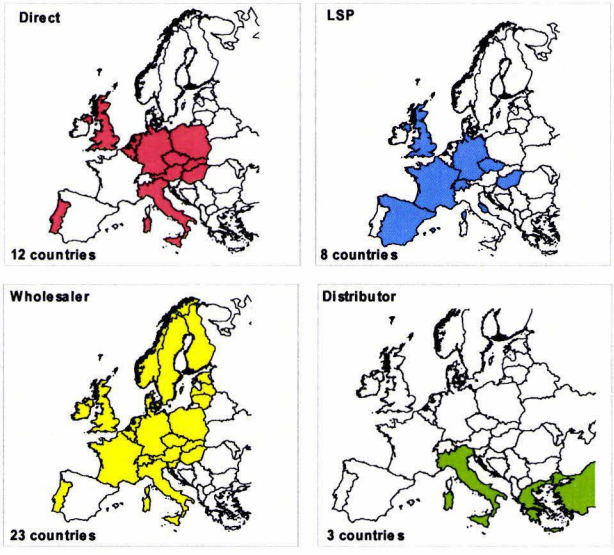
- **Wholesaler**:

  A wholesaler is specialized in selling, storing and distributing the medicines to certain customer groups in a given region or country. Often they obtain sophisticated distribution system to deliver to their market (i.e. to hospitals and pharmacies) several times a day;

- **Distributor**:

  A distributor takes over the distribution for a certain market/ region using his own network and/ or wholesalers. Often this involves mid to long term contracts with certain exclusivity. Beside distributional services, a distributor takes responsibility in regulatory topics as well as in most cases for marketing and sales activities.

In appendix 9 an overview of the analysis of the distribution channels to each European country is given. It shows the total sold packs in 2005, the different channels of the respective country and the percentage of the volumes through each channel. Also, right of the flag, the demand split of the end customer Hospital and Pharmacy are given as a percentage. Below a schematic overview and the results are given:



Direct Channel
Italy, Germany, United Kingdom, Poland, Portugal, Netherlands, Belgium, Austria, Hungary, Czech Republic, Luxembourg & Slovakia.

LSP Channel
Italy, France, Spain, Germany, United Kingdom, Switzerland, Hungary & Czech Republic.

Wholesalers Channel
Distribution via wholesalers can be found in all countries except Greece, Spain and Turkey.

Distributor Channel
Distributor channels can be found in the countries Italy, Greece and Turkey.

Figure 29 Distribution Channels in Europe

7.3.2 Groups of (end-) customers

A very important characteristic which influences the transportation costs enormously is the type of group that will be delivered to. The pharmacies have often orders of only 1 or 2 packages per shipment while the hospitals order many different packages with different SKU's each time. There are several different types of (end-) customers classified by Amgen:

- Dialysis Centers
- Distributors
- Hospitals
- Inter Company (most if the time those are other Amgen affiliates)
- Wholesalers

Figure 30 shows the total number of sold packs and orders for each group for the year 2005 and with this data the average packs per order can be calculated. The results were that the group 'hospitals' orders in general 24 packs per order and the pharmacies, of which 68 percent is located in Germany ordered 1,5 packs per order. Although there are seven different kinds of groups, actually there are only two types of end-customers: the *hospitals* and the *pharmacies*. This is because the wholesalers and distributors are only partners or a link between Amgen and the real end-customers of the hospitals and pharmacies. Dialysis Centers take only a minor part of the total sold units and can be placed in the group 'hospitals' due to the same average packs per order.

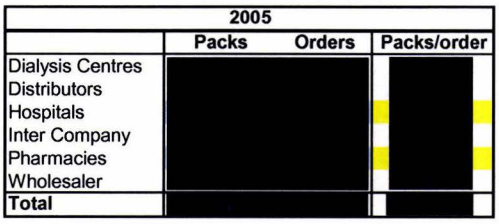


Figure 30 Sold Packs and Orders for each Group

7.3.3 Regulations

7.3.3.1 Introduction

The European Union (EU) prescribed that the companies in the Member States of the EU have to obtain a license if they manufacture or distribute medicinal products. There are in general two types of licenses, namely the *manufacturing license*, when medicinal products are manufactured and a *wholesale license* that authorize to only distribute the medicines. The European regulatory definition of medicinal products is described in the 'Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human-use' and this directive applies to medicinal products for human-use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process. The essential aim of any rules and directives concerning the production and distribution is to ensure that the medicines are produced in a safe way and that every produced medicine meets the appropriate quality level to safeguard public health.

However the directive 2001/83/EC are directives or guidelines set up by the EU and every Member State can implement the directives differently in their own national legislation. For The Netherlands the duty to have a license is described in article 2 of the 'wet op de geneesmiddelenvoorziening' (WOG). A Dutch license is only required if the production or the final process is taken place within the Netherlands and this rule applies also generally for other EU countries. For the production of the medicines, the Netherlands has at this moment 4 types of licenses (the manufacturers license encompasses all trades; the other 3 licenses are limited to particular trade):

- *The manufacturers license* (de fabrikantenvergunning) (this license has 3 variants);
  For pharmaceutical companies which are producing and distributing medicines.
- *The subcontractor license* (de loonfabrikantenvergunning);
  For companies who restricts themselves to execute one or more subpart of the total production process of a medicinal products in task and for the benefit of someone else.
- *The importer license* (de importeursvergunning);
  Companies who want to distribute in the EU imported medical products of no EU member countries.
- *The parallel-wholesale businesses license* (parallel-groothandelsvergunning).
  For companies that limit themselves to only packaging, labeling and delivering of pharmaceutical products and which have been brought in the trade in a EU-member country.

If a pharmaceutical company obtains a manufacturing license this includes automatically an authorization to distribute by wholesale the medicinal products which may be in general delivered in the entire EU (see directive 2001/83/EC article 77.3). When no manufacturing activities are taking place and a certain company is only distributing by wholesale medicinal products a manufacturing license does not have to be obtained and only a wholesale license will be sufficient. There are signs that the 4 licenses mentioned above, so beside the wholesale license, will be traced to one manufacturing license.

7.3.3.2 GMP & GDP

The pharmaceutical industry operates at a high level of quality assurance and to achieve its pharmaceutical quality objectives in their manufacturing processes of medicinal products they have to comply with the Good Manufacturing Practices (GMP). This policy of GMP ensures that products released for distribution are of the appropriate quality.

In addition, to maintain the quality of the products and the quality of the service offered by wholesalers, article 79 of directive 2001/83/EC (referring to the guidelines of directive 92/25/EEC) ensures that wholesalers must comply with the principles and guidelines of Good Distribution Practices (GDP) published by the Commission of the European Communities. In the "Guidelines on Good Distribution Practice of Medicinal Products for Human Use", several guidelines in order to meet GDP requirements are described on the subjects personnel, documentation, premises and equipment (for example storage), deliveries to customers and the processes of the returns.

7.3.3.3 Important Regulations in Relation to Amgen ELC in Breda

The most important regulatory requirements in relation to this project and then in particular to the ELC is article 77(3) of Directive 2001/83/EC:

77.3.

Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

This means that based on the existing manufacturing license (and therefore a wholesale license), ELC Breda is able to deliver directly to all *licensed wholesalers* in the European Economic Area[9] (the EEA) because of the open markets and the right to distribute products to every EEA country without the need of any import license. In most of the EU countries license holders are allowed to distribute alongside the licensed wholesaler directly to hospitals and pharmacies as long as national regulations do not require further restriction. In generally the distribution to hospitals in the EEA is possible except in the Nordics where this is not common and where the goods have to be distributed to local wholesalers. The distribution direct to pharmacies is normally allowed within the EEA countries but through national restrictions it is restricted in the Nordics and countries such as Portugal and Spain. Portugal and Spain require that national stock is held for example at the local affiliate because they obligate the license holder to have permanently available in quantity and variety all the drugs required to satisfy in time the demand. Furthermore if in Poland invoicing are handled by the national affiliates this will lead to the requirement of a wholesaler license, which can be fulfilled without major investments. So there may be exceptions and to find this out thoroughly the authorities in the countries have to be called and asked whether they would accept recognizing Amgen ELC license to deliver directly the hospitals and the pharmacies and whether extra requirements if necessary will be needed.
For the countries outside the EEA, so for example Switzerland, it is harder to distribute to customers directly. However Switzerland has a Mutual Recognition Agreement (MRA), which is a bilateral agreement between Switzerland and the EU, there are certain obligations to import from and export to Switzerland. Therefore small shipments to retail pharmacies for example seems not to be practical. On the other hand direct deliveries from an LSP in Switzerland to retail pharmacies and hospitals is not restricted.

7.3.3.4 Important Regulations in Relation to an Amgen warehouse somewhere in the EU

Setting up a warehouse by Amgen somewhere in the EU requires a new wholesale license. To obtain such a license the warehouse and the organization need to meet the GDP requirements (see the guidelines described in directive 92/25/EEC) and this will be checked and be controlled by the local authorization where the new warehouse is built. To obtain a wholesale authorization applicants must fulfill minimum requirements regarding: premises, installations and equipments, trained staff, ensure of continued supply etc. It shows that the quality system operated by distributors/wholesalers ensures that medicinal products which are distributed are authorized in accordance with Community legislation. This means that storage conditions are observed at all times, including during transportation, that contamination from or of other products is avoided, that an adequate turnover of the stored medicinal products takes place and that products are stored in appropriately safe and secure areas. In addition to this, the quality system should ensure that the right products are delivered to the right addressee within a satisfactory time period. A tracing system should enable any faulty product to be found and there should be an effective recall procedure. When a warehouse and the organization meet the requirements, a wholesale license will be granted by the Member State and will allowed distribution of medicinal products to the EEA countries with the same restrictions as described in the previous paragraphs.

