New Product Introduction in the Pharmaceutical Industry

Hansen, Klaus Reinholdt Nyhuus; Hvam, Lars; Grunow, Martin; Akkerman, Renzo; Gani, Rafiqul

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by Klaus Reinholdt Nyhuus Hansen

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Klaus Reinholdt Nyhuus Hansen
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Technical University of Denmark
DTU Management Engineering
Produktionstorvet 424
DK-2800 Kongens Lyngby
Denmark

Tel: + 45 4525 4800
E-mail: phd@man.dtu.dk
Printer: Schultz Grafisk A/S

Supervisors:

Professor Lars Hvam
Operations Management, Production and Service Management
DTU Management Engineering
Technical University of Denmark
Kongens Lyngby, Denmark

Professor Martin Grunow
Production and Supply Chain Management
TUM School of Management
Technische Universität München
Munich, Germany

Professor Renzo Akkerman
Operations Management and Technology
TUM School of Management
Technische Universität München
Munich, Germany

Professor Rafiqul Gani
Computer Aided Process Engineering Centre
Department of Chemical and Biochemical Engineering
Technical University of Denmark
Kongens Lyngby, Denmark

Assessment Committee:

Associate Professor Peter Jacobsen
Operations Management, Production and Service Management
DTU Management Engineering
Technical University of Denmark
Kongens Lyngby, Denmark

Professor Jan Olhager
Department of Industrial Management and Logistics
Faculty of Engineering
Lund University
Lund, Sweden

Senior Research Associate József Váncza
Deputy Head of the Research Laboratory of Engineering and Management Intelligence
Computer and Automation Research Institute
Hungarian Academy of Sciences
Budapest, Hungary

Preface

This dissertation represents research performed by the author from September 2009 to July 2013 and has been submitted to DTU Management Engineering, Technical University of Denmark in fulfillment of the requirements for achieving a PhD degree. The research has been carried out at DTU Management Engineering and at TU München in conjunction with a visiting scholar position there. The content mainly consists of the latest versions of the scientific publications produced during the PhD study, which have all been submitted for review or published. The project has been supervised by Professor Lars Hvam, Professor Martin Grunow, Professor Renzo Akkerman and Professor Rafiqul Gani. The project has been financed by DTU Management Engineering as part of their research program.

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Though I am proud to have produced the work presented here by myself, it would not have been possible without having the support of numerous people. People, who believed in me and showed me the way when things seemed hopeless.

First and foremost, I owe a huge thanks to Professor Martin Grunow, who has acted as my main supervisor. He helped me formulate the project and kept me on my track, when I was straying. I have the utmost professional respect for him and I am time and again impressed with his keen perception, to-the-point comments and sharp questions in such a wide range of topics, that I find myself left in awe.

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It was a pleasure to be invited into the CAPEC group, which was only possible due to the kindness of Professor Rafiqul Gani, who also acted as co-supervisor. I have enjoyed taking part in all the events I have participated in and I have learned a lot both in relation to my project and about process system engineering. I have only the best memories of the people from CAPEC.

Two of the most important people for doing a Ph.D. have for me been Christina and Monika, who have helped me with all the administrative work; often more than required of them. Their help has been invaluable in navigating the rules and regulations of DTU and TUM.

There are so many colleagues, that I have in some way or another worked with at both DTU and TUM. Some have provided social relief while others have contributed to my project. A huge appreciation goes out to especially Ole, Marie, Lykke, Thordis, Pelle, Andreas, Peter and Lars from DTU Management Engineering and Daniel, Sina, Rado, Philip, Bryndis and Verena from TUM School of Management and especially Poorya Farahani, who I moved from DTU to TUM with.

All my dear friends in Herning, Copenhagen and München who I have been spending time with, talking to, joking with and playing floorball with. You have given me a respite by allowing me the chance to think about other things than my thesis.

My full appreciation I give to my parents, whose comforting phone calls have always supported me more than you know. Having your love means I never feel truly alone; not even when sitting alone and working late at night.

Finally to my love, Elli, who has supported me through the tough final part of my thesis. Having you by my side means the world to me and I look forward to spending much more time with you. I am so glad for having met you.

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Abstract

Due to the limited time of the monopoly provided by patent protection that is used for recouping the R&D investment, pharmaceutical companies focus on keeping time-to-market for new products as short as possible. This process is however getting more uncertain, as the outcome of clinical trials is unknown and negotiations with authorities have become harder, making market introduction more difficult. This dissertation treats the new product introduction process in the pharmaceutical industry from an operations perspective. The overarching aim of this dissertation is to improve the planning methodology in this critical process. In an empirical study, the process is first analyzed in detail, leading to the identification of several gaps in the industry's current planning approaches. To support a set of key operational decisions towards market launch, a model is subsequently developed, considering uncertainty and several important industry characteristics. The model is used to gain several insights on the use of risk packaging and on keeping time-to-market short. As capacity in secondary pharmaceutical production is critical for product availability, a capacity planning model for a new drug delivery system is also developed. It captures the ramp-up phase in a better way, while considering inventory build up, plant validation and limited shelf life. The performance of several ramp-up functions is tested and insights into ramp-up management are presented. The dissertation is concluded with showing the new proposed planning structure, concluding in the preceding chapters and outlining future research possibilities.

Resumé

Grundet den begrænsede levetid på det monopol som patentbeskyttelsen giver og som benyttes til at indhente investeringen i forskning og udvikling, fokuserer farmaceutiske virksomheder på at holde time-to-market nede for nye produkter. Hele denne proces er dog blevet mere usikker grundet det ukendte udfald af kliniske tests og forhandlinger med myndigheder, hvilket besværliggør markedslanceringen. Denne afhandling beskæftiger sig med introduktionen af nye produkter i den farmaceutiske industri set fra et produktionsstyringsperspektiv. Det overordenede mål er at forbedre planlægningsmetodikken i denne kritiske proces. Processen er analyseret i detaljer gennem et empirisk studie som fører til identifikationen af flere huller i industriens nuværende planlægningsmetoder. Til understøttelse af en række centrale operationelle beslutninger frem mod markedslanceringen, udvikles en model, som betragter usikkerhed og flere af industriens vigtige karakteristika. Modellen bruges til at opnå indsigt i brugen af risk packaging og på at holde time-to-market nede. Idet tilstrækkelig kapacitet i sekundær farmaceutisk produktion er en forudsætning for produkt tilgængelighed, udvikles også en kapacitetsplanlægningsmodel for et nyt medicineringssystem som bedre fanger ramp up af den ny produktionsproces, imens opbygningen af lagre, validering af fabrikker og begrænset holdbarhed betragtes. Flere forskellige ramp-up funktioner testes og indsigt omkring ramp-up ledelse præsenteres. Afhandlingen konkluderes med at vise den ny foreslået planlægningsstruktur, sammentrække resultaterne for de foregående kapitler og opridse fremtidig forskningsmuligheder.

Chapter 1: Introduction

A pharmaceutical drug is defined by the US authorities as *"articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"* (U.S. Food and Drug Administration, 2010a). Most drugs are developed and produced by pharmaceutical companies and the commercialization of pharmaceutical drugs has in the last decade grown into a large industry. In the EU, the industry made up 3.5 % of all value added in 2009, while it made up 17 % of industrial R&D investments (cf. Eurostat via EFPIA (2010b)). Due to the high value of pharmaceutical drugs, the industry produces the highest added value per employee. At the same time, annual R&D spending on new drugs represent 2.76 % and 1.90 % of GDP for the US and EU, respectively, which are also the two largest markets (EFPIA, 2010b). It is vital for pharmaceutical companies to continually develop and launch new drugs as each drug has a limited life cycle.

In this thesis, the new product introduction process is analyzed from an operations management and supply chain management perspective. In this first chapter, the industry structure and new product introduction process are outlined, before challenges in managing operations during the new product introduction process are presented, and several research questions formulated.

1.1. Industry structure

Despite a series of acquisitions in the past years, the number of companies in the industry is growing as increased partnering and outsourcing also enable new companies to partake in the development and manufacturing of pharmaceutical drugs (Hunt et al., 2011). Some of the principle organizations in the industry and their interrelations are illustrated in Figure 1.1. The principal stages of pharmaceutical production are also illustrated. In the following, these organizations and processes are briefly described.

Pharmaceutical corporations

At the center of the industry are the large pharmaceutical corporations, who develop and manufacture pharmaceutical drugs. Developing a new drug is a long, expensive and uncertain process. Most drugs fail to ever reach the market as they do not perform as expected or show unfortunate side-effects. For preserving commercial continuity and to diversify the risk of the R&D projects, companies always have several different products in the pipeline in different stages of maturity. Managing these pipelines is an important strategic issue for the companies and pipeline planning has been developed to support companies in how to invest in different R&D projects.

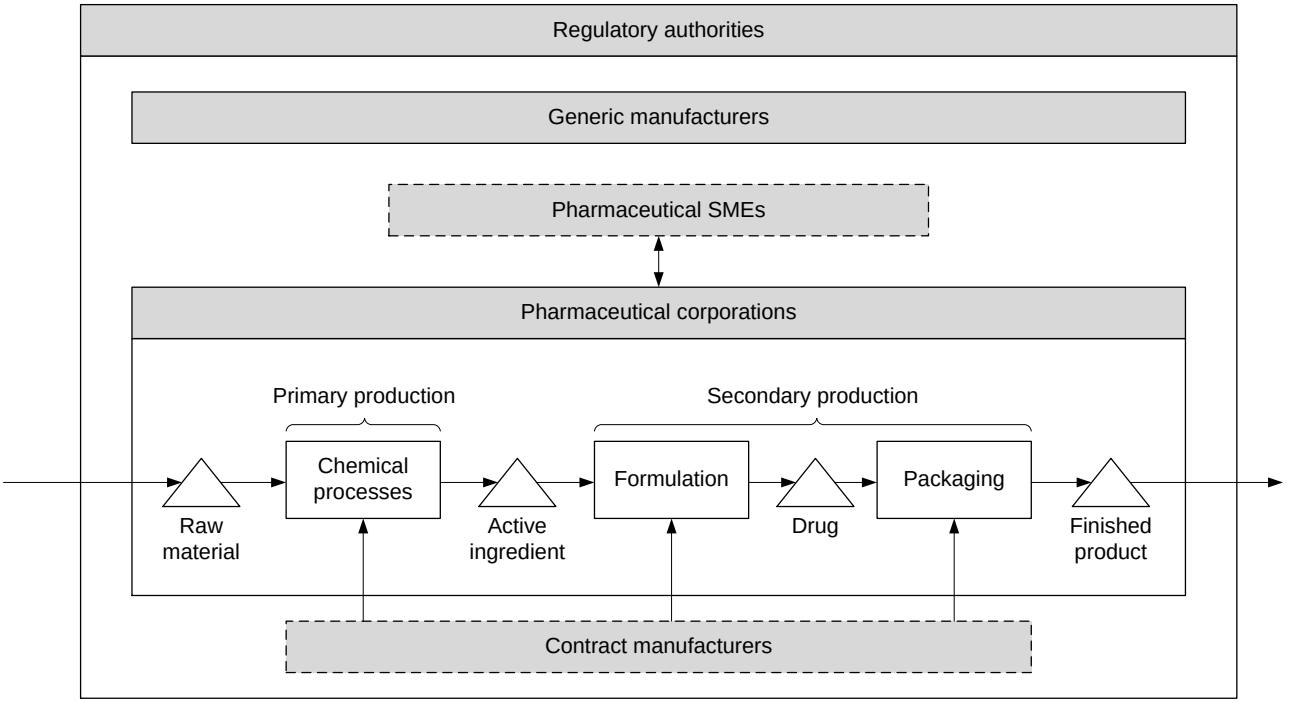

Figure 1.1: Overview over the pharmaceutical industry.

The production of pharmaceutical drugs, as described in Bennett and Cole (2003), can be divided into two stages; primary and secondary production. Between the stages, inventories are found.

Primary production refers to the production of the active pharmaceutical ingredient [API]. Raw material is put through a series of chemical processes where liquids are pumped between different reactors, transforming the liquids into the desired compounds. Secondary production consists of turning the API into a consumable drug in e.g. vial or pill form. Sometimes more complex drug delivery systems are used such as special syringes, inhalers or other devices. After this step the drug is packaged and labeled for the specific market where it is intended to be sold.

Production is subject to many strict requirements described in a series of guidelines called Good Manufacturing Practices [GMP] issued by the Food and Drug Administration [FDA], (U.S. Food and Drug Administration, 2010b). These requirements safeguard patients by putting high demands on quality and cleaning to avoid (cross) contamination in production. This can however also lead to setups in the order of weeks. To reduce the number of setups, long campaigns are used in which several batches of each product are produced in succession in primary production. It is not uncommon for an entire year's demand to be produced in one campaign (Grunow et al., 2003). With many different processing steps integrated in large networks, that produce many different products, production planning is very difficult and plans are not easy to change. Secondary production has a shorter lead time than primary production. API production is usually managed independently of secondary production due to the high complexity. API inventory is used to buffer for any demand

variations and act as a natural decoupling point. Secondary production is demand driven, whereas primary production is strictly make-to-stock.

Regulatory authorities

Governmental bodies regulate the industry within one or more countries and hence govern all companies as seen in Figure 1.1. The most influential regulatory body is the FDA in the US, but also the European Medicines Agency [EMA] is gaining more influence due to the centralization of regulatory tasks in the European Union. These authorities put up guidelines and regulations for how pharmaceutical companies should behave. Most noteworthy are the prescribed clinical trials, which require companies to test their drugs on a sizable population in a controlled manner such that the efficacy of the drug can be proven and any possible side effects discovered.

To protect the public, the authorities also issue the GMP guidelines that govern how production should be handled in a clean, safe and controlled manner. To gain access to a market, the local authorities have to validate production before a drug can be sold in that market. Afterwards they will regularly perform inspections of production sites to ensure the guidelines are still followed. For every market, a possibly different authority gives the final market authorization after reimbursement levels, maximum price etc. have been negotiated.

Generic manufacturers

When the patent on a drug expires, generic manufacturers are quickly ready with cheap copies, which drive the price down. Hereafter the drug can be considered a commodity. Drugs that go off-patent are often transferred to the big pharmaceutical companies' own generic divisions, so the pharmaceutical division can focus on new drugs. Generic manufacturers launch a high number of drugs every year, and much of the methodology that we develop here is also applicable for them.

Pharmaceutical SMEs

Referring to small and medium sized enterprises [SME], this group of companies are normally only capable of either performing services for the large multi-national pharmaceutical companies such as offering e.g. pilot plant capacity for prototype batches or perform the first steps of drug development. The price of running the clinical trials are often so high that these companies have to partner up, when they have a drug ready for later stages of the clinical trials. Generally, different levels of partnering, outsourcing, mergers and acquisitions are found in the industry as all companies constantly try to balance their R&D pipeline of new potential drugs.

Contract manufacturers

This group of companies run production sites and sells their capacity to the pharmaceutical companies for a premium. This option of outsourcing some volumes or even entire processes, gives the pharmaceutical companies the flexibility they otherwise lack in their rigid production systems. A comprehensive treatment of the interactions between these companies and coordination of their operations is presented in Boulaksil (2010).

1.2. New product introduction process

Figure 1.2: Overview of the new product introduction process (inspired by (FDA, 2004).

The new product introduction process is the process stretching from first discovery to market launch and covers developing, testing and manufacturing a new product (cf. Figure 1.2). After first discovery, a patent is filed. Hereafter follow pre-clinical studies to test toxicity of the drug, before it is put into a series of human trials called the clinical trials. These tests should prove whether the drug works as intended without too many adverse side-effects. If so, the drug will be approved and can be marketed with a monopoly provided by the patent protection. If not, the drug will never reach the market and the entire investment in trials and R&D is lost. A more thorough review of this process and all the different tasks herein will be presented in chapter 2. One set of clinical trials is enough for applying for approval with authorities in several countries, given that the trials comply with the standards set by each authority. Due to the cost and length of the trials, companies seek to do only one set to cover all markets.

Another regulatory task, which is often performed by different authorities, is giving the final market authorization after concluding the reimbursement negotiations with the companies. In these negotiations, maximum price and reimbursement level are settled. Claims used in the labeling of the drug to describe e.g. side-effects and target patient groups are also discussed. For too strong claims, the authorities can withhold market authorization. The reimbursement negotiations are conducted in very different ways in different countries (Garattini et al., 2007). Especially the procedures in the EU are long and troublesome (Cohen et al., 2007). Prices are also set differently, based on e.g. comparisons of price and reimbursement levels in other countries, production and R&D cost, or results from cost-benefit analyses. The negotiations are important as the reimbursement often covers most of the patients' expenses for the treatment and because many countries only allow drugs

with such an authorization to be prescribed by general practitioners (Cook, 2006). Getting the market authorization is hence a prerequisite for gaining any demand in that market.

1.2.1. Trends and challenges

For some years, the new R&D projects in the pharmaceutical industry have been getting increasingly expensive due to ever harder requirements set by the regulatory authorities for proving better efficacy than existing treatments (DiMasi and Grabowski, 2007). They also take longer and are less likely to return a sellable drug afterwards (DiMasi, 2002). OF 10,000 compounds screened, 250 enter pre-clinical trials and 1 drug eventually reaches the market (PhRMA, 2012). Thus, R&D pipelines are no longer thriving with an abundance of potential blockbuster drugs (Hunt et al., 2011). As generic manufacturers launch cheap copies after patent expiration, companies have to be good at developing their drugs fast, if they want to use the exclusivity of the patent protection for recouping their investment and turn a profit. Time-to-Market [TTM] is therefore a key measure for them.

Getting a market authorization for a new drug is also getting harder. According to EFPIA (2010a), it takes more than 100 days from drug approval to the drug is available to patients in most European countries. With the latest financial crisis and ensuing pressure on national budgets, the payers of the medical treatments have become increasingly price conscious (Hunt et al., 2011). This has and will lead to even harder reimbursement negotiations as the responsible payers attempt to push for lower prices. A process which used to be automated (particularly in Germany and the UK) is hence now getting longer, more demanding and above all more uncertain. Pharmaceutical companies are forced to spend an increasing amount of time and resources on these negotiations as seen by the creation of market access departments in many companies (Von Arx and Bernard, 2009). Due to the new EMA procedure with mutual recognition, the reimbursement negotiations are the only place where national authorities can influence which drugs enter their market.

1.3. Operations during new product introduction in the pharmaceutical industry

With a time-limited monopoly to recoup the investment, the price of most novel drugs needs to be much higher than the production cost. This creates a lot of pressure on the supply chain operations, which has to deliver the product no matter what (Pisano, 1996). With API inventory working as a decoupling point, balancing supply and demand is strictly a matter for secondary production. With a divergent product flow and limited shelf life, production up front of large volumes is not desirable. Figure 1.3 shows the main operations carried out towards market launch of a new drug. The new product strategy - partly dictated by the approval and market authorization process - describes the sequence in which markets are entered. Markets are usually chosen based on their profitability and size. Due to their value and size, EU, US and Japan are entered first. For the rest of the world, launch comes at a later stage, when and if it is profitable. Aggregated demand expectations are used for capacity planning to generate a capacity promise for the tactical level. Capacity planning for

secondary production consists of finding or expanding capacity in a global network while considering several industry characteristics such as validation and limited shelf life.

Demand during market launch varies a lot due to slow product diffusion (Cook, 2006) and time-phased market launches. Right after the final market authorization has been given, companies rush to fill the downstream supply chain, i.e. hospitals, pharmacies and wholesalers, which requires a significant volume of finished product at market launch. Demand planning updated with results from the market authorization forms the basis for material requirements planning [MRP]. In addition to production plans, MRP also finds the volumes to procure from suppliers and send to outsource to contract manufacturers. On the operational level, production and demand fulfillment resemble similar processes as found in other industries.

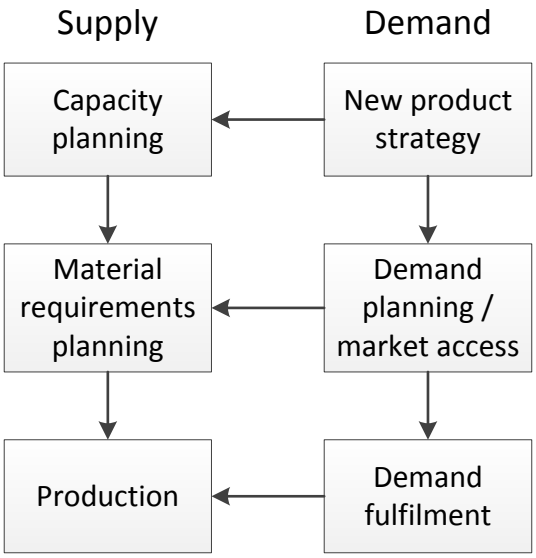

Figure 1.3: Overview of the operations leading up to and during the market launch in the pharmaceutical industry.

Traditionally, companies have focused on following regulatory guidelines, while insuring ample supply at the lowest cost towards the end of the new product introduction process (McKinsey, 2011). With more uncertainty towards final market launch, coordinating supply chain operations in the later stages of the new product introduction process are becoming increasingly challenging. This especially affects the decisions which have to be made further in advance. Due to the long and rigid production process, API volumes have to be planned well before market launch. The capacity to reserve at suppliers and contract manufacturers is also needed.

To ensure product availability, secondary production must be ramped-up before product launch. Ramp-up effects are especially evident if a new complex drug delivery system is introduced. A new product requires new processes that first have to be learned by workers, which reduces the effective

capacity leading up to market launch. With highly varying demand during market launch and underutilized production lines, managers do not know the effective capacity of their production lines. Only by capturing these ramp-up effects can capacity planning ensure product availability without excessive investments in capacity.

The connection between new product introduction and supply chain management is simply not covered by the existing literature (Narayana et al., In press). Instead completely new methodologies are needed to help managers plan operations during the final stage of new product introduction.

1.4. Research objectives

The overall aim of this thesis is to provide a planning methodology for planning operations in the new product introduction process in the pharmaceutical industry, which would keep TTM, risk and operating costs low and help companies retain profitability. This planning methodology will be developed based on existing operation management and planning methodology combined with industry-specific characteristics. A thorough analysis of the new product introduction is offered to find the challenges of the industry. Following the analysis, the scope of the thesis is focused on operations in the last part of the new product introduction process leading up to market launch. Here there seems to be insufficient literature addressing coordinating and planning operations leading up to market launch which also considers highly varying demand.

1.4.1. Research questions

Despite having the entire pharmaceutical industry focusing on TTM and the new product introduction process, it is still not clear what problems the industry is faced with, which have not been addressed yet, or to what extend the existing literature provides any solutions. A thorough explorative study and an overview of the current state-of-the-art are hence required to identify the challenges in the new product introduction process. All significant characteristics of the tasks in the new product introduction process, their mutual relation must be identified to highlight the challenges in coordinating these tasks. The investigation of the literature should identify how these problems have been addressed so far and uncover potential research gaps. This motivates the first research question.

RQ1: What are the challenges facing the pharmaceutical industry during the new product introduction process in reducing time-to-market?

Due to the current regulatory trends, more uncertainty of when and under which conditions companies can market their new pharmaceutical drugs is making operational planning of the market

launch more difficult. Demand for a new product varies significantly after launch due to product diffusion and filling of the downstream supply chain. With several time-phased market launches expected, it is difficult to identify the required volumes of finished product. However, several decisions must be made in preparation of the market launch. A certain volume of API must be produced, packaging material bought, and capacity reserved at contract manufacturers. The need for a methodology supporting launch preparation decisions leads to the second research question.

RQ2: How can pharmaceutical companies better plan operations in preparation of market launches while considering some of the unique uncertainties present around the launch?

Due to the high profit margins on novel pharmaceutical drugs under patent protection, production managers must deliver sufficient quantities of the product at market launch. With shorter construction time of new production lines, capacity planning of secondary pharmaceutical production can be conducted after the outcome of the clinical trials is known. As secondary pharmaceutical production exhibits significant ramp-up effects especially for more complex drug delivery systems, capacity planning is no longer trivial. Slow demand diffusion, time-phased market launches and the production of small volumes for validation well before market launch leaves production lines underutilized at times. As the ramp up of effective capacity is a result of the experience gained from producing a new product, traditional time-dependent ramp-up functions causes an overestimation of the effective capacity. Additionally, unique to secondary pharmaceutical production, several technical requirements such as process validation and limited shelf life must be considered, such that the market launches are not delayed due to capacity limitations. This challenge is outlined in the third research question.

RQ3: How should pharmaceutical companies plan secondary production capacity to reflect ramp up of effective capacity on underutilized production lines such that product availability at market launch is ensured?

By answering these research questions successively in each of the three publications collected in this thesis, the foundation for a planning methodology to support decision making in pharmaceutical supply chains during the late phase of the new product introduction process will be laid.

1.4.2. Thesis outline

To answer the first research question, an empirical study is conducted to find the current challenges in new product introduction. This is done through a literature review, an extensive case study of one company, and several validating interviews with other companies to confirm the findings. From the empirical study, a project network representation and a precedence relationship graph of the central tasks in the new product introduction process are found. From both the literature review and the interviews with managers, insights into the key unaddressed challenges facing the industry are found. Two key observations form the basis for the research in the remainder of the thesis. The results of this study can be found in chapter 2.

Coordination of operations in preparation of new market launches is challenging considering the many uncertainties associated with market launch of a new pharmaceutical drug. In chapter 3, we investigate how to support launch preparation decisions by proposing a model that captures all stages of secondary pharmaceutical production. Uncertainty is treated via two-stage stochastic programming, since the problem structure can be used to reduce the problem size, eliminating the need for a multi-stage model. The model is demonstrated through a case study to support the market launch decisions. Insights on TTM and risk packaging levels are found from comparison of several different supply chain configurations and operations policies.

A method for modeling ramp up of effective capacity on underutilized production lines is developed in chapter 4 and demonstrated for capacity planning of secondary pharmaceutical production. To ensure product availability, a methodology for when to install and ramp up new production lines is developed. With large demand variations during product launch, production lines might not be fully utilized. Ramp up is instead captured more accurately by linking effective capacity to cumulative production volume. Furthermore, technical restrictions such as validation of production for the individual markets and limited shelf life are considered. We compare our volume-dependent approach to traditional time-dependent ramp-up functions. Finally, we develop insights into ramp-up management by comparing different ramp-up curves and the length of ramp ups.

In chapter 5, conclusions for the entire dissertation are gathered and further research areas are identified.

1.4.3. Included publications

The following chapters are all individual publications that are published or under review. They can each be read separate, which may cause some overlap. Combined, they provide a methodology for supply chain planning in the last phase of new product introduction for the pharmaceutical industry. The chapters have been published or submitted as:

Chapter 2: Hansen, K. R. N., Grunow, M. (2010). *Challenges in shortening new product introduction in the pharmaceutical industry.* Proceedings of the 17th International Annual EurOMA Conference, 6-9 June 2010.

Chapter 3: Hansen, K. R. N., Grunow, M. (2013a). *Planning operations before market launch for balancing time-to-market and risks in pharmaceutical supply chains*, submitted for publication in International Journal of Production Economics

Chapter 4: Hansen, K. R. N., Grunow, M. (2013b). *Modelling ramp up in the context of secondary pharmaceutical production*, submitted for publication in International Journal of Production Research

Chapter 2: Challenges in the new product introduction process in pharmaceutical industry

This chapter is an extension of the article published as:

Hansen, K. R. N., Grunow, M. (2010). *Challenges in shortening new product introduction in the pharmaceutical industry.* Proceedings of the 17th International Annual EurOMA Conference, 6-9 June 2010.

Abstract

A patent is the only protection the drug developing pharmaceutical companies have against more cost efficient manufacturers of generic drugs. As the drug's lifecycle effectively end with the expiration of the patent, drug developing companies are forced to utilize the effective protection of the patent by focusing on shortening development time of new products measured as Time-to-Market. But due to the uncertainty of drug approval caused by the negotiations with the regulatory authorities, investment in initiatives for reducing Time-to-Market should also consider the risk of the drug being rejected or the approval being delayed. In this paper the process of introducing a new product in the pharmaceutical industry is considered and the trade-offs which both the industry and the scientific community have to address in the future are identified. This is done through a case study, which identifies the tasks involved in the new product introduction process and analyzes their interdependence. The current state-of-the-art in the scientific literature is reviewed and a series of observations from the case study are made. This results in an identification of the major focus areas for reducing Time-to-Market.

2.1. Introduction

The pharmaceutical industry develops and produces drugs for alleviating illnesses. The most significant activities in the industry consist of drug development, production of the active pharmaceutical ingredient called primary production and production of the drug distribution system, e.g. vials or pills called secondary production. Companies in the industry can perform any number of these activities in different organisational constellations. Lately, increasingly more elaborate collaborations and partnerships have emerged. Looking aside from the plethora of small companies, which are not capable of developing and manufacturing their own products, the industry can be divided into two groups of companies; drug developing companies and manufacturers of generic off-patent drugs. In this paper attention is given to the large companies developing and manufacturing novel pharmaceutical drugs.

Developing and launching a new drug cost a significant amount time and money, since new drugs have to go through series of clinical trials prescribed by regulatory authorities. These trials consist of testing the drug on a large number of patients and monitoring their reaction to the drug, while using other patients given a placebo as a reference group. The trials should prove not only the efficacy of the drug, but also find possible side effects and the pharmacokinetic properties of the drug etc. Each country has its own authority, which need to approve the drug. Best known is the FDA in the US. In Europe there are three ways of getting an approval. Either the authorisation is coordinated by the EMA, which forces approvals in one member country to apply in another. Alternatively, the company can try to get the drug approved in one country and thereafter use mutual recognition for getting the approval in other countries or the company can just get it approved in each individual country (Davis, 2003). Common for all authorities in all countries is, that they need to approve the drug before it can be sold in the respective countries. Depending on the results of the clinical trials they may approve the drug, reject it or require more trials or other changes thereby delaying the launch of the product.

The development of a new drug requires significant capital investments, has a high risk of failure and takes many years to complete. According to DiMasi (2002), the average cost is 802 million US$ for developing a new drug, which has a 21.9 % chance of getting through the process and takes 11.9 years to develop. The price has since this study surpassed one billion US$. Hence, it is most often large pharmaceutical companies or groups of smaller companies who enter this process. The risk is worth running, since the patent protection of the drug offers a time-limited market monopoly. Patents last for 20 years and are normally filed after the discovery of the drug. As 11.9 years are spent on developing it, only 8 years of effective market monopoly are left. When the patent expires cheaper generic substitutes are readily available and sales suffer as a consequence. Getting the new drug into the market sooner thereby making better use of the patent protection is the best way for the developing companies to increase the total lifecycle revenue of a drug. Therefore pharmaceutical companies are focusing their efforts on reducing the Time-to-Market of their new drugs.

In the next section the research questions are outlined followed by a description of the research methodology. A case study carried out in a drug developing company is described, which is used to analyse the activities involved in the new product introduction process. This results in a project network, which shows the structure of the process. Afterwards the literature and its relation to new product introduction process are described and finally a series of observations from the industry are presented, which could inspire future research.

2.2. Research question and methodology

To answer the first research question, RQ1, an overview of the new product introduction process as it is perceived by practioneers and treated by researchers, is needed. This should also lead to observations and further research. Hence, the first research question is split into the following subquestions.

Research Question 1a [RQ1a]:

What major tasks are involved in the new product introduction process in the pharmaceutical industry and how are they interrelated?

The aim is to define a generic set of tasks including precedence relationships for identification of the critical activities. This identification is done on the basis of a case study plus interviews from several other companies to check the validity of the case study. The next step is to consider what previous work has already been reported in the scientific literature.

Research Question 1b [RQ1b]:

How does the scientific literature cover the challenges in new product introduction process for the pharmaceutical industry?

The central question, which remains to be answered relates to how the TTM can be improved and which processes to focus on. During the interviews with managers, a series of observations were made, as to which challenges remain to be addressed for the benefit of practioneers and scientists alike.

Research Question 1c [RQ1c]:

Which tasks have to be addressed to reduce Time-to-Market for the entire new product introduction process?

2.2.1. Sample selection

The main data input for this article comes from a series of interviews done with managers from the industry. Due to the large size of pharmaceutical companies and number of people involved in the new product introduction process, managers from a variety of functions such as R&D, Production, Supply Chain functions, Regulatory Affairs and Marketing have been interviewed to obtain a complete picture of the process. Only from one company, the case study company, have all managers in all these positions been interviewed. This case company forms the centre, but as stated in Eisenhardt (1989), more cases are needed to prove generality and validity. This has been achieved through control interviews for all management functions at 8 other companies.