7.4 The Included European Countries

The main conclusion that can be drawn from the analysis is that direct distribution to hospitals and pharmacies is in general allowed in all western EU countries except the non-EU country Switzerland and the Nordics. As a result of the information and the restrictions provided in previous paragraphs and the Buck analysis (see appendix 10), all European Countries distributed by Amgen except the countries Switzerland, the Nordics (Denmark, Finland, Norway and Sweden), Ireland, Greece and Turkey will be taken into account and will be used to model the European structure. Switzerland is not a member of the EU and therefore accepts no shipments directly to local hospitals or pharmacies out of the EU into Switzerland (on the other hand direct distribution is allowed from for example a local service provider in Switzerland to the hospitals and

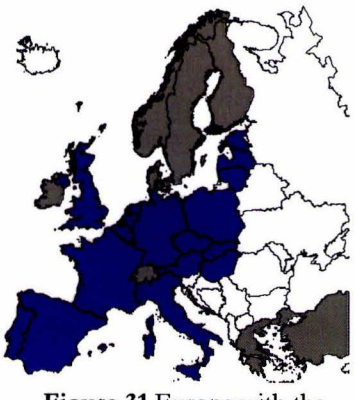


Figure 31 Europe with the Included Countries

[9] These are the 25 Member States of the European Union and the three additional countries Norway, Iceland and Liechtenstein

pharmacies). Furthermore the Nordics accept no direct shipments from abroad or within the Nordics to hospitals or pharmacies and everything has to be distributed via a wholesaler. In Ireland direct distribution from the ELC to Irish hospitals is allowed in theory but is not feasible in practice because interpretation of the laws and due to the power of the wholesaler makes direct distribution in practice almost impossible. Due to the geographical position of Ireland it will be probably uneconomic to place a satellite warehouse here. Furthermore Amgen just revealed the news that it intends to invest in a new process development, bulk manufacturing and fill and finish facilities in Cork, Ireland to enlarge their capacity. By that time it will be a possibility to act as a warehouse which is an extra reason to exclude Ireland in this European Pan structure. Through the relative small number of sold units and, more important, the strong commercial status of wholesalers in the above mentioned five markets, those countries will continually be served via the current distribution channels. Greece and Turkey, because of the geographical position, are being distributed by the current distributors who take responsibility in regulatory topics as well as in most cases for marketing and sales activities. Greece and Turkey are not connected to other European countries, which make it difficult to transport the medicines to the end-customer within 24 hours. For those reasons Greece and Turkey will be excluded in the European Pan structure. The countries in figure 31, which are blue, will be included in the model, discussed and explained in the next chapter, and the gray countries are excluded (figure 32 shows the 18 countries which are included)

The 18 countries which will be included in the model					
Austria	Estonia	Hungary	Lithuania	Poland	Slovenia
Belgium	France	Italy	Luxembourg	Portugal	Spain
Czech	Germany	Latvia	Netherlands	Slovakia	United Kingdom

Figure 32 The Eighteen Included Countries

8 Model for a Centralized European Distribution Structure

The previous chapter suggested a centralized European structure for the blue countries as shown in figure 31 for modeling, simulating and optimizing Amgen's distribution supply chain. As described in chapter 7.2.4 an optimization model based on the ADD heuristic will be used to optimize the centralized, European structure for the situation of Amgen.

8.1 Goal of the model

A model together based on the ADD heuristic will be used to optimize the centralized, European structure for the situation of Amgen. The *target* of the model is

Optimization of the transportation and facility costs for a centralized, European structure through migrating local centers to a few Amgen distribution centers in Europe and to check the possibility of cross-border land services (so whether (smaller) markets can be served by truck cross-border from an own warehouse or of a LSP-location outside the country).

8.2 Needed Input Data

The uncapacitated, single-stage model, described in paragraph 7.2.1 considers the trade-off between fixed operating and variable delivery costs. The formulation of this problem mathematically is

Minimize $$\sum_{i \in I} \sum_{j \in J} c_{ij} x_{ij} + \sum_{i \in I} f_i z_i$$

Here the total demand-weighted distance between customers and facilities is minimized but this is not the driver for Amgen. As stated earlier, the freight carriers, which will be used to transport the medicines to the end-customer, are not making any distinction in costs between the distance of the place of collection and the place of delivery but use only the country borders and the weight of the package to determine the **price of the shipment**. Therefore it is not needed to know the exact location of each Amgen end-customer to optimize the European structure and will it possible to use an *aggregation* value on country level. The transportation costs will only depend on the **number of shipments** between countries or within a country and as a result of this the total transportation costs should be minimized. Also the **facility costs** have to be taken into account. So instead of minimizing the total distance, the transportation costs, together with the facility costs, will be optimized for Europe.

The bold words in the previous paragraph give the important input parameters needed to minimize the total transportation costs and facility costs. The ratio hospital-pharmacy for each country will be used to calculate the number of shipments for both the hospital and the pharmacy group in each country. The figure below shows the relationship between these parameters.

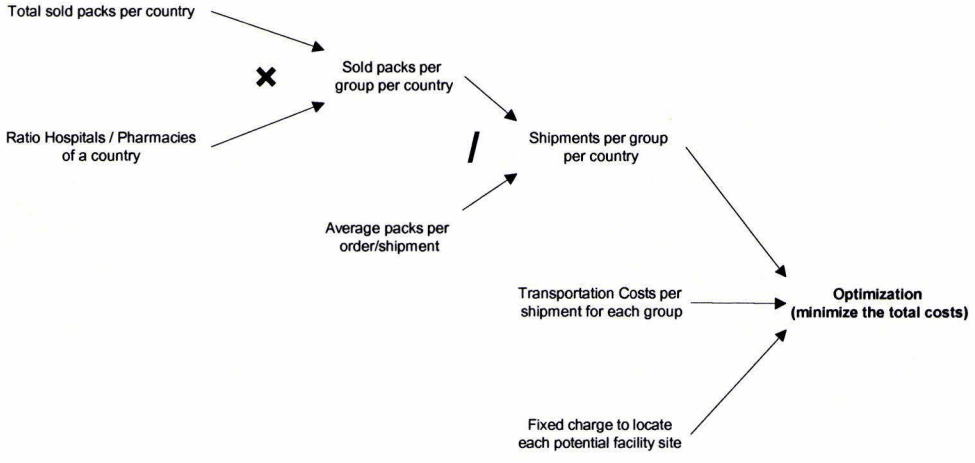


Figure 33 The Relations between the Parameters of the Model

In the next sections the input parameters (1) number of shipments /demand, (2) transportation costs and (3) warehouse costs are discussed in more detail.

8.2.1 Input: Number of Shipments / Demand

Within Amgen several demand forecasts are made to stream the demand and forecast related data flows between the ELC, sales affiliates and the Sales & Marketing headquarters. Two forecasts are made, the Latest Estimate (LE) for the short term and the Long Range Planning (LRP) for the long term. The LRP is a forecast for the next 10 years at a high level, namely in volumes in mcg per year, per brand (Aranesp, Neulasta, Mimpara etc), per indication (for example the Nephrology or Oncology market) and per country and is updated every quarter. The LE is a forecast for two years for the volumes per month for each SKU (so per pack) for every country and is updated monthly (every month the LE sales forecast are collected from the sales affiliates and third party distributors). Finally with those LE's Production Planning and Inventory Control collaborate together with the demand department to plan and match forecasting/demand, production and stock planning.

In paragraph 7.3.2 the importance to make a difference to the end-customers was mentioned briefly. The LRP takes the sales activities of hospitals and retail into account and has therefore a hospital / pharmacy split but the detailed forecast of the LE does not make this split because it is aggregated to the number of sold SKU packs per country. However the ratio hospital-pharmacy for each country in the LRP will be needed together with the estimation of the total sold packs per country (from the LE and LRP) and the average packs per order to be able to calculate the number of shipments for both the hospital and the pharmacy group in each country (the relations between those variables are given in figure 34).

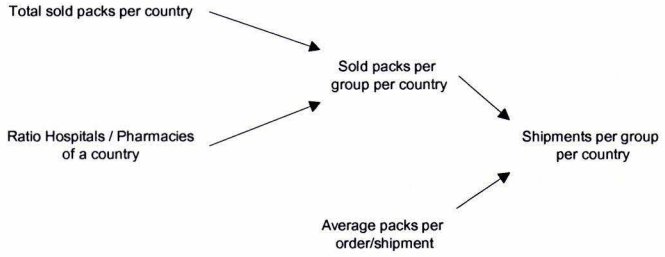


Figure 34 The Relations between the Parameters of the Demand Part

8.2.2 Input: Transportation Costs

As stated earlier the freight carriers, which will be used to transport the medicines to the end-customer, are not making any distinction in costs between the distance of the place of collection and the place of delivery but only use the country borders and of course the weight of the package to determine the price of the shipment.

International freight carriers are offering special express services to shorten the normal transportation time. Most of them are offering next morning or day delivery through almost the whole of Europe. For example UPS is offering an 'Express Service' that guarantees a delivery the next business morning to most business areas in the EU, Norway, Switzerland and Liechtenstein. Also an 'Express Saver Service' exists which guaranteed a delivery the next business day. The carrier DHL is offering an express service too for delivery the next morning or next day, namely the 'Midday' and the 'European Community Express' respectively.

A small part of the total shipments out of the ELC are not distributed via LSPs, wholesalers and distributors but directly distributed to the end-customer. The two main carriers Amgen ELC is using in Europe for direct shipments with next day delivery to the end-customer are UPS and DHL. Breda is close to the European hubs of both carries UPS has a one in Cologne (DE) and DHL has its hub in Brussels (BE). In general the split of DHL and UPS for the shipments from Amgen through Europe in 2005 was 65% to 35% (50.000 shipments against 27.500 shipments). However for more than 70 percent of the shipments to Germany Amgen gives the preference to UPS because of their stronger market position.

Both two international freight carriers are offering almost the same services: deliveries before noon or nine through Europe, track and trace possibilities and a money back guarantee if they failed to deliver on time. In general UPS is offering lower prices for their services and will therefore be used throughout the model to determine the price of shipping an ISC through Europe. First the standard prices from and to the different countries will be determined before a standard discount, which varies from 60 percent for domestic shipments to 80 percent for international shipments because of the good price agreement between Amgen and UPS, will be applied. It is important to notice that the price depends on the package's dimensional weight and not on the actual weight because of the large size-to-weight ratio of the ISC.

Paragraph 7.3.2 discussed the distinction of the two groups 'hospitals' and 'pharmacies' and the differences in the number of packs per order. Amgen are using different types of ISCs of all different sizes and one of the smallest ISC is the M11 with a dimensional weight of 1 kg and the M12 with a dimensional weight of 2.5 kg. The latter ISC is suitable for maximal 8 packages of Aranesp 4pk and therefore suitable for almost all orders received from the pharmacies. For the hospitals an order contains on average 24 packs and therefore a larger ISC is needed: an ISC M4 with a dimensional weight of 10 kg.

8.2.3 Input: Warehouse Costs

8.2.3.1 Potential Facility Sites

From the 18 countries distributed by the ELC and that are included in the model only eight countries are chosen as candidates for locations of a new warehouse. Through several selection criterion and investigation in the potential of a country as a facility site it turned out that not every country that is delivered to is suitable to set up a warehouse. The first selection criterion is that the ELC in Breda is already an existing warehouse and be open all the time. Therefore locating a second warehouse in Belgium for example makes little sense, also because of the relative low volumes shipped to Belgium. The latter is the second criterion: the number of sold packs shipped to a specific country, and will ensure for example that Luxembourg will be excluded as a serious candidate to locate a warehouse. The third selection criterion is the geographically position of a country. The unfavorable geographically position and partly due to the low volumes of for example the CEE countries Lativa and Estonia, it will be uneconomic to locate a warehouse in those countries and is it a better option to locate one in Poland which will take care of the hinterland countries. Figure 35 shows the eight potential warehouse sites to locate a distribution center.

Potential Warehouse Sites			
Austria	Germany	Netherlands (ELC)	Spain
France	Italy	Poland	UK

Figure 35 The Eight Potential Warehouse Location Sites

8.2.3.2 Costs

According to Ballou (1999) costs related to a facility can be represented in terms of

1. **Fixed costs**
   Fixed costs are those that do not change with the level of activity on the facility (for example depreciation, real-estate taxed, rent and supervision).
2. **Storage costs**
   Storage costs are those that vary with the amount of stock stored in the facility. That is, if particular cost will increase or decrease with the level of inventory stored in the facility, then the cost will be classified as storage costs (for example costs of some utilities, capital tied up in inventory and if necessary insurances on inventory value).
3. **Handling costs**
   Handling costs vary with the facility throughput (for example labor costs to store and retrieve items, to pick and pack orders and variable equipment-handling costs).

Fixed Costs

Setting up an Amgen warehouse somewhere in the EU requires huge investments. To make an approximation of the costs for a warehouse, which has to include a cold store and any further associated areas, the ELC will be taken as a starting point. In appendix 11 an analysis at the operational level of a warehouse is given and the distribution centers the ELC and Amgen's US distribution center in Louisville are compared with each other (also some conclusions and thoughts for future research are given). Figure 36 shows the floor plan and an overview of the ELC warehouse. The functionalities and the size of those functionalities in the ELC are:

- Space for goods in & packing (1300 m^2);
- Cold store (650 m^2, suitable for 800.000 packs);
- Component store for e.g. packages, labels, SureClick components and ISCs (2200 m^2).

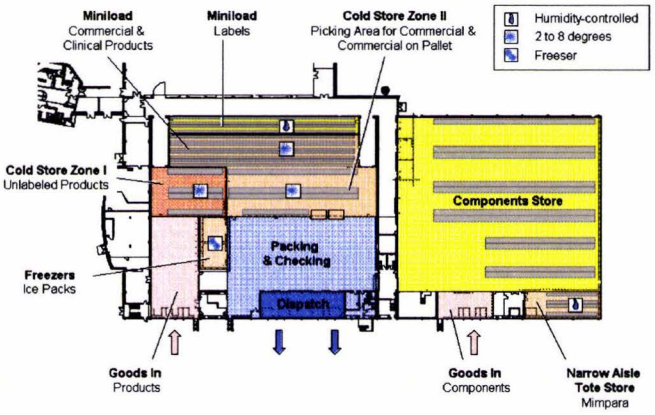


Figure 36 Layout of the ELC

If a new distribution center is located in Europe the requirements and the specifications has at least that of the ELC. The minimum requirements are:

- Incoming products will arrive in big shipments;
- Most of the medicines will be stored in a cold store;
- Some space available to pick and pack orders for the end customers (hospitals & pharmacies);
- A warehouse to store the ISCs (which will be used to distribute the medicines to the customers);
- Size of the ELC due to market size and cross-border landservices.

When setting up a new warehouse the size of the ELC will be needed to handle all orders and shipments. The total shipped packs will be lower but the number of shipments will increase enormously because small retail orders, normally handled by wholesalers and Logistic Service Providers, will be brought in-house.

The size and the capacity of a warehouse influences the height of the construction cost. In the construction world a target of $100 per GSF (Gross Square Feet) is used as construction and equipment costs for a basic warehouse. So every extra square feet increases the construction and equipment costs by $100. For pharmaceutical warehouses, and especially where a cold supply chain is needed, the impact of the size of a warehouse on investment costs is much less. A biotechnology supplier and distributor need to comply with GDP requirements to maintain the quality of the products and the quality of the service (see paragraph 7.3.4). Those requirements, together with the investment costs to build a cold store and having temperature and humidity controlled areas, determine the total investment cost to such an extent that the capacity no longer influence the total investment costs. Appendix 10 gives the costs for a warehouse/cold store and associated areas. This reveals that investment costs will be above 30 million euros and when a plot of land has to be acquired the total cost will be 32 million euros.

Labor costs of supervision and support are fixed costs that do not change with the level of activity on the facility. Although labor costs to store and retrieve items, to pick and pack orders can be classified as handling costs which vary with the facility throughput, it can also be fixed costs if those employees have a permanent appointment. This realistic assumption will be used in the Excel model (unfortunately it is not possible in the model to work with variable costs which depends on the throughput). The number of employees in the ELC main warehouse, sampling and inspection and Pick and Pack are:

- Main WH: 6
- Sampling & inspection: 3
- Pick & Pack: 11 (+4 temp. for 5 hours a day)
- Supervision and Support Office: 7

The number of staff for operating a new warehouse will require fewer employees compared to the ELC. In the main warehouse only the ISCs are delivered, for example once a week, stored and finally used to ship an order to the end-customer. In contrast with the ELC those activities can easily handled by 1 employee. Sampling & Inspection activities in the ELC are mandatory according to EU regulations because the unlabeled medicines arrived from outside Europe (Puerto Rico) but those activities are superfluous when a second warehouse somewhere within the European borders is established. Through efficient pick and pack processes, 15 pick and pack employees will be sufficient to deal with all shipments for a large second warehouse and for supervision and support 5 employees will be needed. Appendix 10 gives the salary costs for the two different groups of employees for the ELC.

Energy costs are an important cost driver too (especially due to the cold store). The consumption of electricity for the ELC for mainly the cold store and some lighting (extrapolating from the consumption of energy during low hours, so during night and the weekends, to exclude the other extra consumption during the day) is 250.000 kWh per month. With an average price of 6.50 eurocent per kWh in the Netherlands the electricity costs are 16.250 Euro per month or 200.000 Euro per year. Finally a small percentage can be taken for overhead costs (maintenance, contingency etc).

Storage Costs

Storage costs are those that vary with the amount of stock stored in the facility and is mainly determined by the capital tied up in inventory. Nowadays every country in Europe has his own distribution channel and even within a country there are several flows possible and stock is stored at a lot of different places at wholesalers, distributors and LSPs and of course the ELC. A wholesaler and distributor will buy the products and become the owner of those medicines but the products at a Logistic Service Provider remain property of Amgen.

In the ELC the products will be packaged and labeled and then be distributed directly or indirectly to the end-customer. For every SKU, Amgen determines a production-policy which determines the time between two production runs (this can vary from 2 to 6 months). The production policy and the number of shipments out of the ELC and LSPs determine the average inventory and thereby the storage costs.

Replacing LSPs for an Amgen warehouses will not have an impact on the storage costs but eliminating several wholesalers may increase the storage costs because the stock will be longer in possession of Amgen. On the other hand, centralization of inventories has the advantage of a decrease of the inventory in stock through making use of

the well known statistical fact that consolidating inventory to fewer locations can substantially reduce total inventory requirements, known as the 'square root rule' (Christopher 2004). While it is an approximation, this rule of thumb gives an indication of the opportunity for inventory reduction that is possible through holding inventory in fewer locations. The rule states that the reduction in total system inventory which can be expected is proportional to the square root of the number of stock locations before and after rationalization. However this rule only holds when the same SKU is kept on stock at different locations. In the case of Amgen each country is different and this results in the fact that the packages and labels for each country are unique. When this is the case consolidating would not give much advantages and the idea will be more like shifting the stock from the ELC to another location. Now Amgen clusters countries in groups to reduce the different numbers of SKUs, making centralizing and consolidating more attractive.

Through the fact that having an Amgen warehouses in Europe instead of the current distribution strategy is more like shifting inventory from one place to another and because of paragraph 3.4.3 shows that the storage costs are only a minor part of the cost price the influence of the storage costs will be minimal on the decision of potential location and therefore be set to zero.

Handling Costs

Handling costs vary with the facility throughput but through the assumption of permanent appointments for all the employees and to get one fixed number of costs to use to optimize the European distribution strategy the cost item handling costs will be set on zero.

8.2.3.3 Regional Differences

The heights of investment and running costs of setting up and running a warehouse in each of those countries will differ compared to each other. However it turns out that the investment costs to build and construct a new warehouse which comply with the Good Manufacturing Practices and Good Distribution Practices is almost the same and only in Poland the investment costs are 12% lower. Employment costs in the countries differs significantly. A survey in 2005 by Mercer Human Resource Consulting, which is given in appendix 12, shows that employment costs in Western EU countries are more than four times those in the East (employment costs include national average pay, social security, and other mandatory and typical voluntary benefits including pension, healthcare, and disability benefits). The figure below shows a part of the result of the survey. The average pay for each country is taken as the national average earnings for full-time male employees. The survey highlights the competitive advantages that Eastern EU countries have over the West and putting aside pay, the survey reveals furthermore that the benefit costs have a significant influence on the total employment costs, ranging from less than 10 percent on the average national income to as much as 50 percent.

A cross-country comparison of employment costs (in €)						
Country	Pay	Social security	Mandatory benefits	Voluntary benefits	Total Pay & benefits	Relative
Europe						
Germany	40,163	8,274	-	2,008	50,445	1,45
UK	38,901	2,972	-	4,668	46,541	1,34
France	31,544	10,913	1,529	1,893	45,879	1,32
Netherlands	**29,354**	**3,023**	**-**	**2,348**	**34,725**	**1,00**
Italy	22,763	7,257	2,023	228	32,271	0,93
Spain	20,605	6,511	-	2,06	29,176	0,84
Austria	22,321	4,832	343	1,116	28,612	0,82
Poland	6,495	1,307	65	390	8,257	0,24

Figure 37 Survey on the Average Pay in the European Countries, **Source:** Mercer Human Resource Consulting

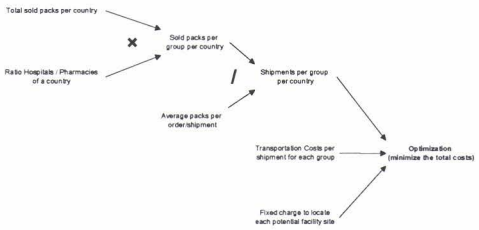
8.2.3.4 Summary

In the previous paragraphs the costs for the three categories of a facility and the regional differences are discussed. The conclusion that can be drawn is that the fixed costs will be the costs which determines the fixed charge to locate each potential facility site and to run the warehouse. These are the investment costs in connection with depreciation, the costs of the employees and the energy costs. An extra item will be added to include the overhead, maintenance or contingency costs. According to the Amgen policy the depreciation of buildings is X months and this method used the straight-line method and using a salvage value of zero. For the employee costs, the costs of an employee in the Netherlands are multiplied with the relative factor of the survey of Mercer Human Resource Consulting. Furthermore an extra item "extra costs" is added for, energy costs, the overhead maintenance and/or for contingency. Because those costs are proportional with the purchasing power within a country, a fixed percentage in relation to the employee costs will be chosen to express these extra costs. The energy costs were 200.000 which is almost 25% compared to the total Dutch employee costs and to express also the other costs, a percentage of 30 percent of the total employee costs will be taken. Appendix 10 gives the final result of the several cost items to obtain the total costs per year for each of the eight potential warehouse sites.

In the previous sections the input parameters (1) number of shipments /demand, (2) transportation costs and (3) warehouse costs, needed for the Excel model, were discussed in detail. Next sections present the development of the Excel model, based on the input parameters described above.