The involved companies are all located in the greater Copenhagen and Malmo area in Zealand, Denmark and South Sweden. This area is known as Medicon Valley for its high density of pharmaceutical and biotech companies. These companies were chosen in part due to their geographical location close to the university and in part for their willingness to participate in the interviews.

2.2.2. Interview protocol

As the nature of this project is exploratory, semi-structured interview were chosen. In this interview form, a structured list of questions is prepared in advance. But during the interview the interviewer can skip some questions and go in depth with others, depending on how the interview evolves. This is suitable as it helps keeping track of the interview, while allowing the interviewer to explore interesting new statements offered by the interviewee (Bakeman and Gottman, 1997). Since most managers' working knowledge of the involved planning and execution of tasks in the new product introduction process was normally confined to a few tasks within their own responsibility area, it made no sense to spend much time on probing for answers outside their respective area of interest.

After a short discussion of the managers' responsibility area, he/she was asked to identify important tasks in the new product introduction process and point to major bottlenecks and problems in the process. This was done on the basis of a project network structure, which was iteratively developed throughout the interviews. With this information it was also possible to find the tasks that prolong the market introduction and lead to an unnecessarily high TTM.

Afterwards questions to all tasks in the process were posed and the manager answered as best he/she could. This served to establish knowledge of the tasks the manager worked with or was responsible for and observations of weak practices were made.

2.2.3. Data collection

All the interviews were conducted from December 2009 to March 2010 and in all 18 managers from 9 companies have been interviewed. All interviews were digitally recorded for later use and sketches of how to improve the project network were gathered from the interviews. Validity and reliability was ensured by having control interviews for each manager position type as mentioned in 'Sample Selection'.

2.3. Case Study

The case study builds on interviews and information gathered from a pharmaceutical company, which for confidentiality reasons shall remain nameless. The company is a drug developing pharmaceutical company, which develops and manufactures a range of APIs and final drugs. All drugs

are of similar chemical structure and are produced at several multi-purpose batch plants in Europe. The R&D organisation including a pilot plants use up more than 20 % of the annual revenue. In all 8 managers from across the organisation were interviewed such that the complete new product introduction process in the company was covered.

The new product introduction process is organised in a matrix structure, which, as became apparent from interviewing the other reference companies, is commonly used in the industry. After the development of a series of new compounds, the most promising candidates are chosen to be further developed and get assigned to a development team. The development team consists of specialists from the different functions in the company i.e. production, R&D, marketing and regulatory affairs. The team's composition depends on the stage in the new product introduction process of the drug. Marketing or pharmacoeconomists are involved in the beginning and end of the process to evaluate economic feasibility and prepare forecasts. Production and Supply Chain managers are increasingly involved, the further along the project proceeds, starting during capacity planning and the design of the production process. Under the responsibility of the R&D department, the production of prototype API for the clinical trials is done in the pilot plants, which are not intended for large scale production. Both R&D and Regulatory Affairs are involved all the way from conception of the drug to final approval. Decisions on whether to continue the development of the drug are taken on revision meetings with the top management.

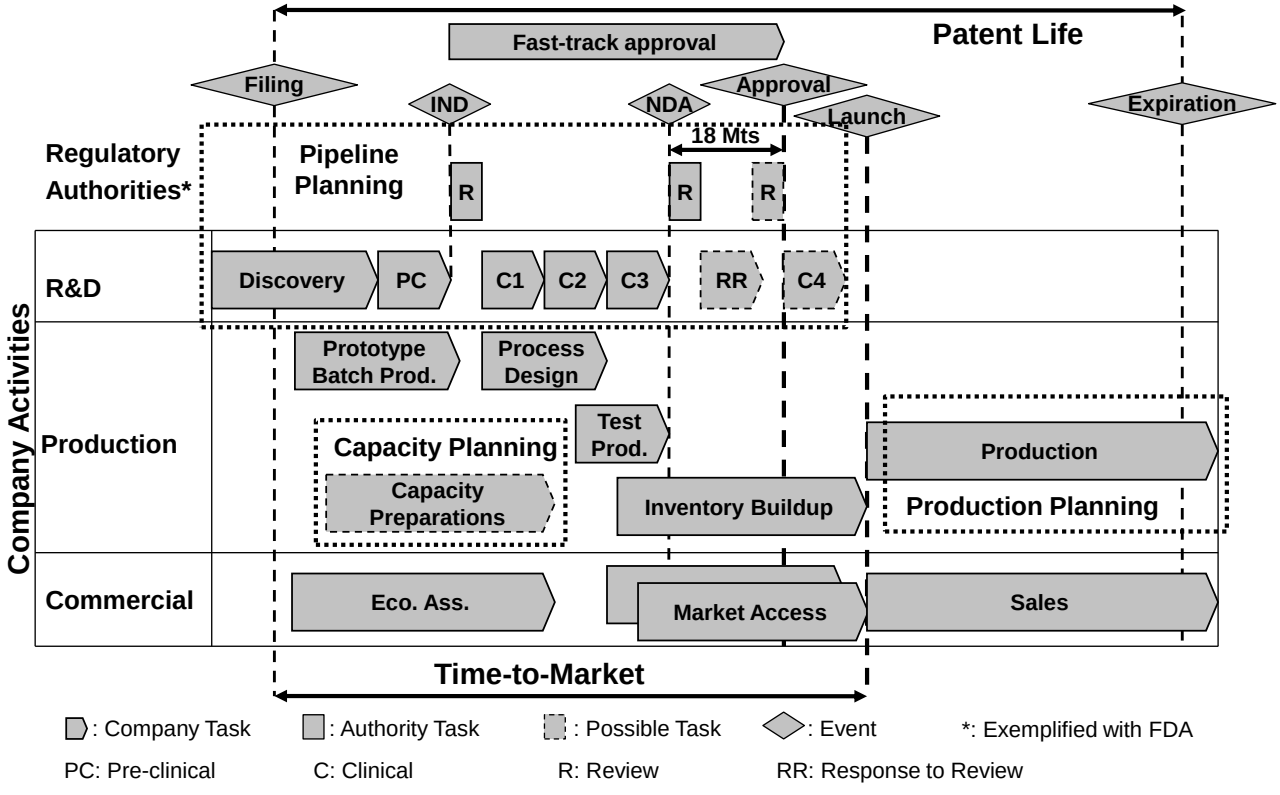

Figure 2.1: Project network representation of the new product introduction process. NB: Task length does not represent task duration.

2.3.1. Identifying the project network

During all interviews, a project network of the new product introduction process was presented and each interviewee was then asked to suggest changes in how they perceived the project network structure. Through this iterative process the project network seen in Figure 2.1 was created. The project network involves three key functions in the company (R&D, Production and Commercial) and those activities carried out by the Regulatory Authorities. The length of the tasks in Figure 2.1 is not indicative of the task lengths or the resource consumption, but helps indicating the timeline in the process from patent filing to patent expiration.

The tasks of the Regulatory Authorities are found at top of the network. R&D and Regulatory Affairs make up the R&D category. Here the first main task is the conception or discovery of the drug itself (cf. the Discovery task). It is at this time the application for the patent is filed and the patent life starts (cf. the filing and expiration events). Next, initial studies of the drug are made in the pre-clinical trials (cf. the PC task) to test its toxicity. Based on the animal experiments in the pre-clinical trial, the documentation is sent to the authorities, here illustrated for the FDA, for review (cf. the first R task) as an Investigational New Drug application [IND]. If it is approved, the company can start the clinical trials (cf. the C1-C3 tasks). After these have been completed, documentation is sent as a New Drug Application [NDA] (cf. the event NDA) for a final review (cf. the second R task). The drug can either be completely rejected, completely approved or the authority can request more data thereby delaying the approval. This will require the company to respond to any comments from the authority and possibly produce the requested data (cf. task RR) before final review and the approval can be given (cf. the task R and the event Approval). A final clinical trial may also be needed after the approval of the drug, if the authorities or company sees the need for one. This could for instance be to try the drug on smaller patient segments such as children or pregnant women. Finally, drugs particularly important in curing previously incurable diseases can gain fast track status (cf. Fast-track approval) where requirements are temporarily lowered. Though the authorities' requirements are difficult to live up to, they are generally clearly stated as guidelines. The uncertainty of approval arises from the company's interpretation of whether observed effects in the patients are statistically significant. The uncertainty is a clear risk for all tasks carried out parallel to the clinical trial. If a trial fails, the prepared capacity become idle and work on other tasks become worthless. In the worst case the entire drug is abandoned or rejected and the company has nothing to show for its investment.

The production of prototype batches in pilot plants for the clinical trials (cf. the Prototype Batch Prod. task) is in some companies a R&D task and a production task in others. Production and supply chain functions are much stronger involved during the design of the production process (cf. the Process Design task) which is done simultaneously with the clinical trials. Depending on the production method and current capacities, additional production resources may have to be made available (cf. capacity preparation). This could either be by clearing capacity at existing production lines or by expanding production facilities with new equipment or even new factories. The reason capaci-

ty preparations are done in advance of the process design is that it may take that a long time to find equipment by phasing out old products or build a factory. For the case company all production processes are so similar, that the same equipment is used, in what is called multipurpose batch plants. Process design is often more process tweaking than fundamental redesign. This relation between capacity preparation and process design may be different for other companies. The production of the drug then starts before the approval is granted, since three high quality and identical batches have to be produced for the authorities as part of the NDA (cf. the Production task). Furthermore, API inventories are normally filled before the market introduction (cf. the launch event) in order to fill up the market immediately after market access has been gained. The production continues until the drug is either removed from the market or moved to generic production, which happens sometime after patent expiration.

In addition to forecasting and promoting the sales volume (cf. the Sales task), commercial tasks involve economical assessments of a drug's potential early in the process (cf. the Eco. Ass. task) and in preparing the entry into new markets (cf. the Market Access task). The latter task consist of further identifying the economic benefit of entering the country or market, but also of planning and conducting negotiations with local authorities to secure subsidies to patients; reimbursement. As new approvals and reimbursement have to be negotiated for each authority, this process is repeated in each country or market for each drug; hence the cascade in Figure 2.1.

The remaining tasks involved in new product introduction are not shown here, partly since they consist of traditional tasks also found in other industries and partly because they are considered parallel to production such as procurement and distribution. It is important to note, that TTM is measured from the patent filing to market launch of the drug. The precedence relationship identified through the interviews can be seen in Figure 2.2 illustrated as a directed graph going from drug discovery and patent filing to finally patent expiration and product removal. Interactions with the regulatory authorities are not shown.

All the interviewed managers pointed to the clinical trials as the major bottleneck in the process. In addition it was mentioned, that several managers' main responsibility was to keep their task off the critical path i.e. to not delay the process. After gaining the approval, it would either be the subsidy negotiations or production that would slow the product launch. As the project network in Figure 2.1 has been created and the precedence of the tasks set in Figure 2.2, RQ1a has been answered.

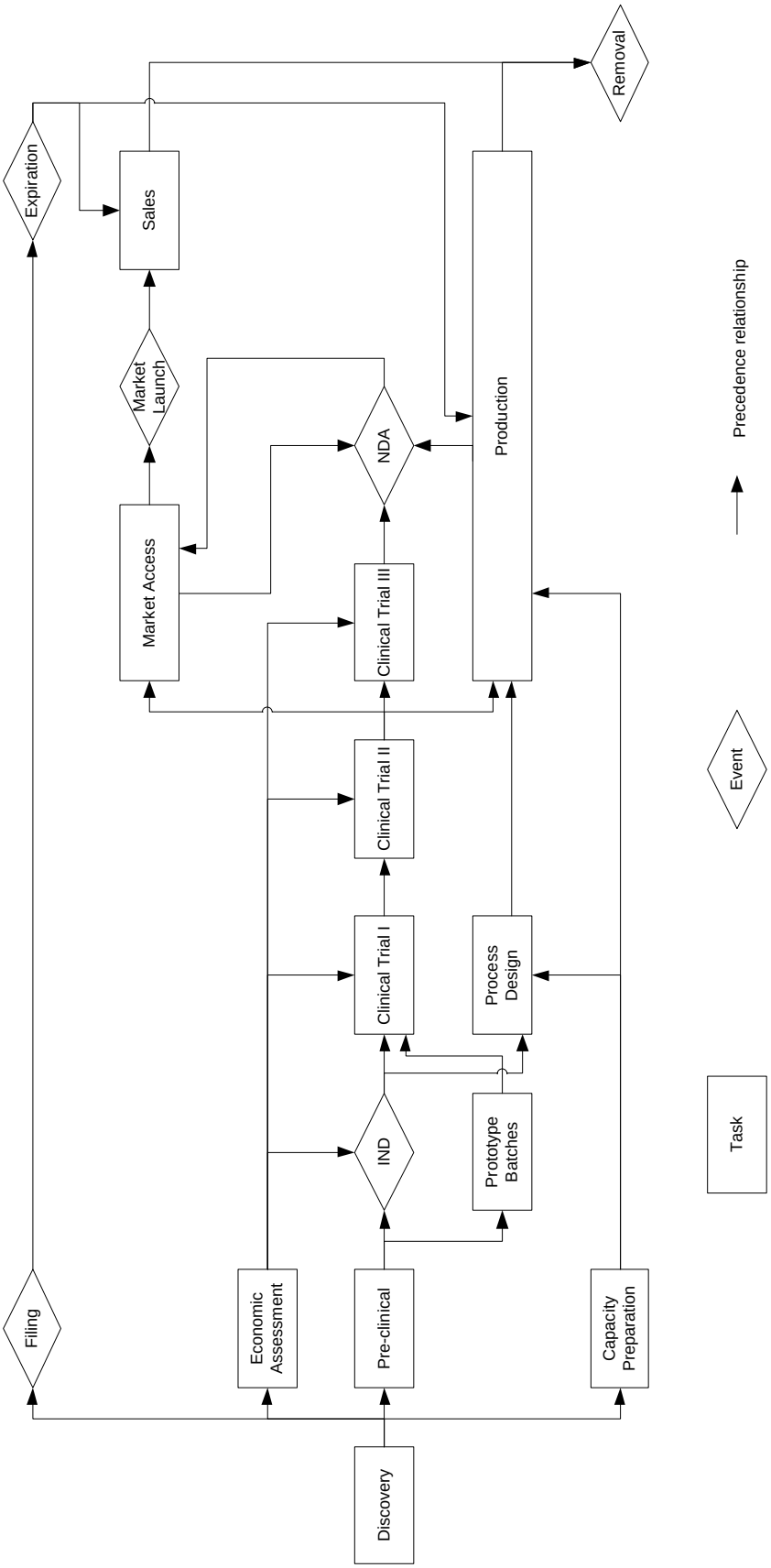

Figure 2.2: The identified precedence relationship illustrated as a directed graph.

2.4. Locating literature in the project network

The review only covers literature for prescriptive and quantitative planning methodology. As can be seen in Figure 2.1 marked with three dotted boxes, previous contributions in the literature have addressed managing and planning some of the tasks in the new product introduction process. The boxes are here drawn around the main tasks, they provide decision support for. Most of these areas have come from process system engineering community. Shah (2004) reviews supply chain contributions for the pharmaceutical industry more directly. Here the current trends in the pharmaceutical industry are listed, which are all relevant for the new product introduction process. The trends include fewer potential research compounds, shorter effective patent protection, more generic substitutes and more price focused customers and authorities. The main contribution of Shah (2004) is a classification of the major areas found in the literature for the pharmaceutical industry:

- Pipeline management or planning
- Capacity planning
- Simultaneously pipeline and capacity planning
- Production planning and scheduling
- Process development and plant design
- Supply chain simulation

There is given no relation to how these planning areas relate to the observed trends. Only first 4 planning areas are really interesting in the new product introduction context as can be seen in Figure 2.1. Pipeline planning is the discipline of planning which products in the pipeline to develop further in the face of uncertainty from the approval. Schmidt and Grossmann (1996) were the first to address this problem. It has since then been followed by Jain and Grossmann (1999), where the authors are the first to also schedule the development tasks with limited resources. Since then, several contributions have proposed other approaches for pipeline planning. Two-stage stochastic programming is used in Colvin and Maravelias (2008), where the authors use non-anticipatory constraints to manage the scenario structure. Later, the authors focus on developing a branch and cut algorithm (Colvin and Maravelias, 2010) and consider task interdependencies (Colvin and Maravelias, 2011). Real-options-based planning is used by Gupta and Maranas (2004) and Perez-Escobedo et al. (2012) address pipeline planning with multi-objective programming. This body of literature does support managing the R&D portfolio while considering uncertainty and it does seem to provide a good trade-off between TTM and risk.