8.3 Manual Model

To develop an Excel model for determining the best European structure for Amgen all the input parameters discussed in the previous paragraphs has to be converted and linked in coherent information that interacts with each other. Figure 33, which is depicted in a smaller form to the right, shows the schematic diagram and the relations of each of the input data needed to calculate the total transportation costs and the warehouse costs.



First a model was made with the control variables to open or close a specific warehouse. Figure 38 shows the cockpit of this manual model. The control variables are in the blue cells with the green borders and a 'zero' stands for closing and an 'one' for opening a warehouse. Furthermore the rows of the table show the 18 distributed countries and the columns show the eight potential warehouse sites. When a cell of a country – warehouse combination is marked green the potential warehouse will distribute the specific country and a red cell means the opposite.

No of DCs	4
Total TransportationCosts	
Total WarehouseCosts	
Total Costs	

Countries which has to be delivered	Italy	France	Spain	Germany	UK	Netherlands	Austria	Poland	
Italy									1
France									1
Spain									1
Germany									1
United Kingdom									1
Poland									1
Portugal									1
Netherlands									1
Belgium									1
Austria									1
Hungary									1
Czech									1
Slovenia									1
Lithuania									1
Luxembourg									1
Slovakia									1
Latvia									1
Estonia									1
	0	2	0	9	0	6	0	1	18
								18	

Potential DC's

The potential DC will distribute the specific country
The potential DC will not distribute the specific country

Manual

Warehouse	Exist?	Nr Countries
Netherlands	1	6
Austria	0	0
France	1	2
Germany	1	9
Italy	0	0
Poland	1	1
Spain	0	0
UK	0	0
Total	4	18

Figure 38 Cockpit of the Direct Distribution Model

For a set of open and closed warehouses each of the distributed countries are allocated to a warehouse on such a way that the total transportation costs are minimized. The model will select for each country of all potential facility sites the warehouse where the transportations costs are the lowest and mark the corresponding cell in the table in figure 38 green. When a warehouse will be closed manually the transportation costs increase to infinity by multiplying it with a BigM (a huge number). Through this construction the closed potential facility site will never be selected to be an option to set up a warehouse and thereby excluded itself automatically. This allocation of a country to the best

open warehouse is finally given in the table together with the corresponding transportation and warehouse costs Appendix 10 gives all the linked input tables used in Excel. To find robust facility locations some other control parameters are built in to change and vary some of the values of the input parameters to simulate different scenarios. These are also given in appendix 10.

8.4 Optimization Model

The model discussed in the previous chapter is a manual model to calculate the total minimum costs for a *given set* of open warehouses. However to come to an optimal solution every combination has to be filled in manually. Although you might think that for this relative small problem it may be solved relatively easily but even for only seven potential facility sites (so besides the ELC here in the Netherlands which is always open) 128 combinations are possible (2^7) and when only one new potential location will be added the number of combinations will be doubled. However through logically reason several combinations can be omitted beforehand but still the combinations can be astronomically large if the problem becomes bigger.

To do this automatically and fast the ADD heuristic rules are used to determine the optimal right order (however this is no guarantee). The procedure is to greedily add facilities to the solution until the algorithm fails to find a facility whose addition will result in a decrease of the total costs. To execute the ADD algorithm automatically in Excel several macro functions are used and several steps are performed. Firstly, the total transportation costs from each potential warehouse site to each of the countries that have to be delivered are calculated through multiplying the total shipments of a country by the price of one shipment. Secondly, the savings in relation to the Netherlands are calculated for each site–country combination. If it turns out that the transportation costs from the Netherlands are cheaper than from the potential new site the savings value is set on 0, otherwise the savings value will be the result of "the transportation costs from the Netherlands to country X" minus "the transportation costs Potential site Y to country X". This step will be executed for each combination and the total savings of adding a warehouse is the summons of all the separate savings values from the potential site to all the different countries. Thirdly the fixed costs associated with setting up and running a warehouse are subtracted from the transportation costs savings to obtain the total yearly savings of adding warehouse Y. Finally, the warehouse with the maximum savings will be selected. Hereafter the iteration will be repeated at step 2 and new savings values will be calculated, not only in relation to the Netherlands but also to the new added warehouse, or in other words from the subset of warehouses for which $z_j = 1$ has been decided (see for the exact steps of the ADD method in a mathematically way appendix 8).

When the steps, described above, are executed, the warehouses are sorted in a decreasing order of total savings which depends on each other. Plotting the total costs, so transportation costs and the costs of the warehouse, against the total number of warehouses a parabolic curve of a quadratic function like figure 39 will be obtained. The minimum is the point where the total costs are the lowest and which represent the optimal solution in this situation.

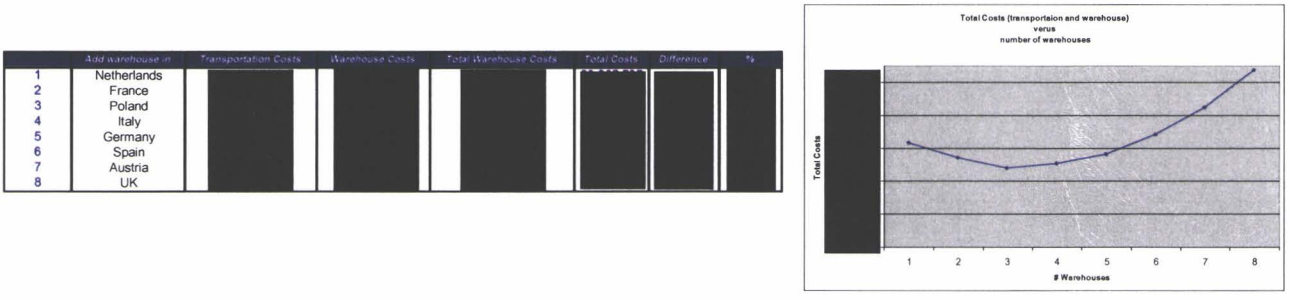


Figure 39 The Total Costs versus the Number of Warehouses

In the case of the situation of 2006 and with a discount of 60% on domestic shipments and 80% on international shipments the conclusion can be drawn that for serving the European countries in a centralized, European structure, three warehouses in total will be needed for the selected countries: the ELC in the Netherlands, one in France and finally one in Poland. In conclusion figure 40 shows which warehouse has to deliver which country (a green combination) and how many countries a specific warehouse has to distributed to in order to fulfill all the demand.

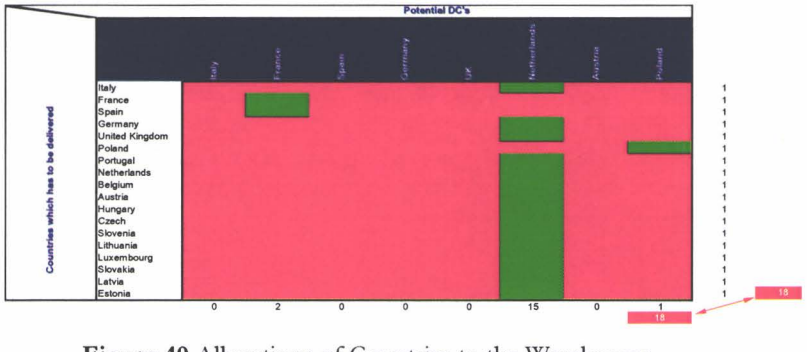


Figure 40 Allocations of Countries to the Warehouses

8.5 Validation

In the previous chapter the development of the decision support tool to determine the number and locations of warehouses for the central European structure is described. Actual implementation of the decisions coming from the tool is only useful if the results provided are valid, i.e. it correctly reflects the reality. The three important input parameters which are the number of shipments /demand, transportation costs and warehouse costs, needed to minimize the total transportation costs. Facility costs are based on real time price agreements and realistic latest estimates of the demand forecast carried out between the ELC, sales affiliates and the Sales & Marketing headquarters. During the development of the Excel model no important assumptions are made that have to be tested and validated. However one substantial issue that has not been discussed so far is the validation of the heuristic in the developed model: the ADD heuristic. Those heuristics are used to solve efficiently 'fixed charge facility location problems' but unfortunately it will only be optimal in special cases and no guarantee exists that it would find an optimal solution (it can be expected that this will hold especially for larger problems when if say 50 warehouse should be located over more than thousand locations through a greedy heuristic and where once a decision is made it will not be changed anymore than when locating only a few warehouses through Europe).

Next a validation of the ADD heuristic in the developed model will be performed to evaluate the performance of the ADD heuristic in this context. In order to make this possible the result of the ADD heuristic will be compared to the best solutions of all 128 combinations (2^7). The previous chapter discussed the steps of the ADD heuristic and one of the final steps is calculating the total savings of adding a warehouse (see column 2 of figure 41). In column three the fixed costs associated with setting up and running a warehouse is given and the results of subtracted those values from the transportation costs savings gives the total yearly savings of adding warehouse Y in the last column (and as can be seen in figure 41 some total savings become negative). To prevent basing the validation on only one scenario the heuristic will be tested on three problem sets and taken the previous steps into account the next three scenarios will be created laying the foundation of all other types of scenarios:

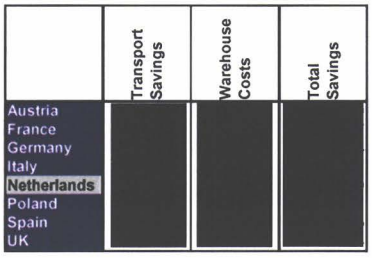


Figure 41 Total Savings of each Warehouse

1. **The 2006 scenario including a fixed charge for the warehouse costs**

This scenario will simulate the year 2006. The sold packs per country per market and the ratio hospital/pharmacy for each country are subtracted from the LE and the LRP for the year 2006. The values for the average packs per order per group are extrapolated from the average of year 2005. The transportation costs from each potential warehouse to a specific country for package's with a dimensional weight of 2.5 and 10 kg through the freight carrier UPS is based on 80 percent discount on international tariffs and 60 percent discount on domestic tariffs of standard UPS rates which are effective from 2 January 2006. A 10,5 percent fuel surcharge is added at the end. Finally for the fixed charge to locate each potential facility site and the costs to run the warehouse (costs per year), the estimates carried out and given in paragraph 8.2.3.4 are taken. For the exact input data see appendix 13.

2. **The 2006 scenario excluding a fixed charge of the warehouse costs**

Through subtracting different kinds of fixed charges of warehouse costs from the transportation savings the attractiveness of opening a specific warehouse changes and even some total savings become negative. Therefore it is interesting to look at the performance of the ADD heuristic when only the transportation costs savings are taken into account (so without any fixed charge for warehouse costs).

3. **The 2006 scenario with warehouse costs 10%**

As said before the attractiveness of a warehouse location depends on the transportation costs savings and the costs of having a warehouse. Through regional differences the latter can differ significantly with each other and influence the attractiveness of certain potential facility sites. When only a small percentage of warehouse costs will be used this order may change and more total savings become positive.