Rotstein et al. (1999) are the first to investigate the impact of production cost and available capacity on profitability. Papageorgiou et al. (2001) extend their MILP model to capture the business structure of a pharmaceutical company and consider several practical constraints. But their model does not account for the uncertainty resulting from the clinical trials. This is addressed by Gatica et al. (2003), which use two-stage stochastic programming approach to capture both failure in the clinical trials and different demand scenarios. Both uncertainty and business structure are captured by Levis and Papageorgiou (2004), who also introduce an effective heuristic for solving the problem.

Maravelias and Grossmann (2001) combine the pipeline planning problem and capacity planning problem and solve them jointly via decomposition.

Production planning is arguably also related to the new product introduction process, since the above mentioned models include some production planning elements, but only on very aggregate level; usually annual quantities. More specific mentioning of production planning has not been found in relation to new product introduction. Nor is the new product introduction mentioned in Méndez et al. (2006) or Shaik et al. (2006), the two most commonly cited review papers on production planning in this field. For the pharmaceutical industry, several sites and products for each company and especially the long setup times quickly make production planning intractable. Campaign planning, in which several batches are produced per setup, has been developed for the pharmaceutical industry to provide a production planning methodology (Grunow et al., 2002). With the use of cascades and heuristic approaches, industrial size problems can be solved (Grunow et al., 2003). While these and many other contributions try to schedule chemical product in an effective way, little attention is given to secondary production due to the less complex processes. Stefansson and Shah (2005) is one of the few contributions. Here different levels of data availability for fluctuating demand are treated.

Due to the large supply networks of pharmaceutical companies, supply chain management has recently been given attention. Sousa et al. (2008) develop two models for tactical and operational planning, which they propose solving in succession. They test their approach on a case from the agrochemical industry, which is similar to the pharmaceutical industry. They extend their work in Sousa et al. (2011), where an industrial sized problem is solved by developing two decomposition approaches with fast solution times and good solution quality. Supply chain issues are addressed in Laínez et al. (2009), where the main topics are capturing financial aspects, the integration of customers and suppliers and managing risk. Though their work is not industry specific, the pharmaceutical industry is given separate mentioning by a review of the capacity and pipeline planning literature. Susarla and Karimi (2012) focus on the coordination of a global supply chain by considering supply network planning with tariffs and transfer prices. They cover the entire supply chain of a company while considering all tasks and yet achieve good results with the use of a heuristic approach. Though the supply chain issues described are relevant, none of the contributions relate their work to the introduction of new products.

When looking for literature on reducing the TTM, only a small fraction is suitable for the pharmaceutical industry. In a review, Krishnan & Ulrich (2001) found several contributions to operations during the new product introduction process. A central problem is that of market launch timing, which trade-offs the value of additional development time for better products with lost market share due to delayed market launch (Cohen et al., 1996). With a time-limited patent on new drugs, market launch timing in the pharmaceutical industry is not a problem. Another stream of literature extending the original Bass or product diffusion model with operational constraints is described in a review by Mahajan et al. (1990). The aggregation level in these contributions is however too high as the full life cycle of products is considered and production is overly simplified. They do hence not provide decision support for the challenges facing managers in the pharmaceutical industry. Two

contributions have been found, which treat do operations during new product introduction in pharmaceutical supply chains specifically. Gjerdrum et al. (2001) use a simulation approach to see the effect of introducing a new product on other products in a pharmaceutical supply chain. Similarly, Sundaramoorthy and Karimi (2004) proposes a model for testing if a new product can be incorporated into an existing multi-purpose batch plant or if some processes must be outsourced. No contributions have been found by the authors, which aim at reducing the TTM by effectively managing the operations involved in the new product introduction process.

Uncertainty within planning is a huge issue for the process industry in general (Papageorgiou, 2009). Shahinidis (2004) review a series of techniques for modeling uncertainty. The use of robust optimization to manage risk inspired by Mulvey et al. (1995) is given particular focus. Tsang et al. (2007b) demonstrates the use of several other techniques such as expected downside risk, opportunity value, value-at-risk and conditional-value-at-risk on a capacity planning model for the pharmaceutical industry, which they present in Tsang et al. (2007a). The remainder of the vast body of risk management literature is not reviewed further here.

Considering the literature and its scope, it seems that there is a gap in the methodology for planning the involved tasks, stretching from the filing of the NDA to market launch. Besides the pipeline planning literature, no other contributions address the industry's demand for a methodology aimed at reducing the TTM while simultaneously considering in inherit uncertainty of the clinical trials and reimbursement negotiations during this phase. With this literature review, RQ1b has been addressed. In the next section, observations from the case study are stated, which highlights the challenges in the industry and thereby shows the way for further research, which could contribute to reducing TTM.

2.5. Insights from the case study

All interviewees pointed to the clinical trials as being the major bottleneck for the whole new product introduction process. Trying new drugs out on patients, finding and analyzing the results are simply lengthy tasks. During the interviews, managers were inquired about the current planning techniques used by the company to plan the clinical trials while considering the entire pipeline. The interviews revealed a simplistic and pragmatic approach to decision making, which consisted of identifying key figures, discussing risk elements and making gut feeling decisions of which drugs to allocate which resources for.

Observation 1: Risk elements seem to be handled with gut feeling and simple measures at best. No consistent methodology is employed for pipeline management.

Whereas the available planning techniques for the pharmaceutical industry have evolved in the literature during the last 10-20 years, it seems the industry has been slow to follow. More focus should be given to the implementation of such techniques. This is however beyond the present scope.

In the case company, the Market Access section was involved early in the new product introduction process as advisors. The reason for this was in part so that they could start preparing the sales organization for the launch, but they were also used as consultants in setting up the clinical trials. Different authorities in different countries demand different tests and documentation to grant their approval. The decision of whether to do certain trials up front to gain faster approval or whether to do these later and get the drug out onto a smaller number of markets fast is not trivial. To the best of our knowledge this has not yet been mentioned in the literature.

Observation 2: There is no or little attention given to how market expansions and clinical trials should be planned simultaneously and what the effect is on the time-to-market.

Research in this area could consist of expanding known pipeline planning models. Two points have to be added. First, the planning of the trial sizes is a very complex procedure which involves highly complex statistical relations for finding the needed trial population which can prove or disprove a claim. Secondly, there is so much overlap between the requirements of the different authorities, that a one-off trial is normally conducted. It was neither possible to establish how big a potential gain would come from this, nor what added risk a reduced trial would cause.

So far only the two most central regulatory authorities have been mentioned, FDA and EMA; but there are many more. In Europe only the market approval can be granted through the centralized system administrated by EMA. For negotiating the reimbursement, the company has to carry out separate negotiations with each member country or possibly each municipality. This leaves a lot of negotiations to be carried out. The order in which these negotiations are carried out is decided based on a business case made by the company, which considers authority requirements, potential market size, potential subsidy and expected negotiation time. As different authorities use different techniques for awarding or evaluating subsidies e.g. comparison to other countries or based on production and R&D cost, the order in which these subsidy negotiations are carried out influence the overall granted level of subsidies. A higher subsidy leads to higher potential price of the drug and increased sales i.e. higher revenue. This creates a trade-off between scheduling negotiations to either obtain higher subsidies or to schedule negotiations such that markets can quickly be accessed. Again, the process of scheduling market access negotiations was described as being based on gut feeling decisions.

Observation 3: A systematic approach to address the trade-off between negotiating for a higher subsidy versus negotiating for a faster market introduction seems to be missing.

There is no doubt that the industry could benefit from such a model, if it could increase the price of a drug in all European countries. The main obstacle with research in this area is the availability and definition of data. Finding out how price setting occur and account for variations in outcome of the negotiations may prove very difficult. Furthermore, there are large variations in how fast these processes are conducted in the different countries and the resource requirements per negotiation are not clear.

In preparation for the launch of a new drug in a market, it is industry practice to build up stock to get the drug to the customers as fast as possible, so production will not halt the market launch. Here planning with some rules of thumb is widely used e.g. 1 year supply on inventory needed at the API stage, a half at the formulation stage and for a quarter of finished products. However following these rules in practice may be difficult over time as several dynamics of both the supply chain and the market has to be considered. On the supply side, lead times have to be considered in both building up the inventory and in consuming it around the launch period. The market side is conversely uncertain with poor forecasts accuracy and uncertainty in the negotiations. Even planning for a high demand scenario alone may not be enough to assure sufficient availability. As an example the last part of the approval process often involves forced changes to the label or packaging material, which lead to forced scrapping of drugs packaged before the final authorization is granted as repacking is not allowed. The decision whether to package the drug up front despite the risk or 'risk packing' offers the trade-off between potentially saving the packaging procedure after approval and reduce the step between approval and launch versus the risk of having to change the label and throw away the entire packaged inventory. Throwing the finished drug away is not only expensive, but leads to a further delay of the launch if the product has to be produced again. Hence the key decisions that need to be supported are finding both production and inventory volumes throughout the supply chain.

Observation 4: Finding production and inventory volumes leading up to market launch is not addressed in the literature nor by the industry. No appropriate method for assessing risk packaging has been found.

Since production and inventory built up in the late stages of the new product introduction process can hold back market launch and thereby get on the critical path, managing these process would directly contribute to lowering the TTM. Furthermore, in order to cut cost, the authorities are be-

coming increasing difficult to negotiate with and several companies are directing more resources towards market access.

A prerequisite for product availability is capacity availability. Due to the long construction time of new sites, capacity planning in the pharmaceutical industry has already been given much attention as these decisions have to be taken before it is known whether the drug will get approved. With this risk, it is often better to postpone as many of the investment decisions for as long as possible. Often investments into the production equipment are delayed which also benefits the process design department, who gets more time to optimize the processes for a higher expected output. Especially, investments in secondary production equipment are postponed as these have shorter construction time. The problem is however, that the equipment has to be installed and the process demonstrated to the authorities as part of the approval process as well as be used for building up inventory. With secondary production exhibiting ramp-up effects, ramp up should also be considered so sufficiently high effective capacity can be reached in time. Capacity planning for secondary production is no longer trivial. Production managers must ensure product supply does not the cause a delay in market entry.

Observation 5: Decision support for capacity plannning of secondary production and the consideration of ramp up, which are prerequsites for product availability and on-time market launch, has to be developed.

From the observations made above, it seems that there are several ways to reduce TTM. Not all of them appear equally promising. The lack of implemented pipeline planning tools is predominantly an industry problem. Expanding pipeline planning with the trial design elements may prove difficult as broken up trials require more subjects than one big once-off trial. Developing a planning or scheduling methodology for the reimbursement negotiation seems possible; however data access and the lack of transparence of the market access process are likely to make this line of research virtually impossible. The operational issues of market launch and capacity planning appear to be the most approachable issues. Both processes are usually not on the critical path in the new product introduction process, but a methodology has to be developed to ensure that remains the case. With this conclusion, RQ1c has been answered.

2.6. Conclusion

In this contribution the new product introduction process in the pharmaceutical industry is studied. A case study is carried out, which consists of interviews with several managers in all functions. For each function, a validation interview with a manager in the same function in another company is made. From the case study a project network is created, which identifies all of the company's major

tasks in new product introduction. These tasks are then linked to each other in a precedence relationship chart. The literature is reviewed with a focus on the planning methodology for new product introduction in the pharmaceutical industry. Several gaps are identified that can reduce time-to-market for new products. The final stage of the new product introduction process seems to be particularly lacking a methodology for managing operations at this critical time. The operations management literature does not seem to offer any methodology which can directly be applied. From the case study, several observations are made about the current planning challenges of the industry and the most promising areas for further research are identified. It is clear that better planning of operations before market launch is needed.

Chapter 3: Planning market launch operations in pharmaceutical supply chains

This chapter is based on an article submitted as:

Hansen, K. R. N., Grunow, M. (2013). *Planning operations before market launch for balancing time-to-market and risks in pharmaceutical supply chains*. submitted for International Journal of Production Economics

Abstract

Research-based pharmaceutical companies are pressed to reduce the time-to-market, since the increase in the duration of the drug development process makes it hard to recoup the R&D cost while under patent protection. Before a launch, sufficient products have to be available to fill the downstream supply chain. Unique for the new product introduction process in the pharmaceutical industry are the risks of delayed market authorization and a required change of the used printed packaging material. Pushing inventories down in the supply chain may reduce the time-to-market, but it also limits the flexibility to react on these risks and may lead to waste when products must be disposed due to rejected packaging. We have developed a model for detailed planning of the market launch phase, while considering lost revenue caused by delays. Our model finds the needed volume of active pharmaceutical ingredient to produce the volume of print packaging material to procure, the volume contracted out to external manufacturers plus the production and inventory volumes on all echelons in the supply chain to accommodate for all possible launch dates. The authorization risks are included directly in our two-stage stochastic model. In order to limit the required computational effort, we use the problem structure to keep the number of scenarios low. The results from a case study based on a real world setting show that the use of our model can lead to significant savings in the cost of launching a new pharmaceutical drug compared to current practices. Finally, a model extension is proposed which is based on robust optimization to illustrate the cost trade-off in reducing time-to-market.

3.1. Introduction

3.1.1. Approval, authorization and time-to-market

All new drugs have to go through a series of clinical trials prescribed by regulatory authorities e.g. the FDA or European Medicines Agency [EMA]. Here the efficacy and side-effects of the drug are determined and documented (Lipsky and Sharp, 2001). The cost and length of pharmaceutical R&D projects are tightening due to increasing requirements for these trials (DiMasi, 2002, PhRMA, 2012). If the drug is approved by the authorities, the drug can be marketed under the protection of the patent. Since patents are filed early in the R&D phase, when promising compounds are found,

only a short time remains before the patent expires. As soon as the drug goes off patent, generic manufacturers launch similar drugs, which drive the price on the drug down. Hence developers of new pharmaceutical drugs have a strong focus on reducing time-to-market [TTM], which prolongs the profitable period under patent protection. The importance of TTM is illustrated in Figure 3.1. Assuming that the market penetration curve is the same regardless of launch date, a launch at T_1 increases the time under patent protection compared to a launch in T_2 and the company thereby extends the peak revenue. In practice the peak revenue level may also be lower for a launch in T_2. The market share may be reduced as competitor products possibly have gained ground during the delay. With the approval process lasting 12 years, little time is left for marketing the drug with patent protection (DiMasi, 2002). We however only focus on the short period around the market launch. Figure 3.1 also shows a surge in demand right after launch. We refer to this as the supply chain filling effect, which is caused by extra demand of filling the downstream supply i.e. wholesalers, hospitals and pharmacies (Cook, 2006).

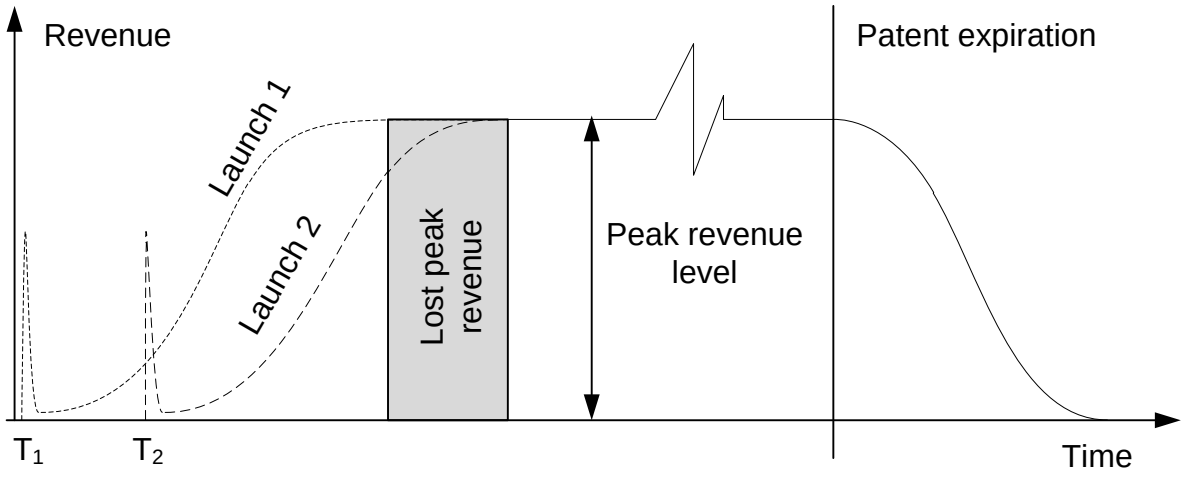

Figure 3.1: Illustration of the lost peak revenue.