The figure on the next page shows the results in open warehouses and the costs of the optimal solution through checking all possible combinations (see appendix 14) with the results of the ADD heuristic for each of the three scenarios.

	All Possibilities	ADD Heuristic
Scenario 1	Netherlands, France, Poland Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro	Netherlands, France, Poland Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro
Scenario 2	Netherlands, France, Germany, Poland, Italy, Spain & Austria Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro	Netherlands, France, Germany, Poland, Italy, Spain & Austria Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro
Scenario 3	Netherlands, France, Germany, Poland, Italy, Spain Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro	Netherlands, France, Germany, Poland, Italy, Spain Transportation Costs: X euro Warehouse Costs: X euro Total Costs X euro

Figure 42 Comparison of the Results of All Possibilities and the ADD Heuristic

From figure 42 the conclusion can be drawn that for all the three scenarios the results obtained with the ADD heuristic coincide with the analytical result of checking all possible combinations and that the ADD heuristic works well on this type of (small) problems giving optimal answers.

9 Scenario Analysis

Chapter 8 has primarily focused on the development of the model together with defining important variable input parameters. In addition, the infeasibility of manual evaluation of facility locations was emphasized when the problem becomes too large. Through using the ADD heuristic together with macro functions the optimization will be executed semi automatically. As facility location involves most of the time incredible high costs and are long-lasting decisions, it is important to find robust facility locations solutions and to carry out a sensitivity analysis that addresses the problem of input data uncertainty. This chapter deals with some scenarios and a sensitivity analysis to find the robustness of a specific solution.

9.1 Two Categories of the Control Variables

To find out how robust a solution is the model must have some control variables that can be varied to simulate different scenarios. Referring to the input parameters, two different categories of control variables can be identified which are:

1. The demand or the number of shipments to each country;
2. The costs aspect, including the shipment costs of distributing an Insulated Shipping Container to the end customer or the costs of setting up and running a warehouse.

The next section discusses both categories in more detail.

9.1.1 The Demand or the Number of Shipments of a Country

The facility location solution has to be profitable for the facility lifetime, even as environmental factors change. One of the most important factors for the profitability of a warehouse is the demand or the number of sold units in served countries now, but also in the future. The number of sold units determines the number of shipments and the number of shipments influences the profitability of the warehouse. If the number of sold packs will decrease for example in a specific country or area, the advantages of setting up and running an extra warehouse decrease. This emphasizes the importance of analyzing a scenario that reflects future trends.

The number of sold units for the year 2006 is derived from the LE (the Latest Estimate forecast for two years with the volumes per month for each SKU for every country). This is given in appendix 13. To simulate a future scenario, the year 2010 will be taken. The forecast for the products currently on the market are calculated by the increase or decrease percentages of 2010 compared to 2006, based on the Long Range Planning. However pipeline products that are currently in phase 3, that will be launched in the coming years, have to be taken into account.

Pipeline Products

At this moment Amgen has eight main products on the market and invest a great part of the annual sales in research and development. The promising pipeline with selected clinical and preclinical programs and molecules for many new potential products. The product pipeline will change over time as programs and molecules move through the drug development process, including progressing to market or failing in clinical trials, due to the nature of the development process. Nevertheless in the last four years, Amgen's development pipeline has doubled in size and it has also diversified. Each new product has to go through several phases and studies, which can take more than 10 years before the FDA or the EMEA approves the product for commercial sales.

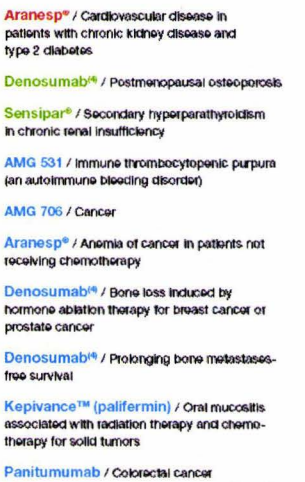


Figure 43 Phase 3 Pipeline Products

At this moment figure 43 shows new molecules / products and current products for new therapeutic areas which are in the last phase, phase 3, of Amgen's pipeline. In phase 3 clinical trials are carried out to investigate the safety and efficacy of a product candidate in a large number of patients who have the disease or condition under study. Finishing phase 3 successfully and after the approval of the FDA or EMEA the product can be launched on the market. As can be noticed from figure 43, three new products are mentioned, which are planned to be launched during the next few years. Those are Denosumab, Panitumumab and AMG 706. Information about the launch date and the predicated sales volumes are given in appendix 15.

With the information provided in the appendix, the sold packs for every country for the currently sold commercial products for the year 2006 and 2010 (the latter includes the new products) can be determined and those figures are given in appendix 16.

9.1.2 The Costs Aspect

The cost aspect obtain the impact of varying shipment costs of distributing an Insulated Shipping Container to the end-customer and the impact of varying set-up and running costs of a warehouse. The variations of costs that will be examined are:

Transportation Costs

1) Transportation Costs with a 60% discount on the standard UPS price for domestic shipments and 60% discount on the standard price for international shipments;
2) Transportation Costs based on current price agreements between UPS and Amgen (approximately a discount of 59% on the standard UPS price for domestic shipments and 72% discount on the standard price for international shipments);
3) Transportation Costs with a 60% discount on the standard UPS price for domestic shipments and 80% discount on the standard price for international shipments;
4) Same as scenario 3, but with the extra assumption that the international shipment tariffs of Poland is the same as the international shipment tariffs of Germany. This because the international shipment tariffs of Poland are huge compared to the domestic shipments tariffs of Poland and the international shipments tariffs of Germany;
5) Transportation Costs with a 80% discount on the standard UPS price for domestic shipments and 80% discount on the standard price for international shipments.

Warehouse Costs

6) Estimated warehouse costs determined in paragraph 8.2.3.4;
7) A cheaper warehouse costs scenario with lower investment costs and construction costs and fewer warehouse employees through efficiencies and economies of scale. This because Amgen's processes, practice and installations are always far superior than those of the competitors which brings additional costs. The reduction compared to the total costs of scenario 6 is almost 40 percent;
8) All warehouse costs are X Euro to fade away the cost advantages of some of the potential warehouse locations. Fixing the warehouse variable, the effects of the other parameters can be determined because the size of investment and running costs of each of the potential warehouse locations are set equally now.

A complete overview of the input parameters for the eight scenarios described above is given in appendix 16.

9.2 Scenarios

Regarding the logistical parameters in the model, a difference was made between the demand and the cost variables which are the two main control parameters of the model. To simulate different scenarios and to find out the effect of changing a specific variable, all other variables have to remain unchanged. Furthermore to gain a clear and complete view of the sensitivity of specific variables the next table will be used:

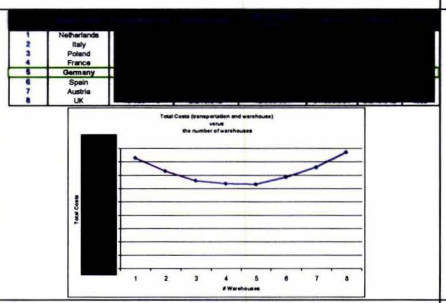
2006 or 2010		Warehouse Costs		
		Normal Warehouse Costs	Reduction of 40%	All Warehouse Costs 1,25 million
Transportation Costs	Current Price Agreements (≈Discount Int/Dom: 72%/59%)			
	Discount Int/Dom: 60%/60%			
	Discount Int/Dom: 80%/60%			
	Discount Int/Dom: 80%/60% and cheaper tariffs Poland			
	Discount Int/Dom: 80%/80%			

Figure 44 Scenario Table

So for each year (namely 2006 and 2010) 15 different scenarios will be evaluated. The following results will be determined:

1) The order of DCs which produce the greatest cost savings for the entire system;
2) The transportation costs for each step;
3) The (total) warehouse costs;
4) The total costs;
5) The absolute and the relative difference between each step.

In appendix 17 all the 15 scenarios with the companion graphs for the year 2006 are given and for the year 2010 this overview can be found in appendix 18.

To give a clearer view figure 45 shows the different transportation scenarios with the normal warehouse costs for 2006. The cost curves are all like a parabolic curve of a quadratic function: the total costs decrease after adding extra warehouses through transportation costs advantages and after a certain number of warehouses the total costs increase again through the little gain of transportation costs advantages and through the higher costs of adding extra warehouses.

The order of warehouses for each scenario below the graph are arranged in an order of the appropriate facility whose addition will result in the maximal decrease of the total costs and therefore obtaining the greatest cost advantages. For each scenario the optimal solution of the set of warehouses is given in green. It can be seen that a difference in the amount of the discount between the international and domestic tariffs results in a lower optimal number of open warehouses.

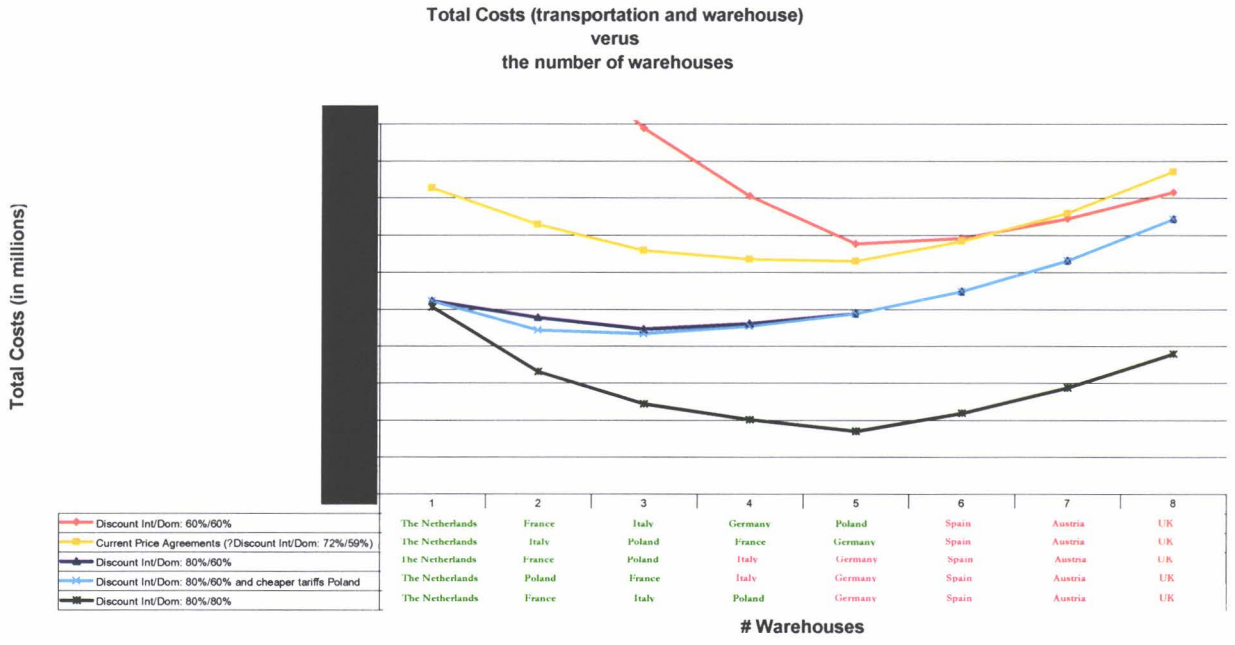


Figure 45 Results of the different Transportation Scenarios on the Total Costs and the Order of the Warehouses for the Year 2006

Explanation of the graph

The dark blue line will be taken as an example. This line represents the scenario of an obtained discount of 80% on the standard UPS price for international shipments and 60% on the domestic shipment tariffs. The first column, column 1, means that only one warehouse is open, namely the ELC, to distribute all the European countries that are included in the model with a total transportation costs of X million Euros. The second warehouse, which addition results in the maximum decrease of the total costs, is a warehouse in France and although the total warehouse costs will increase, the total costs still decrease with this addition. The third best location is a warehouse in Poland, resulting in a total cost of X million Euros. When the fourth best facility location is added, namely Italy, the total costs will increase and the optimal set of warehouses for this scenario is therefore the ELC, France and Poland.