Though much work has been done by the industry to streamline the process of obtaining the approval, the process of receiving market authorization has received less attention (Danzon et al., 2005). Drugs are subsidized by governments and health insurances through reimbursement of (a part) of the price. The settling of a reimbursement agreement is effectively a prerequisite for selling to a new market. To obtain reimbursement and market authorization, a set of reimbursement negotiations with the local authorities has to be carried out, in which, in addition to fixing the maximum price and reimbursement levels, labels and leaflets are approved. While the approval itself can be conducted centrally in Europe through for example EMA, the authorization process has to be carried out locally. A process which in 2010 varied in length from country to country as can be seen by the average time between approval and authorization in Table 3.1.

Table 3.1: Examples of average time between approval and authorization (EFPIA, 2010a).

Country	Average time in days
UK and Germany	1
Ireland	101
Spain	260
France	289
Italy	306
Belgium	403

In the past years, the health care costs in most western countries have been rising. Especially after the latest financial crisis, governments have decided to cut expenditures. This leads to reimbursement negotiations significantly longer than the values in Table 3.1 and lower reimbursement levels. These new negotiations are a substantial change over the automated registration of new drugs, which has traditionally been practice in countries such as the UK and Germany. Both the length of the process as well as the reimbursement level are more uncertain while profit margins are dropping (Rossetti et al., 2011). This holds for most western countries. In 2012, for example, the procedure in Germany changed from a one-day automated authorization process to a process which lasts up to half a year. However, each day a blockbuster drug is delayed, the lost revenue can be in the order of millions of euros. Pharmaceutical companies should therefore treat the reimbursement negotiations in a more systematical way (Danzon et al., 2005). There is hence a need for improved market launch planning capturing the authorization risks and aiming to limit the lost revenue.

3.1.2. Operations planning before market launch

To further delimit the problem treated in this paper, we use the distinction between strategic and tactical decisions in market launch (Trim and Pan, 2005). The relation of market launch decisions to other corporate function and planning areas (pipeline, capacity and production planning) can be seen in Figure 3.2. On the strategic level, decisions are made on which demographic and geographical markets to enter considering (i) regulatory requirements, (ii) demand forecasts, (iii) the R&D plans and (iv) the uncertainties of the clinical trials and the approval process. Strategic decisions are taken well before a drug is launched and align the product development to the company strategy. A misfit here may lead to outsourcing or partnering of the remaining development of a drug. While the tactical level in Trim and Pan (2005) refers to marketing decisions, we here consider supply chain decisions.

To avoid contamination in production, the authorities impose strict cleaning regulations on the production equipment. These cleaning requirements lead to long setup times in the order of weeks for the production of the active pharmaceutical ingredient [API]. As a result, long campaigns in which numerous batches are produced for each setup arise, making API production very inflexible (Grunow et al., 2003). These API production plans are largely fixed and cannot be adapted to sudden changes. To plan for API production, aggregated API supply volumes and due dates are needed in advance. Similarly, the procurement volumes of printed packaging material [PPM] and the production volumes outsourced to contract manufacturers [CM] have to be determined with some notice in advance due to the lead time of these companies and depending on the contractual agreements especially between the outsourcer and contract manufacturer (Boulaksil et al., 2011). The final stages of production in which the API is formulated into e.g. pills, put in blister packs and packaged must also be considered. Aggregated formulation and blister production volumes are needed as these production processes also involve campaign planning, which however has a much shorter time horizon than production planning for the API (Stefansson and Shah, 2005). Packaging operations can be changed with short notice, but the capacity of the packaging equipment must however be reserved up front. All of these volumes are needed as inputs into master production planning in secondary production of pharmaceutics.

The focus of this paper is to plan operations (see Figure 3.2) in the pharmaceutical supply chain to build-up inventory prior to market launch such that TTM is kept short, while considering uncertain launch dates given the outcome of the authorization process. We focus on the above six key decisions, which we will refer to as the launch preparation decisions. These are the required API, PPM, CM and formulation and blister volumes and the reservation of packaging capacity throughout the planning horizon.

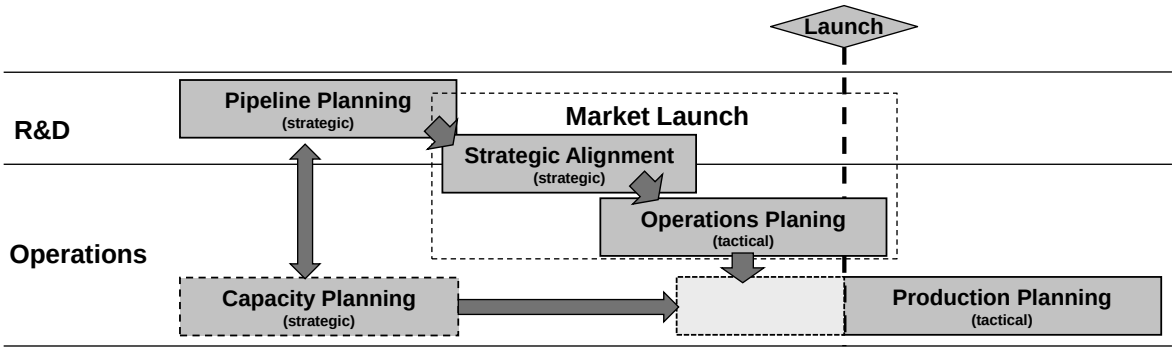

Figure 3.2: Scope of market launch and the planning area in new product introduction.

3.1.3. Authorization risks

Three separate risks originate from the authorization negotiations; 1) uncertain length of the negotiations, 2) uncertain reimbursement level and price and 3) the risk of a required change of the used leaflets and labels (PPM).

1) The length of the reimbursement negotiations can vary significantly. Since the authorities seek to cut down expenditures, the negotiations become more difficult and their length hard to predict.
2) In setting and negotiating the maximum price and reimbursement level, the authorities typically use different systems for evaluating and assigning these. For example, in the UK a process is used, whereby the drug is rated and both maximum price and reimbursement are then given without much discussion. Other countries set maximum prices by comparing to reference countries or by use of cost-benefit analysis (Garattini et al., 2007).
3) Authorities can force the pharmaceutical company to change the naming and wording on the PPM (referred to as a forced label change). They do so, if they find the text on the PPM misleading, e.g. with regard to the claimed benefit, recommended use, side effects or target patient group. In this case the company will have to scrap all of their products which are already packaged, as repacking is not allowed. Products which are nonetheless packaged before authorization is obtained are thus said to have been *risk packaged*. This may be suitable to reduce TTM.

The price of the drug affects the demand of the drug. The uncertainty of the reimbursement negotiations therefore inflates the demand uncertainty, which due to the lack of historical data is large anyway. For new products, demand forecasts built on estimates created by experts, who use the performance of the drug shown in the clinical trials combined with their knowledge of the target patient group to forecast demand. Besides an expected scenario, best and worst case scenarios are usually identified (Cook, 2006). These demand scenarios depend on the market authorization process as the outcome of a cost-benefit analysis made by the authorities dictate how they rank the drug and hence how much will be prescribed.

3.1.4. Paper contributions and structure

The contribution of our work is a methodology for supporting the launch preparation decisions, which have to be taken prior to market launch. The most important decisions are the required API supply volume, the procurement volumes of PPM and the volumes outsourced to contract manufacturers in addition to the formulation and blister production volumes and the reserved packaging capacity. We address the trade-off between risk and TTM in launching a new pharmaceutical drug by:

- Identifying the relevant risks (see above).
- Proposing a two-stage stochastic MILP model for addressing market launch planning and the identified risks in the pharmaceutical industry, including all relevant supply chain echelons and using the model structure to keep the model tractable.
- Testing our modeling approach through a numerical analysis based on a realistic industry case.

This paper is structured as follows. The next section contains a review of the literature on supply chain issues relevant for the introduction of new products in the pharmaceutical industry. Hereafter follows the problem outline and a description of the scenario modeling in section 3.3, leading up to a presentation of the model in section 3.4. In section 3.5, a case study from a large pharmaceutical company is introduced and the most important findings are shown in section 3.6. Risk management is discussed in section 3.7, before concluding remarks are given in section 3.8.

3.2. Literature review

Factors that influence the ability of new products to penetrate a market have had the interest of the marketing community for a long time. The model introduced in Bass (1969) for forecasting the demand of a new product based on estimated market size and on two coefficients relating to innovation and imitation has gained widespread popularity. A large body of literature has since treated new product diffusion. Reviews can be found in Mahajan et al. (1990) and Peres et al. (2010). Diffusion models and forecasting for market launch planning of a new pharmaceutical drug is described in Cook (2006). Here an s-shaped curve is found to describe the market diffusion well, though other models for particular slow and fast diffusion are also found.

As demand fulfillment is constrained by capacity, new product diffusion models have been extended to consider capacity expansion, inventory build-up periods and production and sales plans for the life cycle of an innovative new product. Jain et al. (1995) were the first to consider limited capacity by creating an intermediate group of waiting applicants (interested customers) between the potential adopters (the market) and the adopters (served customers). Their extended Bass model was applied to an Israeli phone company with a monopoly, while assuming none of the waiting customers would leave the queue. In Kumar and Swaminathan (2003), the Bass model is extended further with capacity constraints for finding separate sales and production plans. As demand cannot always be backlogged without loss of sales, finding a sales plan is not trivial. In an extensive numerical analysis, the authors make a comparison between a myopic policy looking to sell as much as possible at all times versus a build-up policy, where inventory is built up before demand is served. No unambiguous result is found. Several insights on optimality of the build-up policy and the possibility of a delayed roll-out are obtained. By introducing a convex production cost curve, the authors describe, how the model can also be used for finding appropriate capacity levels. Risk

packaged inventories are not considered i.e. there is no risk related to build up inventory. Having a similar research objective, Ho et al. (2002) also extend the Bass model with supply constraints in a very similar approach. In contrast to Kumar and Swaminathan (2003), they claim that it is always optimal to sell as much as possible given that production is using all capacity. The authors also point out, that the news vendor problem cannot be used as it does not account for non-stationary demand and continue to deduce several properties for optimal operating conditions, life cycle profit, optimal TTM and capacity level. To address supply chain design for new products, Amini and Li (2011) propose a model extending from the Bass model, which directly incorporates supply chain configuration decisions and safety stock placement. As in Kumar and Swaminathan (2003) the model is compared to both a myopic and a build-up policy. The scope of these models is however highly aggregate. In addition, they also do not consider uncertainty. Hence these papers do not aim at and are not suited for supporting launch preparation decisions. A related stream of research focusing on market entry decisions should also be mentioned, lately represented by Özer and Uncu (2013). Here lost sales of delaying market entry are traded-off against extra development time for electronic components. In the pharmaceutical industry, this problem does not exist, because the product development has been completed and the product tested.

Supply chain issues in the pharmaceutical industry are reviewed comprehensively in Shah (2004). The new product introduction process was identified as the largest industry challenge. The following key planning areas were identified: pipeline planning, capacity planning and production planning. The scope of these planning challenges can be seen in Figure 3.2. Recently, Laínez et al. (2012) made an updated review of the latest developments in planning for the pharmaceutical industry. Apart from a thorough review of capacity and pipeline planning, they also cover supply chain management issues. The topics most related to our work are drug supply for the clinical trials and supply network planning in general. Market launch planning is not directly addressed.

Some contributions directly address the introduction of a new product in the pharmaceutical industry. Rossetti et al. (2011) present an empirical study of trends in pharmaceutical supply chains. Though they cover increasing pressure on the reimbursement levels and negotiation process, they mostly focus on the link between manufacturers and wholesalers. Gjerdrum et al. (2001) look at new product introduction in general and use the pharmaceutical industry as an example. The authors develop a simulation model of a pharmaceutical supply chain which can be used for assessing the consequences of introducing a new product. Sundaramoorthy and Karimi (2004) address supply chain management during new product introduction for the pharmaceutical industry. Here, a campaign planning model for API production in a multipurpose batch plant is developed to test how the introduction of a new product affects the existing products. The model considers deterministic demand, but the authors argue that their model can address demand uncertainty via reactive scheduling. Reactive planning however is difficult to implement in the pharmaceutical industry due to the rigidity of the production plans for campaign production. Since the described uncertainties can suddenly materialize during market launch, it seems doubtful whether reactive scheduling is a sufficient methodology to address these uncertainties. Instead, solutions that account for the uncertainties up front are needed. Furthermore, a more aggregated view of the whole supply chain is needed due to considerable lead times.

This paper is to the best of our knowledge the first to develop a methodology for planning operations up to market launch, in particular for the pharmaceutical industry. It covers the gap between the approval of a new pharmaceutical drug and the launch of the product. We focus our attention on providing decision support for the launch preparation decisions in the face of the uncertainties from the authorization process.

3.3. Problem definition and modeling approach

3.3.1. Scope, assumptions and variables

The production of API or primary production is followed by the production of the final packaged product or secondary production, which has a considerably shorter planning horizon. The key processes in secondary production are the formulation of the API (e.g. into pill form), packaging of the drug into blisters and then final packaging into boxes with leaflets and labels (cf. Figure 3.3). The formulation of the bulk drug is the same for all markets. In the blistering stage, products are market specific as the blisters contain some information related to the final market. Unlike the volumes produced in the packaging stage, they will not be affected by a forced label change as no information is put on the blisters which might be subject to last minute changes. Due to different languages and texts on the PPM, a packaged drug can only be sold on one market. As it is by law forbidden to repackage or transship the drug, a rejection of the PPM makes any finished product inventory obsolete. Procurement of leaflets and labels (i.e. PPM) also has to be considered. Due to the setups involved in the printing process, rush and small orders of PPM are infeasible or very expensive. Today's supply chains frequently also involve contract manufacturers in secondary production with whom framework contracts need to be negotiated and capacities reserved. The resulting contractual agreements with the PPM supplier and CM lead to capacity restrictions, which have to be considered in launch preparation planning.

The scope of our model covers production and inventory of API, CM, formulation, blistering, PPM supply and packaging of the final product (cf. Figure 3.3). To support the launch preparation decisions, only aggregate production and inventory volumes are required. In contrast, the detailed scheduling of jobs is not considered. The news vendor model is not suitable for a number of reasons. The demand is non-stationary (cf. (Ho et al., 2002)). We consider additional uncertainties and a full supply network. We require complete demand fulfillment after market launch but allow for a variation in the timing of market launches. Hence, we formulate a MILP model based on the following assumptions:

- In order to capture TTM, lost revenue due to delayed market launch is considered. Lost market share due to delay is not modeled.
- After market launch, all demand must be fulfilled as patients must have access to their medication.

- The outcomes of the authorization processes for different markets are independent due to the different institutions involved in the authorization process in the different markets. This holds for both duration of the process and label changes. Reimbursement levels are somewhat dependent, but we capture this uncertainty only as one of many factors influencing demand uncertainty. Demand uncertainty is independent as each regulatory body has its own approach to the cost-benefit analysis.
- Due to the short time horizon considered, shelf life, which is normally around two years, the discount rate and other financial constraints are not considered.

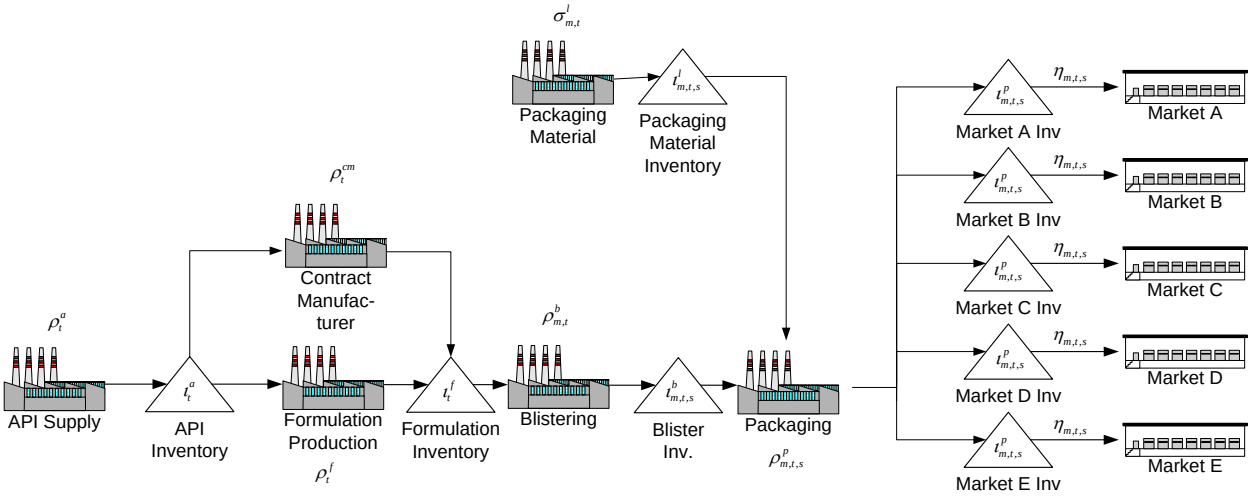

Figure 3.3: Supply chain considered (see variable definition below).