Figure 46 depicts again the relation between the total costs and the number of warehouses for each transportation costs scenario but now for the year 2010. The total costs are higher through the fact that the number of sold packs, and thereby the number of shipments to the countries, increase in the next few years.

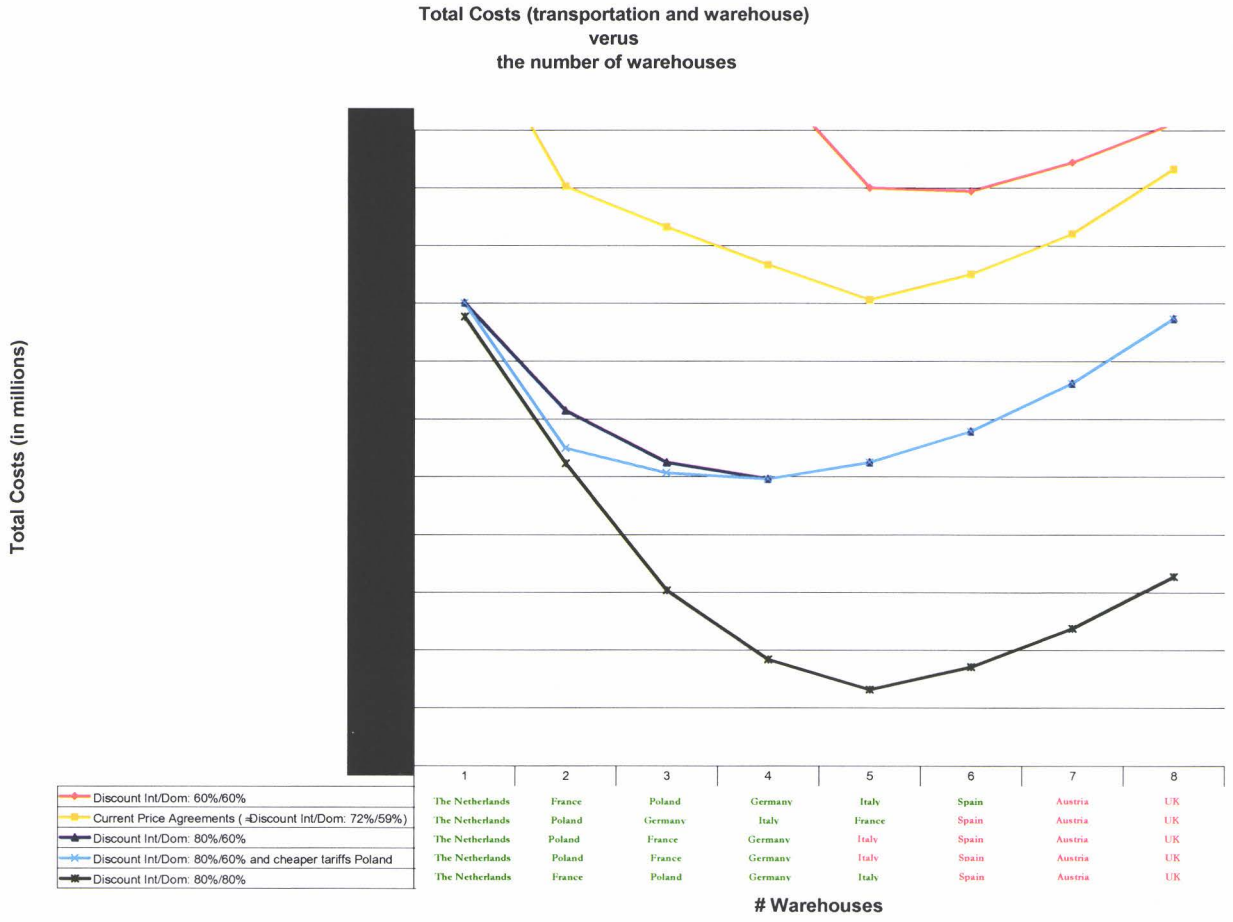


Figure 46 Results of the different Transportation Scenarios on the Total Costs and the Order of the Warehouses for the Year 2010

9.3 Maintaining the Wholesaler Channel

Setting up Amgen warehouses to distribute to all the hospitals and retail pharmacies directly, result in an elimination of all the LSPs and wholesalers in Amgen's supply chain. However, an important point when LSPs and wholesalers are removed is to ensure that the end customers, who are served by those parties, are maintained. The end-customers behind the LSP are known within Amgen, so these customers can easily be reached, but to reach the end-customers of the wholesalers requires a lot more investigation. As can be seen in figure 47 and appendix 9, several countries have a 'big' wholesaler channel. The second column represents the demand split of the end-customer: Hospitals and Pharmacies, and the third to the fifth columns show the percentages of the total flow out of Amgen or an LSP to the groups hospitals, pharmacies and wholesalers.

Country	Demand End-Customer	Flow from Amgen or LSP to		
		Hospitals (% of total flow)	Pharmacies (% of total flow)	Wholesaler (% of total flow)
Italy	(H=81% & P=19%)			
France	(H=61% & P=39%)			
Spain	(H=100% & P=0%)			
Germany	(H=34% & P=66%)			
United Kingdom	(H=73% & P=27%)			
Poland	(H=58% & P=42%)			
Portugal	(H=100% & P=0%)			
Netherlands	(H=43% & P=57%)			
Belgium	(H=95% & P=05%)			
Austria	(H=35% & P=65%)			
Hungary	(H=80% & P=20%)			
Czech	(H=47% & P=53%)			
Slovenia	(H=59% & P=41%)			
Lithuania	(H=44% & P=56%)			
Luxembourg	(H=60% & P=40%)			
Slovakia	(H=74% & P=26%)			
Latvia	(H=59% & P=41%)			
Estonia	(H=54% & P=46%)			

Figure 47 Demand Split End-Customers & Wholesaler Channel

The pharmacists and hospitals behind the wholesalers have the ease of ordering medicines from different manufacturers at one single partner. If Amgen eliminates these wholesalers, a chance may exist that the end-customer will switch brands to sustain the wholesaler. The readiness and willingness of these end–customers to stick

to Amgen products should therefore be checked. Due the chance of losing market share, the effect of maintaining the wholesaler channel in each of the countries is investigated in this paragraph.

Assuming that the volume percentages to the wholesalers remain unchanged (however this is not really realistic for the CEE countries), the percentages direct to the hospitals (column 3, figure 47) and direct to the pharmacies (column 4, figure 47) are used to evaluate this scenario for the year 2006 and 2010.

For the year 2006 no addition of a specific warehouse result in a decrease of the total costs (transportation and warehouse costs) but for the year 2010, a distribution center in Germany will be profitable (see figure 48). This is in line with the results of the scenarios described paragraph 9.2. A warehouse in Poland will become also profitable when either cheaper warehouse costs are used or when shipment tariffs out of Poland decrease and it will be possible to deliver the other CEE countries from this distribution center. Furthermore figure 48 reveals a huge decrease in the rank and preference to locate a warehouse in France.

2010	Add warehouse	Warehouse Costs	Difference of the Total Costs
1	Netherlands		
2	Germany		
3	Poland		
4	Spain		
5	Italy		
6	Austria		
7	France		
8	UK		

Figure 48 Maintaining the wholesalers with normal warehouse costs for year 2010

9.4 Results Part II

The results from these simulations, given in appendix 17 and 18 and the figures above, are:

Main conclusion:

- **Setting up a warehouse in Poland is profitable in all scenarios.**

  The results of the simulations of all scenarios are that it is advisable to set up an Amgen warehouse in Poland. For all the transportation- and warehouse-scenarios for the year 2006 and 2010, Poland is present every time in the optimal set of warehouses.

- **Setting up a warehouse in France is profitable in all scenarios when the wholesaler channel is eliminated.**

  The results of the simulations of all scenarios, described in paragraph 9.2, were that it is advisable to set up an Amgen warehouse in France. For all the transportation- and warehouse-scenarios for the year 2006 and 2010, France belongs every time to the optimal set of warehouses. However when the wholesaler channel remains the preference to locate a distribution center in France decrease because the costs advantages of the France retail market will completely fade away when French wholesalers are obtained.

- **In many scenarios it is advisable to set up a warehouse in Germany, especially if the increase in the number of sold packs is taken into account.**

  A warehouse in Germany is feasible now if a discount is given on the domestic tariffs that are in line with the international tariffs (so either 60 or 80 percent). If this is not the case, the break even point to set up a warehouse in Germany will be reached in the next few years, before 2010, because more packs will be sold (see the year 2010).

Some further findings are:

- **A warehouse in Italy is not profitable.**

  Almost 60% of the volume to Italy goes to the distributor Dompe. In the past, Amgen was obligated to collaborate with Dompe, but now a part of the total volume goes directly to hospitals through sales activities carried out by the Italian Amgen site office. If the collaboration between Amgen and Dompe will sustained, the number of shipments through the potential Amgen Italian warehouse will be low so that owning an Amgen warehouse is not feasible anymore.

- **A warehouse in the UK, Austria and Spain is not profitable.**

  As can be noticed from the result of the simulations, a warehouse in the UK, Austria and Spain is not favorable. The UK's international transportation tariffs are unfavorable due to the geographical position of the UK, compared to the international shipments tariffs out of the Netherlands. A small shipment cost advantage can be obtained in the situation of setting up a warehouse in the UK for their own domestic market when UPS is offering the same discount on both tariffs. However those costs savings will never

justify the costs of setting up and running the warehouse. Furthermore it is more than likely that UPS will offer a bigger discount on the international tariffs than on the domestic ones, because they are an international global freight carrier. If this is the case the tariffs from the Netherlands to the UK will be even cheaper than the UK's domestic tariffs and no costs advantages can be obtained at all.