We consider a market launch of a new product in a number of markets $m \in M$ in time periods $t \in T$. Given the lead times involved and the variations in the length of the authorization process, the model therefore covers a time horizon of 3-9 months divided into weeks.

The uncertainty due to the demand uncertainty and the authorization risks is handled through a two-stage stochastic modeling approach. In a two-stage stochastic model, variables are divided into two categories (Birge and Louveaux, 2011). First stage variables (also called the design variables) are used for making 'here-and-now' decisions. Second stage variables (or the recourse variables) are used for making decisions after the uncertainty has materialized, i.e. are used for making 'wait-and-see' decisions. For our problem, no probability distribution can be found as no historic sales information is available for new products. However, a set of scenarios $s \in S$ can normally be generated by experts, which enables the use of the deterministic equivalent of the two-stage stochastic programming formulation or simply scenario-based optimization or recourse programming. The 'here-and-now' decisions are modeled as scenario independent variables. Central are API and CM production and the label procurement variables as these decisions must be made well ahead due to the involvement of external parties (CM and PPM supplier) and due to the

lengthy and inflexible API production. Formulation and blister volumes are also first stage variables, since they are needed as input for secondary production planning. Furthermore, a master production schedule for the packaging capacity must be made to prepare the packaging facility for the coming launch. By reserving capacity, demand fulfillment for all scenarios is ensured. The scenario dependent 'wait-and-see' variables are all remaining variables including exact launch date, packaging and inventory variables. Since packaging and distribution are relatively simple processes, they are considered scenario dependent as they can be changed with short notice. An overview of first and second stage variables can be found below.

Design or 'here-and-now' variables

$\omega_{m,t}$	= 1, if PPM is ordered for market *m* in period *t*; 0, otherwise.
$\sigma^{l}_{m,t}$	volume of PPM (or labels) ordered for market *m* in period *t*.
$\rho^{b}_{m,t}$	volume of blisters packaged for market *m* in period *t*.
$\rho^{a}_{t}, \rho^{f}_{t}, \rho^{cm}_{t}$	volume produced of API, formulation at the company site and at the CM in period *t*, respectively.
$\iota^{a}_{t}, \iota^{f}_{t}$	inventory level of API and formulation in period *t*, respectively.
$\varsigma^{p}_{m,t}$	packaging capacity reserved for market *m* in period *t*.

Recourse or 'wait-and-see' variables

$\beta_{m,t,s}$	= 1, if a launch is conducted in market *m* in period *t* in scenario *s*; 0, otherwise.
$\eta_{m,t,s}$	product volume required for market *m* in period *t* for scenario *s*.
$\rho^{p}_{m,t,s}$	volume of packaged products for market *m* in period *t* in scenario *s*.
$\iota^{p}_{m,t,s}, \iota^{b}_{m,t,s}, \iota^{l}_{m,t,s}$	inventory level of packed products, blisters and labels respectively for market *m* in period *t* and scenario *s*.
$\gamma^{p}_{m,t,s}, \gamma^{l}_{m,t,s}$	volume of scrapped packaged products and PPM caused by a forced label change for market *m* during period *t* and scenario *s*, respectively.
$\varepsilon_{m,s}$	net cost of scenario *s* in market *m*.

3.3.2. Scenario modeling

Even through there is a strong requirement for modeling approaches which consider more than one type of uncertainty in solving practical problems, there is only a limited number of such contributions (Mula et al., 2006, Barbosa-Póvoa, 2012). We model the three key uncertainties described in section 1 with the scenario structure shown in Table 3.2. When the authorization is awarded, the authorities also reveal if a change of the packaging material is required. If a change is required, then the launch decision has to be adjusted. Simultaneous with the authorization, the reimbursement level is also set, which impacts the sales price and demand. Also, the requirement to change the label has an influence on the demand as drugs may have to be scrapped and re-produced. It is assumed, that all uncertainties are known as soon as the authorization is given.

Table 3.2: The possible scenarios for launching the new product in a single market.

Scenario	*Authorization granted*	*Label change required*	*Demand*
1	Slow	Yes	Optimistic
2			Realistic
3			Pessimistic
4		No	Optimistic
5			Realistic
6			Pessimistic
7	On-time	Yes	Optimistic
8			Realistic
9			Pessimistic
10		No	Optimistic
11			Realistic
12			Pessimistic
13	Early	Yes	Optimistic
14			Realistic
15			Pessimistic
16		No	Optimistic
17			Realistic
18			Pessimistic

As As can be seen in Table 3.2, there are 18 different scenarios $s \in S$ of the reimbursement negotiations for *each* market. Looking at all the markets, one such scenario will occur for each market. As all combinations are possible, the number of scenarios in the full combinatorial expansion set $\bar{s} \in \hat{S}$ grows exponentially with the number of markets; $\left|\hat{S}\right| = |S|^{|M|}$. A full combinatorial expansion of the 18 scenarios for each market from Table 3.2 for e.g. 5 markets would lead to $18^5 \approx 1{,}890$ million scenarios; a number which is computationally intractable. This is a well-described problem with two-stage stochastic programming, which the modeling approach

should account for (Sodhi and Tang, 2009). We use the problem structure with divergent product flows to separate all decisions for the different markets. By using both the simple scenario $s \in S$ and the market index $m \in M$ for all scenario dependent variables, decisions for each market are taken independently of other markets. The number of variables in our approach is reduced from $|M| \cdot \left|\hat{S}\right| = |M| \cdot |S|^{|M|}$ to only $|M| \cdot |S|$ per time period for every type of variable. For example, the number of packaging variables for the full combinatorial expansion $\rho^{p}_{m,t,\bar{s}}$ is thus reduced from 9,450 million (= 1,890 million x 5 markets) variables per time period to $\rho^{p}_{m,t,s}$, with only 90 (18 x 5 markets) variables per time period in our modeling approach, if 5 markets are considered. For scenario dependent constraints, a similar reduction in numbers results.

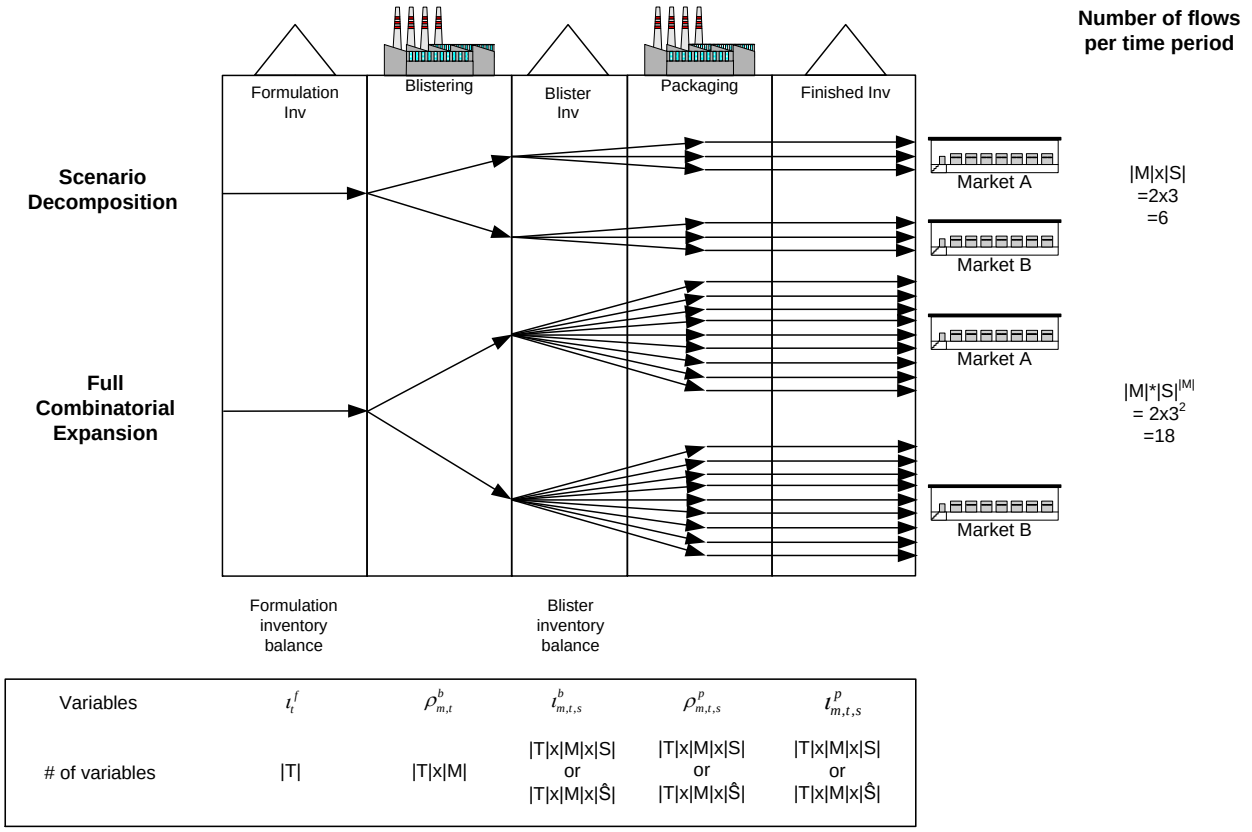

Figure 3.4: An example of the reduction of flows for the simple case of 2 markets and 3 scenarios (|S| = 3).

The divergent flow in the supply chain (cf. Figure 3.4) is modeled as follows. In the formulation stage, the product is identical for all markets. Due to the different commercial names, the drug becomes market specific in the blistering stage with the inventory balance decoupling the flow:

$\iota_t^f = \iota_{t-1}^f + \rho_{t-LTF}^f + \rho_{t-LTCM}^{cm} - \sum_{m \in M} \rho_{m,t}^b \quad \forall t$. The coupling between the scenario independent and the scenario dependent variables is made in the blistering inventory balance: $\iota_{m,t,s}^b = \iota_{m,t-1,s}^b + \rho_{m,t-LTB}^b - \rho_{m,t,s}^p \quad \forall m,t,s$. The incoming blister volume is scenario independent, but packaging volumes dependent on the scenarios consume different amounts of the inventory in different scenarios. The divergent structure expanding from one generic formulation volume to $|M| \cdot |S|$ flows of market and scenario dependent packaging volumes can also be seen in Figure 3.4. In this small example in Figure 3.4 with only two markets and 3 scenarios ($|S| = 3$), the number of variables is reduced from 18 to 6 per time period.

With the duration of the authorization process being uncertain, the scenario-dependent decision variables must be managed properly. When using the deterministic equivalent of a two-stage stochastic program, scenario-dependent variables before materialization of the uncertainty have to be identical as no more information is available. To address this challenge, two different approaches have been suggested. In Hahn and Kuhn (2012) it is addressed by defining variables within the time fence as scenario independent. However, if no well-defined time fence exists because the materialization of the uncertainty depends on an event which is not fixed in time, no appropriate variable definitions can be derived. Instead non-anticipatory constraints were developed in Goel and Grossmann (2006) for forcing decisions to be identical up to a time-varying point when some of the uncertainty has materialized. We use these non-anticipatory constraints to group decision variables together according to when authorization is granted in the respective scenario. Figure 3.5 shows how this is done. Here all decisions are identical prior to market authorization. After the authorization is given, different decisions can be taken. Up to earliest possible authorization, all packaging volumes and the packaged inventory have to be the same. For scenarios with early authorization (scenario 13-18), scenario dependent decisions can then be taken once the outcome of the authorization is known. Decisions for all other scenarios (scenario 1-12) still have to be identical. After on-time authorization, decisions in scenarios 7-12 can be made dependent on the outcome of the authorization process, while decisions in scenarios 1-6 have to be fixed until the delayed authorization has been given.

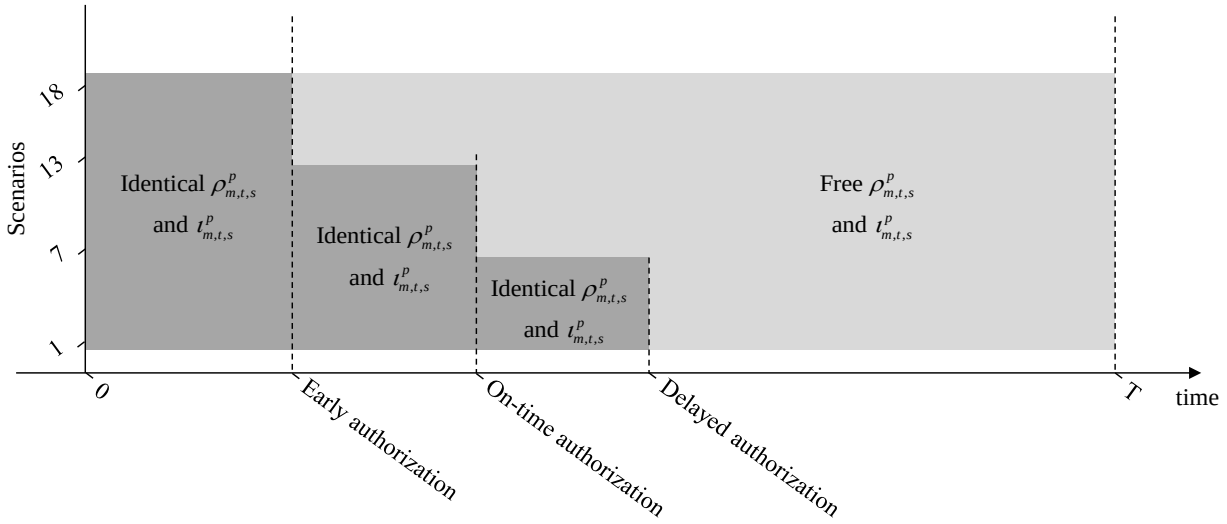

Figure 3.5: Illustration of how decisions are grouped together with non-anticipatory constraints.

3.4. Model formulation

Parameters

$A_{m,t,s}$	= 1, if a market authorization is given for market m in time period t in scenario s; 0, otherwise.
$CAPF_t, CAPCM_t, CAPB_t, CAPL_t, CAPP_t$	capacity for production of formulation, volume send to the CM, blisters, labels, packaged products in period *t*, respectively.
CFP, CPL	cost of scrapping one unit of packaged product or one unit of labels, respectively.
$DEM_{m,t,s}$	demand for market *m*, *t* periods into the launch for scenario *s*.
HA, HF, HL, HB, HP	holding cost per period for API, formulation, PPM, blisters and packaged products, respectively.
$IPT_{m,t,s}$	= 1, if the inventory of market *m* during period *t* for scenario *s* has to be discarded due to a forced label change; 0, otherwise.
$LTF, LTCM, LTB, LTL, LTP$	lead time for formulation, the CM, blisters, labels and packaged products, respectively.
OCP	ordering costs for an order of PPM.
$P_{m,s}$	probability that for market *m* scenario *s* occurs.

PA, PF, PCM, PB, PP	production cost of API, formulation, CM, blistering and packaging, respectively.
$PR_{m,s}$	demand at peak revenue level for market *m* in demand scenario *s*.
REV_m	sales price for market *m* minus direct sales cost.
SFE_m	the needed product for filling the downstream supply chain in market *m*.
U	sufficiently large number.

Objective function

$$\min \sum_{m\in M}\sum_{s\in S} P_{m,s}\cdot\varepsilon_{m,s} \quad +\sum_{t\in T}(HA\cdot \iota_t^a + PA\cdot\rho_t^a + HF\cdot\iota_t^f + PF\cdot\rho_t^f + PCM\cdot\rho_t^{cm} + \sum_{m\in M}(PB\cdot\rho_{m,t}^b + PB\cdot\sigma_{m,t}^l + OCP\cdot\omega_{m,t})) \tag{1}$$

Subject to:

Scenario-specific cost

$$\varepsilon_{m,s} = \sum_{t\in T}(HL\cdot\iota_{m,t,s}^l + HP\cdot\iota_{m,t,s}^p + HB\cdot\iota_{m,t,s}^b + CFP\cdot\gamma_{m,t,s}^p + CFL\cdot\gamma_{m,t,s}^l + PP\cdot\rho_{m,t,s}^p) + REV_m\cdot PR_{m,s}\cdot\sum_{t\in T}\left(\sum_{t'\le t}(A_{m,t',s}-\beta_{m,t',s})\right) \qquad \forall m\in M, s\in S \tag{2}$$

Market launch

$$\sum_{t\in T}\beta_{m,t,s}\le 1 \qquad \forall m\in M, s\in S \tag{3}$$

$$\sum_{t'\le t}A_{m,t',s}\ge\beta_{m,t,s} \qquad \forall m\in M, t\in T, s\in S \tag{4}$$

Product requirement

$$SFE_m\cdot\beta_{m,t,s}+\sum_{t'<t}DEM_{m,t-t',s}\cdot\beta_{m,t',s}=\eta_{m,t,s} \qquad \forall m\in M, t\in T, s\in S \tag{5}$$

Packaging

$$\iota^{p}_{m,t,s} = \iota^{p}_{m,t-1,s} - \gamma^{p}_{m,t,s} + \rho^{p}_{m,t-LTP,s} - \eta_{m,t,s} \qquad \forall m \in M, t \in T, s \in S \qquad (6)$$

$$\rho^{p}_{m,t,s} \leq \varsigma^{p}_{m,t} \qquad \forall m \in M, t \in T, s \in S \qquad (7)$$

$$\sum_{m \in M} \varsigma^{p}_{m,t} \leq CAPP_{t} \qquad \forall t \in T \qquad (8)$$

Non-anticipatory constraints

$$\rho^{p}_{m,t,s} \leq \rho^{p}_{m,t,s'} + U \cdot \sum_{t' \leq t} A_{m,t',s} \qquad \forall m \in M, t \in T, s \in \cup_{i \in n} S^{i}, s' \in S^{n}, n \in 1,2,3 \qquad (9)$$

$$\rho^{p}_{m,t,s} \geq \rho^{p}_{m,t,s'} - U \cdot \sum_{t' \leq t} A_{m,t',s} \qquad \forall m \in M, t \in T, s \in \cup_{i \in n} S^{i}, s' \in S^{n}, n \in 1,2,3 \qquad (10)$$

$$\iota^{p}_{m,t,s} \leq \iota^{p}_{m,t,s'} + U \cdot \sum_{t' \leq t} A_{m,t',s} \qquad \forall m \in M, t \in T, s \in \cup_{i \in n} S^{i}, s' \in S^{n}, n \in 1,2,3 \qquad (11)$$

$$\iota^{p}_{m,t,s} \geq \iota^{p}_{m,t,s'} - U \cdot \sum_{t' \leq t} A_{m,t',s} \qquad \forall m \in M, t \in T, s \in \cup_{i \in n} S^{i}, s' \in S^{n}, n \in 1,2,3 \qquad (12)$$

Blistering

$$\iota^{b}_{m,t,s} = \iota^{b}_{m,t-1,s} + \rho^{b}_{m,t-LTB} - \rho^{p}_{m,t,s} \qquad \forall m \in M, t \in T, s \in S \qquad (13)$$

$$\sum_{m \in M} \rho^{b}_{m,t} \leq CAPB_{t} \qquad \forall t \in T \qquad (14)$$

Formulation

$$\iota^{f}_{t} = \iota^{f}_{t-1} + \rho^{f}_{t-LTF} + \rho^{cm}_{t-LTCM} - \sum_{m \in M} \rho^{b}_{m,t} \qquad \forall t \in T \qquad (15)$$

$$\rho^{f}_{t} \leq CAPF_{t} \qquad \forall t \in T \qquad (16)$$

$$\rho^{cm}_{t} \leq CAPCM_{t} \qquad \forall t \in T \qquad (17)$$

API

$$\iota_t^a = \iota_{t-1}^a + \rho_t^a - \rho_t^f - \rho_t^{cm} \qquad \forall t \in T \qquad (18)$$

Label supply

$$\iota_{m,t,s}^l = \iota_{m,t-1,s}^l - \gamma_{m,t,s}^l - \rho_{m,t,s}^p + \sigma_{m,t-LTL}^l \qquad \forall m \in M, t \in T, s \in S \qquad (19)$$

$$\sigma_{m,t}^l \le U \cdot \omega_{m,t} \qquad \forall m \in M, t \in T \qquad (20)$$

$$\sum_m \sigma_{m,t}^l \le CAPL_t \qquad \forall t \in T \qquad (21)$$

Scrap

$$\gamma_{m,t,s}^p \ge \iota_{m,t-1,s}^p \cdot IPT_{m,t,s} \qquad \forall m \in M, t \in T, s \in S \qquad (22)$$

$$\gamma_{m,t,s}^l \ge \left(\iota_{m,t-1,s}^l + \sigma_{m,t-LTL}^l\right) \cdot IPT_{m,t,s} \qquad \forall m \in M, t \in T, s \in S \qquad (23)$$

$$\gamma_{m,t,s}^l \ge \sigma_{m,t-LTL}^l \cdot \sum_{t-LTL \le t' \le t} IPT_{m,t',s} \qquad \forall m \in M, t \in T, s \in S \qquad (24)$$

Domain restrictions

$$\beta_{m,t,s} \in \{0,1\} \qquad \forall m \in M, t \in T, s \in S \qquad (25)$$

$$\omega_{m,t} \in \{0,1\} \qquad \forall m \in M, t \in T \qquad (26)$$

$$\rho_{m,t,s}^p, \iota_{m,t,s}^b, \iota_{m,t,s}^l, \iota_{m,t,s}^p, \eta_{m,t,s}, \gamma_{m,t,s}^p, \gamma_{m,t,s}^l \ge 0 \qquad \forall m \in M, t \in T, s \in S \qquad (27)$$

$$\rho_{m,t}^b, \sigma_{m,t}^l, \varsigma_{m,t}^p \ge 0 \qquad \forall m \in M,\ t \in T \qquad (28)$$

$$\rho_t^f, \rho_t^{cm}, \iota_t^f, \rho_t^a, \iota_t^a \ge 0 \qquad \forall t \in T \qquad (29)$$

$$UPM_{m,s}, \varepsilon_{m,s} \ge 0 \qquad \forall m \in M, s \in S \qquad (30)$$

The objective of the model in Eq. (1) is to minimize the expected value of the total cost of the launch plan. The costs consist of the scenario dependent cost $\varepsilon_{m,s}$ for each market, CM cost, PPM ordering and volume cost, blistering cost and production and holding costs of the API and

formulation. The scenario dependent cost (Eq. (2)) considers lost peak revenue which is calculated as the delay between authorization and launch multiplied with peak daily demand and the sales price from each market. Lost peak revenue is as such a measure for TTM represented in the objective function. Additionally, the cost of the scenario dependent scrap volumes, packaging and holding cost of blisters, labels and packaged volumes are considered. The drug can only be launched once per market (Eq. (3)). According to Eq. (4) launches cannot be conducted before authorization is granted. Eq. (5) finds the required amount of finished products needed. In this constraint, volumes for the filling of the downstream supply chain as well as the demand are considered. The upstream supply chain used to produce these finished products is modeled through constraints Eq. (6)-(21). Equations (6), (13), (15), (18) and (19) are inventory balances, equations (7), (8), (14), (16), (17) and (21) are capacity constraints. Eq. (7) determines the capacity reserved for each market to ensure that the required amount can be produced, $\varsigma_{m,t}^{p}$. The sum of these capacities over all markets needs to be smaller than the total packaging capacity (Eq. (8)). Eq. (9), (10), (11) and (12) are non-anticipatory constraints, which force decision variables on packaging volumes and finished product inventory before authorization to be identical for all scenarios to reflect that information about the future development is not available at this time (cf. the discussion in the previous section). In Eq. (20) the variable $\omega_{m,t}$, is set to 1 when PPM is ordered. This binary decision variable is required to capture the cost structure of for PPM. All PPM and risk packaged products on stock have to be scrapped, if a forced label change is required (Eq. (22)-(24)). Note that, through Eq. (24) all inbound PPM volumes also have to be scrapped. All remaining constraints, Eq. (25)-(30), are domain restrictions.

3.5. Case study

The key characteristics of typical pharmaceutical companies have been used to test the performance of the model in a series of numerical tests. A set of data has been created based on the information obtained in interviews with managers from 9 different pharmaceutical companies.

The supply chain shown in Figure 3.3 is considered with all the illustrated elements and five different markets. The time horizon is set to 50 weeks. All costs are based on the production cost of the API being set to 1.0 monetary units. PPM cost is e.g. usually around 10 % of API cost and hence, *PL* is set to 0.1. The remaining costs in Table 3.3 have been created in similar fashion. The ordering cost of new PPM used to approximate the volume discount, is set to 25. The scrap costs represent the cost related to getting rid of the waste which often requires special treatment. Holding costs are set to 0.4 % per week of the product value at the respective stage in the supply chain.

Table 3.3: Cost parameters.

Cost of Scraped Products		*PPM Ordering Cost*	*Production Costs*					
CFP	*CFL*	*OCP*	*PA*	*PF*	*PCM*	*PB*	*PL*	*PP*
0.1	0.01	25	1.0	0.1	0.2	0.1	0.1	0.15

The definition of the scenarios and market data depends on company, new drug type etc. To account for this variation, a number of problem instances have been created. Data intervals for individual markets from different European regions have been created by scaling data from Danzon et al. (2005). European markets are particularly interesting as they share the approval process (via EMA) but have separate authorization processes. The key data for the markets is given in Table 3.4. From these intervals, combinations of values were randomly drawn to give 25 different market data samples. Revenues 10 times higher than production cost are not unusual in the pharmaceutical industry.

For the scenarios, two sets with different probabilities for a nominal negotiation length (which is usually given by the authorities), 2 weeks faster negotiation or a 2 weeks delay were considered. Hence the probability sets (early, nominal and delayed) are given by {20%; 40%; 40%} and {10%; 30%; 60%}. The best and worst case demand scenarios are either ± 40 % or ± 60 % of the realistic demand level with worst, realistic and best case scenario demand occurring with a probability of 25 %, 50 % and 25 %, respectively. The full combination of the authorization probabilities (2), the demand variation (2) and the market data samples (25) lead to 100 different instances in total.

Maximum capacities and lead times can be found in Table 3.5. Capacities for PPM and CM are kept constant over time. For the remaining stages, capacity is increased from 0 to full capacity over the first 26 weeks (half a year). This curve can be seen as a linear approximation of the ramp-up process. Due to investment considerations, formulation capacity is set to the lowest total demand and CM will be used for the remaining volume, while inexpensive packaging and blistering capacity is set to the highest possible demand. Demand is described by an s-shaped market penetration curve (cf. (Cook, 2006)), which takes 25 weeks to achieve full market penetration and reaches 50 % peak demand after 14 weeks. The supply chain filling effect for new markets, SFE_m, is set equal to the accumulated demand of the first 14 weeks.

In Figure 3.6 the aggregated expected demand with on-time authorization and realistic case demand for all markets and the increase of packaging capacity can be seen for sample 15. The supply chain filling effect can obviously not be covered by just-in-time production. This effect is even more pronounced for higher demand scenarios and earlier market authorizations.

Table 3.4: Market data.

Markets	*Sales price*	*Expected peak demand level*	*Risk of a forced*	*Markets*
A	[9;13]	[800;1,000]	[10;20]	[10;15]
B	[2;4]	[200;500]	[5;10]	[20;25]
C	[6;8]	[1,000;1,500]	[5;15]	[15;20]
D	[9;13]	[100;400]	[15;25]	[10;15]
E	[8;10]	[400;600]	[10;20]	[8;12]

Table 3.5: Capacities and lead times.

Stage	*Maximum capacity*		*Lead time*	
	Notation	*Value*	*Notation*	*Value*
Packaging	CAPP	4,000	LTP	1
Blistering	CAPB	4,000	LTB	0
Formulation	CAPF	2,500	LTF	1
PPM	CAPL	4,000	LTL	3
CM	CAPCM	4,000	LTCM	2

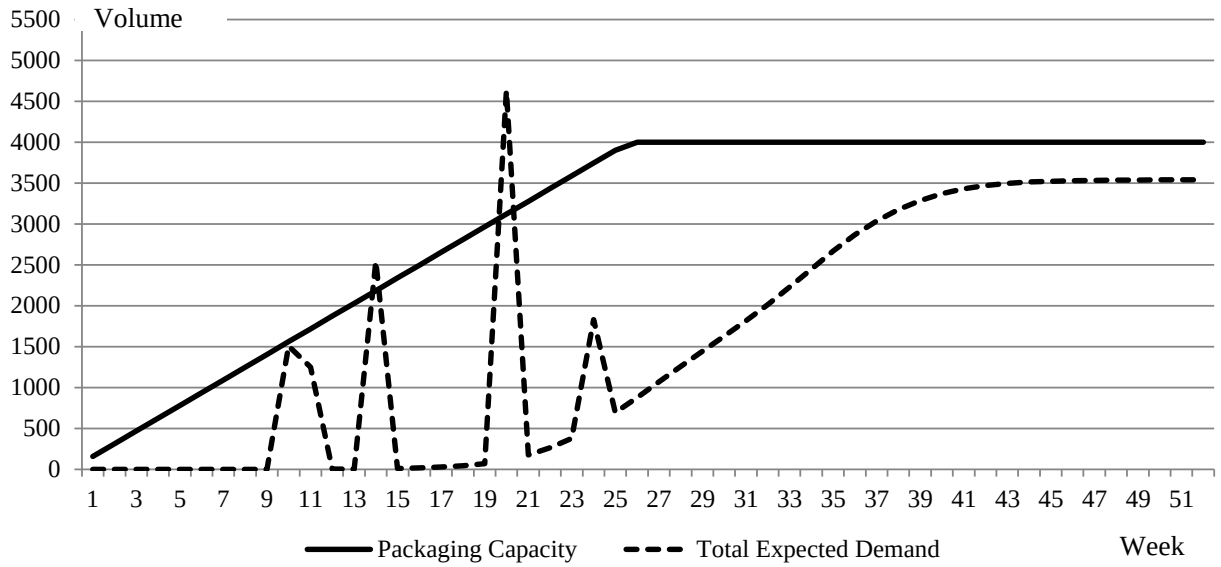

Figure 3.6: Example of increase in packaging capacity and aggregated expected demand for on-time authorization and best case demand for all markets from sample 15.

3.6. Numerical analysis

3.6.1. Baseline case

The model was implemented in OPL Studio 6.0. Each problem instance has 2,280 binary, 15,775 continuous variables and 123,391 constraints. All 100 instances were solved to optimality on a Dell Precision M65 with an Intel Core 2 T7200 2.00GHz processor and 2 GB RAM with 936 seconds of calculation time per instance on average.

An example of the three central launch preparation decisions can be seen for sample 15 in Figure 3.7. API supply volumes vary initially as the first inventory is build up. After period 15, the limited capacity of the supply chain can be seen, and CM volumes are used from period 36. 36 different PPM orders are made. Due to the ordering cost few orders with less than maximum volume are seen. The drop in all volumes in the last periods is due to end-of-horizon effect.

Considering all 100 samples, the split between the different average costs in Table 3.6 shows the dominance of the production cost, but also shows the size of the lost peak revenue, which is comparatively small, indicating that in the optimal solution high priority is given to a short TTM. 126 units of finished product and 10,871 units of PPM are expected to be scrapped. The large difference is due to the difference in cost and lead time of PPM compared to finished products. The CM produces 18 % of all the formulated volume.