In addition, Austria is not advisable to locate a dedicated facility and this holds also for Spain. The latter will only be a possibility in the future if not enough discount can be achieved on the international tariffs of the freight carrier.

- **The optimal set of warehouses is most of the time four (excluding Italy, see the first point of further findings).**

  Most of the time the optimal set of warehouses is four, unless UPS or another global freight carrier will offer a bigger discount on the international tariffs than on the domestic ones, because of their international global freight carrier status. If the international tariffs receive a bigger discount it is attractive to serve a county in certain circumstances from abroad which results in a lower number of warehouses needed for Amgen's centralized structure. However this holds only for the short term because by 2010 the optimal set is location of warehouses in the Netherlands, France, Poland and Germany.

- **A low sensitivity of the warehouse costs.**

  Cheaper investment costs and running costs result for few scenarios, a higher number of Amgen warehouses. However, this view holds more for the year 2006 for the scenarios with a difference in discount on the domestic and international tariffs. Due to the increase in sold packs, the shipment cost advantage of placing an extra warehouse is more significant than the extra additional warehouse costs. Therefore the sensitivity of warehouse costs is not high and does not influence the optimal set of warehouse enormously. Only the rank of Poland will decrease when all warehouse costs will be equal, but the optimal set of warehouses remains unchanged.

- **Transportation costs influence greatly the total costs.**

  A great part of the total costs are transportation costs. Of course this depends on the scenario and on the discount, provided by UPS. In general the warehouse costs are less than 20% of the total.

PART III

Conclusions and Recommendations

10 Conclusions & Recommendations

This final chapter presents the general conclusion and recommendations of the project based on the results obtained from both parts. Additionally several thoughts are given for future research.

Part I, presents an in depth analysis on the German retail pharmacies to investigate the possibilities to integrate this specific group of end-customers into Amgen's supply chain and to choose the best distribution strategy for Amgen to distribute to the German retail pharmacist. Different distribution strategies have been discussed and a strong preference was given for the current strategy with the logistic service provider Fresenius; it is the cheapest option and 4 out of 7 qualitative measurements are positive and last but not least, no reasons to question Fresenius and their performances exist. As a result, the direct distribution out of the ELC to the German retail pharmacies was not a profitable and feasible solution and is hard to realize for this specific market. However the main advantage of the direct distribution strategy is to become closer to the customers and therefore more supply chain control and flexibility can be achieved.

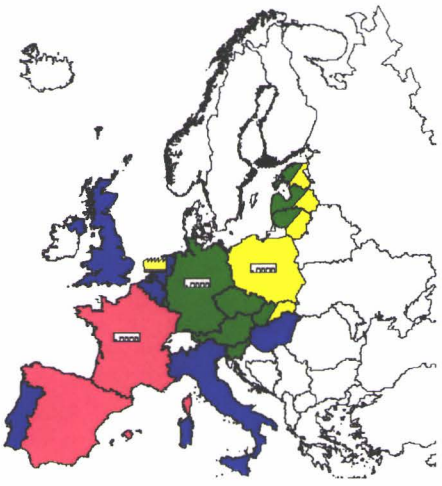
Part II, describes the development of a model in order to optimize the transport and facility costs for a centralized, European structure and to find out the possibility of cross-border land services. The main reasons for Amgen to look at the possibilities of having one centralized European structure are:

- The lack of space of the ELC and the necessitates to scale up to facilitate future growth;
- The trend of consolidating at European level by competitors;
- The desire to be closer to the customer and having more flexibility;
- The possibility to decrease counterfeiting through having greater supply chain control.

The results given in the previous chapter lead to the following conclusion and recommendations:

Open a warehouse in France, Poland and Germany

For a centralized, European distribution structure to distribute all the hospitals and pharmacists in most of the European countries directly, but without the Dompe shipments, Amgen should open distribution centers in France, Poland and finally one in Germany. The results of part II complements the wishes of distributing directly to the German retail Pharmacists; not out of the ELC but out of the new Amgen warehouse located in Germany. The result from the investigation on the German retail pharmacists reveals that the current distribution strategy, so via a LSP, was the best option. It was not profitable to apply another distribution strategy to those pharmacies and the option of a complete new warehouse was not feasible at all. Broadening the scope in part II to an European level, and taking all the different volumes of each country into account with cross border possibilities, results in setting up a German warehouse as the optimal solution. Locating a distribution center in Germany is attractive through aggregating the total volume of Germany and other countries instead of concentrating only on a small part of a specific market which leads to sub-optimization. As a result the German retail pharmacists can now be delivered directly from this new warehouse and provide therefore also a desirable answer to part I.



ELC	France	Poland	Germany
The Netherlands	France	Poland	Germany
Belgium	Spain		Austria
Hungary			Czech
Italy		? ←	Estonia
Portugal		? ←	Latvia
United Kingdom		? ←	Lithuania
			Luxembourg
		? ←	Slovakia
			Slovenia

Figure 49 The Optimal Solution for Amgen's Centralized, European Structure

The figure above depicts the ELC in the Netherlands and the three warehouses in France, Germany and Poland. When the color of a specific country matches with a color of a country where a warehouse is located, the country is allocated to this warehouse. This is also shown in the table.

The cost advantages which can be obtained when the four warehouses are opened successive, assuming a 60% discount on the standard UPS price for domestic shipments and 80% discount on the standard price for international shipments and normal warehouse costs estimations, are given in figure 50.

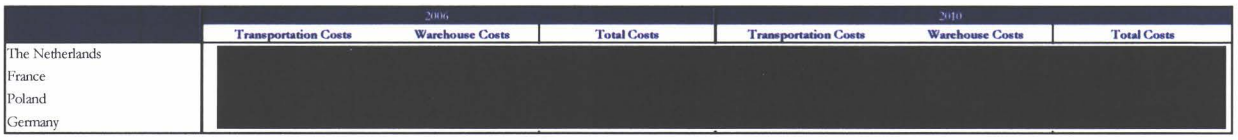


Figure 50 Costs Advantages of Open the Four Warehouses Successive

The results of the simulations are not illogical. France is one of the biggest market for the ELC and through having a local distribution center in France, many transportation cost advantages can be made. Therefore set up a warehouse in France is mainly because of the high volume and the huge number of shipments to the France retail pharmacists and hospitals. It should also be noted that it is important to eliminate French wholesalers to obtain the market of the retail pharmacies otherwise not enough transportation costs advantage can be made to make the France warehouse profitable and feasible. Another advantage to locate a warehouse in France is because of the neighboring country Spain, the third largest market. Hospitals are the only end-customers in Spain and the cheapest country to send an ISC that is large enough for a hospital order from abroad is France.

A distribution center in Poland is very attractive for several reasons. The first one is the very low domestic transport tariffs. Those tariffs are 50% lower than other domestic tariffs of other European countries. Therefore setting up a warehouse in this country ensures large savings on the costs of the shipments. The second reason is the fact that Poland is the sixth biggest market of the ELC; more than 224 thousand packs were shipped in 2005. The third reason is the cost of set up and running a warehouse in Poland. To locate and build a new warehouse in Poland is, compared to other EU countries, 12 percent cheaper. Furthermore the employee costs are only 24 percent of the employee cost in the Netherlands (see figure 57) and therefore the total warehouse costs per year are more than 50 percent less compared to other countries.

A warehouse in Germany is feasible if a discount is given on the domestic tariffs that are in line with the discount given on the international tariffs. If this is not the case, the break even point to set up a warehouse in Germany will be in the next few years, because more packs will be sold in Germany and the countries Germany will be distributing to. A note has to be made: The simulation program reveals that the countries Estonia, Lativa, Lithuania and Slovakia should be delivered by the German distribution center instead of the Polish one. However, common sense will say that it is easier and cheaper to distribute those countries out of Poland because of the geographical position. If the transportation costs are investigated it shows that the international shipment tariffs out of Poland are huge compared to the domestic shipment tariffs of Poland and the international shipment tariffs of Germany or other European countries. The expectation is that those costs will decrease whether it will be a possibility to deliver those countries from the distribution center in Poland. For this reason the four countries are colored both green as yellow and figure 49 shows an arrow with a question mark. As the demand over the next few years in Poland and in the other CEE countries increases, it becomes more and more attractive to locate a warehouse in Poland. This can be seen in the rank of Poland when the year 2006 will be compared to 2010 in appendix 17 and 18.

It should be emphasized the importance of price negotiations with UPS (or with another pan European freight carrier) for the shipment tariffs for the domestic markets of the four warehouses and for favorable international tariffs to the countries each distribution center deliver to. This is very important and large cost advantages can be obtained. This clearly can be seen in the next figure with different discounts on the domestic and international tariffs:

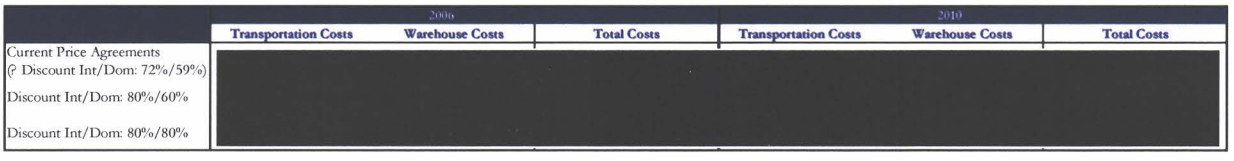


Figure 51 Impact of a Price Agreement with a Freight Carrier on the Total Costs (in Euros)

The total transportation costs and thereby the total costs depend greatly, after a lot of negotiations, which cannot be done now in this phase, on the price agreement made with those carriers. If good price agreements on transportation costs can be achieved, huge costs advantages can be made and millions of euros can be saved.

Additionally, the recommended distribution strategy is better suited to meet the increasing requirements of the future in terms of volume growth and increasing complexity of the supply chain. The ELC remains the primary warehouse, where the unlabeled products arrive from US and Puerto Rico and will be packaged and labeled country specific. Periodically, the three warehouses in Germany, France and Poland will be replenished by a cooled truck from the ELC. The lay-out and the organizations of the warehouses, which is already shortly mentioned in paragraph 8.2.3.2, will follow the functionalities in the ELC and the next areas will be needed (1) a cold store where most of the medicines will be stored (2) a warehouse to store the ISCs (which will be used to distribute the medicines to the customers) and (3) some space available to pick and pack orders for the end customers (hospitals & pharmacies). The distribution centers need to meet the GDP requirements and must fulfill minimum requirements regarding premises, installations and equipments, trained staff, ensure of continued supply etc.

Furthermore the recommended distribution strategy will provide significantly better risk mitigation. More Amgen's warehouses can reduce single point failures and ensure better supply to every patient, every time. Another reason to have an own managed and controlled supply chain are the improvements that can be achieved in terms of on time delivery, flexibility, the cold chain process and a decrease in error rates. The lead-time will not change and will be very similar as today, because the biggest international global freight carriers are offering special express services and guarantee a delivery before noon or nine o'clock next morning in the EU. Cut off times for order entry and transit times will be mostly unchanged.

Amgen demands far higher standards than normal in relation to processes, practice and installations. Those are superior than those of the LSPs and some wholesalers. Setting up Amgen owned warehouses reduce the number of LSPs and wholesalers and their part of distribution and improve in all likelihood the quality of service to the end-customers. However, an important point to make is if LSPs and wholesalers are removed out of Amgen's supply chain, supply end-customers who are delivered by those parties are maintained (especially to make the French warehouse profitable). The end customers behind the LSP are known within Amgen, so these customers can easily be reached but to reach the end customers of the wholesalers require more effort. As can be seen in appendix 9 several countries have a 'big' wholesaler channel. Participant of the local site affiliates of Amgen have to ensure to steer this process in the right direction. The ordering process is a point of attention. Pharmacies and hospitals have to change the ordering process. It is possible that special adjustments have to be made, because both parties are working with different order numbers. Portugal is already being delivered to directly from the Netherlands so this procedure can be examined to ascertain whether it can be applied successfully to other countries.

Further Research

In this section several point of interest will be named for further research. One of the most important points to investigate, and that is interesting for further research, is the attitude of the end customers behind the wholesaler towards Amgen's central European distribution structure. These pharmacists and hospitals are ordering several medicines from different manufacturers at only one wholesaler. If Amgen eliminates those wholesalers, a chance may exists that the end customer will switch brands because of the ease of ordering everything from one supplier. The readiness and willingness to stick to Amgen products should therefore be checked. Questions as how to exactly deal with this phenomenon, the transformation process of the ordering process, or whether the order handling process will be handled by an external call-center or be done in own control, like the shared service department at the ELC, have to be answered.

Furthermore the possibilities of using local freight carriers instead of a global freight carrier can be examined. However price is not the only main criteria but on time service, the reliability of the carrier and the possibilities of track and trace are important points as well before any collaboration is possible. On the other side, the more Amgen will work with local carriers, the fewer discounts can be achieved with the global carriers and a more diverse and complex network will be created.

Each country supplied by Amgen is different and this results in the fact that the packages and labels for each country are unique. When this is the case consolidating through only store inventory on a few locations would not give much cost advantage and the idea will be like shifting the stock from the ELC to another location. Amgen clusters countries in groups to reduce the different numbers of SKUs, which makes centralizing and consolidating more attractive. For Aranesp SureClick one cluster is for example Germany, the Netherlands, United Kingdom and Ireland (see appendix 19). However Germany has their own warehouse and therefore the same SKU is held on stock at two places which results in more total stock. Nevertheless this has a positive side because of risk mitigation. Also Portugal is delivered to by the ELC while Spain is delivered by the distribution center in France. For Aranesp SureClick Portugal and Spain is not a cluster but for other products it is and it will be interesting to find out the pros and cons to deliver for example Portugal from France instead of the ELC. It will be of interest to investigate in a further research the clusters for each product and how this will influence the store locations and the total stock holding costs. But, as been shown earlier in this report, the stock holding costs are only a minor part of the total distribution costs.

Due to a number of factors the biotech industry will grow enormously. These include the aging of the population, increasing access to emerging global markets and the ongoing developments in medical research. The bigger companies, like Amgen, will continue to grow through mergers and acquisitions activities and by managing the life cycles of their marketed products whilst simultaneously investing billions of dollars in R&D to keep up a steady flow of new, important drugs. The supply chain will be bigger, larger and more complex. To deal better with the increasing requirements of the future in terms of volume growth and the increase of complexity, to obtain more demand chain control and more flexibility and to be closer to the customer, Amgen needs to change their current supply chain to maintain their competitive position in the future.

Therefore we see with the new distribution strategy improvement opportunities for Amgen as a whole. For now, the solution provides good insight and enables Amgen to get a better understanding with the help of the simulation model to optimize their centralized supply chain within the scope as defined in this thesis. Nonetheless, I hope that in the near future the line of thought is extended and that, after the determination of the input parameters or through environmental factors, the model will be extended and be used again to verify and draw new conclusions…

11 References

Aikens, C.H. (1985). *Facility Location Models for Distribution Planning.* European Journal of Operational Research, Volume 22, Issue 3, p. 263-279.

Amgen (2004) – Annual Report

Amgen (2005) - *Dispensing Machines Business Case*, Breda 31 August 2005.

Accenture (2005) - *Analysis of Service Level Required Currently by Amgen's Clients*, Barcelona 17 June 2005.

Ballou, R.H. (1999). *Business Logistics Management.* Prentice-Hall Inc., New Jersey.

Bertrand, J.W.M., Wortmann, J.C., Wijngaard, J. (1998). *Productiebeheersing en Material Management.* Educatieve Partners Nederland BV, Houten. (Dutch)

Campbell, A.M., Savelsbergh, M.W.P. (2004). *Delivery Volume Optimization.* Transportation Science, Volume 38, Issue 2.

Christofides, N., Beasley, J.E. (1983). *Extensions to a Lagrangean Relaxation Approach for the Capacitated Warehouse Location Problem.* European Journal of Operational Research Volume 12, p 19–28.

Christopher, M. (2004). *Logistics and Supply Chain Management*, 2nd ed. Pearson Education Limited, Harlow.

Cornuejols, G., Nemhauser, G.L., Wolsey, L.A. (1990). *'The Uncapacitated Facility Location Problem', in Discrete Location Theory (P.B. Mirchandani and R.L. Francis, eds).* Wiley, New York, Chapter 3, p. 119-171.

Daskin, M.S. (1995). *Network and Discrete Location: Models Algorithms and Applications.* Wiley, New York.

De Kok, A.G., Visschers, J.W.C.H. (1999). *Analysis of Assembly Systems with Service Level Constraints.* International Journal of Production Economics, Volume 59, Issue 1-3, p. 313-325.

De Kok, A.G. (2000). *Analysis of One Product / One Location Inventory Control Models.* Handout Eindhoven University of Technology.

De Kok, A.G., Fransoo, J.C. (2003*). Handbook Operations Research. Supply Chain Management: Design, Coordination and Operation, Chapter 12.* Handout Eindhoven University of Technology.

Diks, E B, de Kok, A G. (1998). *Optimal Control of a Divergent Multi-Echelon Inventory System.* European Journal of Operational Research, Volume 111, Issue 1, p. 75-98.

Diks, E B, de Kok, A G. (1999). *Computational Results for the Control of a Divergent N-Echelon Inventory System.* International Journal of Production Economics, Volume 59, Issue 1-3, p. 327-337.

Erlenkotter, D. (1978). *A dual-based Procedure for Uncapacitated Facility Location.* Operations Research, Volume 26, p. 992–1009.

Feldman, E., Lehrer, F.A., Ray, T.L. (1966). *Warehouse Location under Continuous Economies of Scale.* Management Science, Volume 12, Issue 9, p. 670-684.

Hakimi, S.L. (1964). *Optimum Locations of Switching Centers and the Absolute Centers and Medians of a Graph.* Operations Research, Volume 12, p 450-459.

Heikkilä, J. (2002). *From Supply to Demand Chain Management: Efficiency and Customer Satisfaction.* Journal of Operations Management, Volume 20, Issue 6, p. 667-804.

Hillier, F.S., Lieberman, G.J. (2001). *Introduction to Operations Research.* McGraw-Hill, Singapore, Seventh edition.

Jacobsen, S.K. (1983). *Heuristics for the Capacitated Plant Location Model.* European Journal of Operational Research, Volume 12, Issue 3, p.253-261.

Kempen, P.M., Keizer, J.A. (2000). *Advieskunde voor Praktijkstages.* Wolters-Noordhoff, Groningen. (Dutch)

Khumawala, B.M. (1972). *An Efficient Branch and Bound Algorithm for the Warehouse Location Problem.* Management Science, Volume 18, Issue 12, p 718.

Klose, A., Drexl, A. (2005). *Facility Location Models for Distribution System Design.* European Journal of Operational Research, Volume 162, p 4-29.

Kuehn, A. A., Hamburger, M. J. (1963). *A Heuristic Program for Locating Warehouses.* Management Science Volume 9, Issue 4, p 643

Miebach Logistics – *Presentation Phase I: Intermediate Results – Assessment and Strategic Outlook – Summary*, Breda & Thousand Oaks, January 19th 2006.

Mirchandani, P.B., Francis, R.L. (1991). Discrete Location Theory. Wiley, New York.

Montgomery, D.C., Runger, G.C. (1999). *Applied Statistics and Probability for Engineers.* 2nd ed. John Wiley & Sons.

Owen, S.H., Daskin, M.S. (1998). *Strategic Facility Location: A Review.* European Journal of Operational Research, Volume 111, p 423-447.

Porter, M. (1980). *Competitive Strategy.* The Free Press, New York.

Rosling, K. (1989). *Optimal Inventory Policies for Assembly Systems Under Random Demands.* Operations Research, Volume 37, p 565-579.

Rouwenhorst, B.,Reuter,B., Stockrahm, V., Houtum, G.J. van, Mantel, R.J., Zijm, W.H.M. (2000). *Warehouse Design and Control: Framework and Literature Review.* European Journal of Operational Research, Volume 122, p. 515-533

Sridharan, R. (1995). *The Capacitated Plant Location Problem.* European Journal of Operational Research, Volume 87, Issue 2, p 203–213.

Silver, E.A., Pyke, D.F., Peterson, R. (1998). *Inventory Management and Production Planning and Scheduling.* John Wiley & Sons, New York.

Spitter, J. M., Hurkens, C. A. J., Kok, A. G. de, Lenstra, J. K., Negenman, E. G. (2005). *Linear Programming Models with Planned Lead Times for Supply Chain Operations Planning.* European Journal of Operational Research, Volume 163, Issue 3, p. 706.

Tompkins Associates International (2005). *The warehouse manager's guide to effective order picking.* Publ. of Tompkins Associates International, Cambridge.

Verschuren, P. J. M., Doorewaard, H. (2000). *Het Ontwerpen van een Onderzoek.* Lemma, Utrecht.

12 Abbreviations

BIP = Binary Integer Problem

CFLP = Capacitated Facility Location Problem

CODP = Customer Order Decoupling Point

DC = Distribution Center

ELC = European Logistics Center

EMEA = The European Agency for the Evaluation of Medicinal Products

EU = European Union

FDA = U.S. Food & Drug Administration

GDP = Good Distribution Practice

GMP = Good Manufacturing Practice

GSF = Gross Square Feet

IP = Integer Problem

ISC = Insulated Shipping Container

LE = Latest Estimate

LP = Linear Programming

LRP = Long Range Planning

LSP = Logistic Service Provider

RFID = Radio Frequency IDentification

SCOP = Supply Chain Operation Planning

SD = Standard Deviation

SKU = Stock-keeping unit

SS = Safety Stock

SSFL = Single-Source Facility Location

UFLP = Uncapacitated Facility Location Problem

VC = Variation Coefficient

VMI = Vendor-Managed Inventory