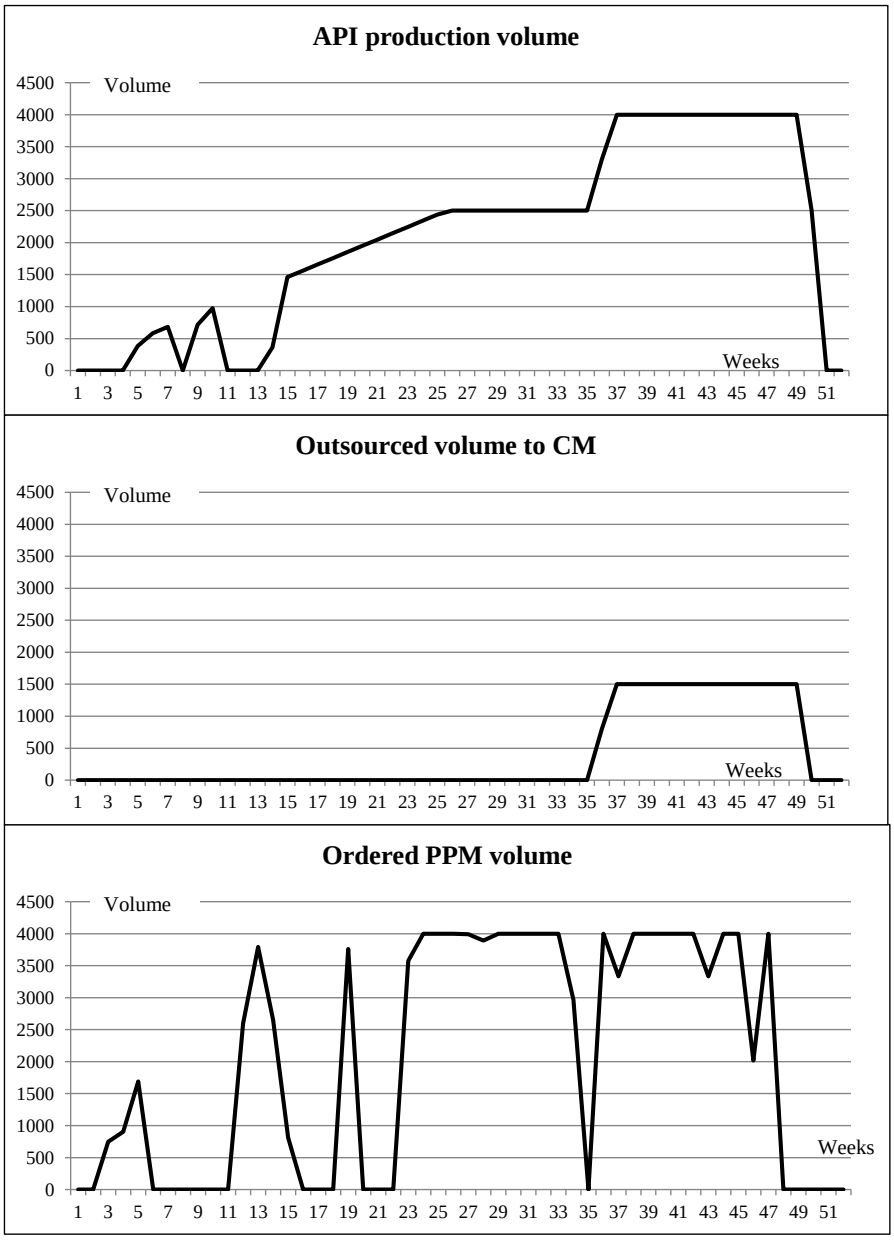

Figure 3.7: The three central launch preparation decisions for sample 15.

Table 3.6: The average expected cost for all 100 samples of the baseline case.

Cost type	*Cost*	*% of total cost*
Exp. lost peak sales	16,214	9.32%
Exp. production cost	148,876	85.59%
Exp. scrap cost	121	0.07%
Exp. holding cost	3,802	2.19%
PPM ordering cost	1,065	0.61%
CM cost	3,859	2.22%
Total cost	173,938	-

Table 3.7: Average expected delay and risk packaging percentage over all 100 samples for the baseline case.

Market	*Revenue*	*Expected launch delay for market [weeks]*	*Expected peak demand level*	*Percentage of supply chain filling covered by risk packaged inventory for market [%]*
A	[9;13]	0.29	[800;1,000]	15 %
B	[2;4]	2.00	[200;500]	0 %
C	[6;8]	0.51	[1,000;1,500]	27 %
D	[9;13]	0.33	[100;400]	11 %
E	[8;10]	0.35	[400;600]	5 %

The best measure of TTM for our problem is the expected delay of market launch. Table 3.7 shows the expected delay and the share of risk packaging for each market. As packaging for smaller markets can be done in the week of the market launch, risk packaging is mostly required for larger markets, for which the capacity is insufficient to produce the supply chain filling volume just-in-time as can e.g. be seen in Figure 3.6. The smaller markets B, D and E correspondingly require lower levels of risk packaging. The expected delays instead follow the sales price for the markets. Especially the less profitable market B and C are postponed. This corresponds to statements from managers who do not hesitate to down prioritize lower valued markets.

3.6.2. Impact of supply chain structure and operations policies

To gain managerial insight into the management of product launches in the pharmaceutical industry, further numerical experiments have been carried out. These include extensive tests of (a) different

supply chain configurations and (b) operations policies such as risk packaging and overstocking prevalent in the industry.

The overall results of the numerical tests can be seen in Table 3.8, in which the key measures, expected cost, shipped volume, API, PPM and scrap volumes, have been indexed against the baseline case. For each market, the expected delay or TTM and risk packaging level i.e. the percentage of the supply chain filling volume on inventory immediately prior to launch is given in Table 3.9.

Supply chain configurations

In this section, we test attractive configurations of the supply chain different to the one presented in the case study. To find out how the PPM supplier influences the market launch, the two main PPM parameters used in our model are varied. We double the PPM lead time to see if reordering could delay the market launch. We also investigate whether doubling the ordering cost would lead to fewer PPM orders. Furthermore, we test a configuration without a contract manufacturer and expand formulation, blistering and packaging capacity with 20 % to find the value of additional capacity as a way of buffering against risk. Finally, we double all sales prices. This could represent products with a higher profit margin such as biologics.

Table 3.8: Overall results indexed with the baseline case.

	Case	*Exp. cost*	*Exp. shipped vol.*	*API vol.*	*PPM vol.*	*Scrap vol.*		*Ratio send to CM*
						Packaged	PPM	
	Baseline case	100	100	100	100	100	100	100
Different supply chain configurations	Doubling PPM lead time (3 weeks → 6 weeks)	101	100	99	100	96	111	98
	Doubling ordering cost (25 → 50)	101	100	100	100	99	106	99
	No contract manufacturer	105	95	87	88	78	65	0
	20 % more capacity	99	100	101	101	51	88	61
	Double all sales prices	106	102	108	108	110	157	121
Operations policies	Strictly enforced risk packaging*	101	100	101	101	569	134	93
	Strictly prohibited risk packaging	101	99	99	100	0	110	101
	Overstocking API	123	103	124	112	116	205	119
	API arriving in period 1	108	99	98	98	89	114	58

*: 24 samples where infeasible and were hence not included in the results.

Table 3.9: Solution structure of the numerical test.

Case		*Expected launch delay for market [weeks]*					*Percentage of Supply Chain Filling covered by risk packaged inventory for market [%]*				
		A	B	C	D	E	A	B	C	D	E
Baseline case		0.29	2.00	0.51	0.33	0.35	0.15	0.00	0.27	0.11	0.05
Different supply chain configurations	Doubling PPM lead time (3 weeks → 6 weeks)	0.39	2.06	0.62	0.42	0.49	0.12	0.01	0.28	0.12	0.04
	Doubling ordering cost (25 → 50)	0.30	2.08	0.55	0.35	0.35	0.13	0.01	0.26	0.12	0.05
	No contract manufacturer	0.59	4.27	1.43	0.78	1.31	0.10	0.00	0.20	0.12	0.06
	20 % more capacity	0.24	1.83	0.39	0.21	0.33	0.06	0.01	0.16	0.02	0.03
	Double all sales prices	0.17	0.59	0.23	0.21	0.12	0.17	0.05	0.27	0.12	0.04
Operations policies	Strictly enforced risk packaging*	0.34	1.91	0.48	0.28	0.35	1.00	1.00	1.00	1.00	1.00
	Strictly prohibited risk packaging	0.41	2.03	0.70	0.47	0.35	0.00	0.00	0.00	0.00	0.00
	Overstocking API estimate	0.13	0.19	0.17	0.19	0.09	0.16	0.08	0.28	0.16	0.06
	API arriving in period 1	0.35	2.20	0.65	0.37	0.37	0.11	0.00	0.24	0.13	0.05

*: 24 samples where infeasible and were hence not included in the results.

If the PPM lead time is doubled, the overall results are strongly affected, showing that PPM supplier lead time is critical for the market launch (twice the increase of doubling the ordering cost). The increase of the PPM ordering cost appears to have limited effect on the structure of the solutions. This shows that fast delivery of the PPM is far more important than discounts and ordering cost. Hence PPM suppliers should be selected based on lead time rather than price. Removing the contract manufacturer does have a large effect on the result as it limits the available formulated product ready at market launch. Without a contract manufacturer, insufficient quantities are produced and fewer products can be ready for launch in time. As a consequence the expected delay increases and the total cost goes up. Risk packaging is low as it is not possible to produce enough to risk package more. The test of increasing capacity proves that risk packaging is the result of low capacity. The increase also reduces both the total cost and TTM allowing managers to balance this effect against the investment in additional equipment. Doubling the sales prices increases the total cost due to the higher lost peak revenue. Reducing TTM becomes even more important. Accordingly, the expected delays are halved. This is made possible by increasing risk packaging, PPM ordering, scrap and CM use. These test show that even with different problem settings, our model still provide valuable decision support for launch preparation decisions.

Operations policies

Two different policies for risk packaging are tested against the baseline case. One is strictly enforced risk packaging, which prescribes that at least the supply chain filling volume has to be packaged and on inventory at the earliest authorization date. The other is strictly prohibited risk packaging in which no packaged product is allowed on inventory prior to market launch. Both strict risk packaging policies lead to higher cost than the baseline case. For enforced risk packaging, the increase is caused by additional scrapping. The available products lost this way also cause an additional delay for market A. For the prohibited risk packaging, the extra cost is caused by the increased TTM and the corresponding lost peak revenue. Our modeling approach offers a 1 % reduction of the total market launch and production cost in the first year by better balancing the cost and opportunities related to risk packaging.

Due to (a) the lack of methods to accurately find the required API supply volume, (b) the stability of the API (i.e. no product expiration and hence scrap) and (c) the long lead time of the API, the required amount is often overestimated, according to managers. In general, the policy implemented by a number of our industry contacts forces overstocking the API inventory before market launch to cover all demand in all scenarios plus enough to account for incidents like forced label change. By introducing this volume in period 1 in our model, we were able to test the current practice against our model. The use of our model does lead to far better results as it lowers cost (-23 %) by reducing scrap and obviously also lowers holding cost. Even if we force our model to also provide all API at the beginning of the planning horizon (API arriving in period 1), the saving still is 14 % of the total cost throughout the entire planning horizon.

However current practices lead to shorter expected delays and faster TTM. The difference in shorter expected delays comes from more risk packaging. This riskier behavior of overstocking API hence shows that managers are more likely to take on greater risk later, since they then have plenty of API anyway and might just as well use it instead of letting it sit in inventory. Large amounts of scrap result. When managers overstock API, they exclusively focus on reducing expected delays of the market launches i.e. shortening TTM, while losing the overall cost implications out of sight. This effect would be even more pronounced, if product perishability would be taken into account.

3.7. Balancing TTM reduction with costs through robust optimization

Using overstocking to reduce TTM is an indirect approach to lower TTM, which also leads to high holding cost and scrap cost as demonstrated in the previous section. In this section, we investigate how TTM can be reduced directly with lower unnecessary cost. With high sales prices, even short delays lead to considerable lost peak revenue. If a delay occurs in one scenario, its cost would be much higher than the expected cost over all scenarios. Hence, TTM can be reduced directly by reducing the variance of the cost for all scenarios.

We use robust optimization to demonstrate this (cf. e.g. Mulvey et al. (1995)). Since we are only concerned with delayed markets, we only consider the positive deviation of the costs of each scenario above the expected cost i.e. first order upper partial moment or upper partial mean [UPM] (Nawrocki, 1999). First, we introduce a new variable, $UPM_{m,s}$, which is a continuous variable representing the upper partial mean in market m of scenario s. The parameter λ is a weight for the upper partial mean, which is a measure for the risk aversion of the decision maker. We introduce the following changes to our model.

$$\begin{aligned}\min \sum_{m\in M}\sum_{s\in S} P_{m,s}\cdot\varepsilon_{m,s} \quad & +\sum_{t\in T}(HA\cdot \iota_t^a + PA\cdot\rho_t^a + HF\cdot\iota_t^f + PF\cdot\rho_t^f \\ & +PCM\cdot\rho_t^{cm} + \sum_{m\in M}(PB\cdot\rho_{m,t}^b + PB\cdot\sigma_{m,t}^l + OCP\cdot\omega_{m,t})) \\ & +\lambda\cdot\sum_{m\in M}\sum_{s\in S} P_{m,s}\cdot UPM_{m,s} \end{aligned} \tag{31}$$

$$UPM_{m,s} \geq \varepsilon_{m,s} - \sum_{s'\in S} P_{m,s'}\cdot\varepsilon_{m,s'} \qquad \forall m\in M, s\in S \tag{32}$$

In Eq. (31), the objective function is expanded with the term for $UPM_{m,t}$ weighted with λ. $UPM_{m,t}$ is set in Eq. (32) as the positive difference between the value of all scenarios in a market and the expected solution for all scenarios. The value for λ depends on the risk aversion of the responsible manager, in that increasing risk aversion is reflected in increasing values of λ. Eq. (2) to

(30) remain the same. The effect has been tested and the results can be seen in Figure 3.8. Scrap, ordering and CM cost are small and fairly stable and have been omitted. TTM is reduced as can be seen in the shorter expected delays in Table 3.10, though the expected delay for each market is rather unstable. For $\lambda = 2$, TTM has been significantly reduced for only 3 % additional cost. The increase in cost in attributed main to production and holding cost and only to a lesser extend higher scrapping cost. It should be noted, that since robust optimization reduces the variance (UPM in our case), solutions with the same delay over all scenarios may occur. This effect is an obvious shortcoming of this risk management approach. As λ has no natural upper bound, each manager has to decide, how much he or she is willing to pay for a lower TTM. In our case for λ values between 0 and 2, the Pareto relationship between lost peak revenue and the total cost is shown in Figure 3.9. The more risk of a market launch delay a manager is willing to take, the lower are the expected cost of the entire market launch. Conversely, if the manager is risk averse, a lower risk of a delay can be ensured by accepting a higher expected total cost.

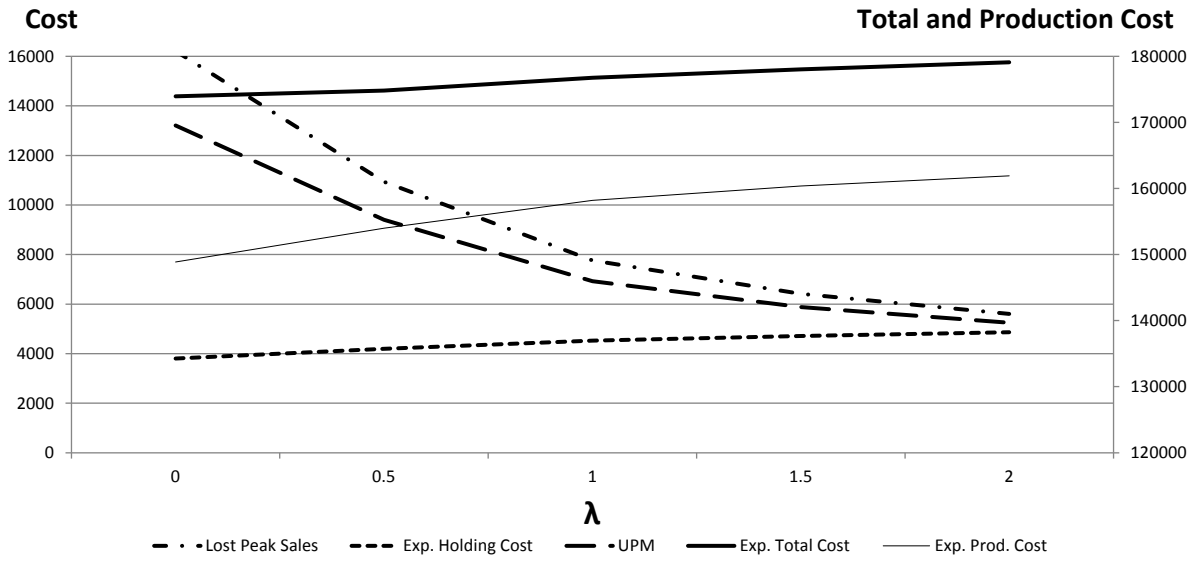

Figure 3.8: Results for different λ values.

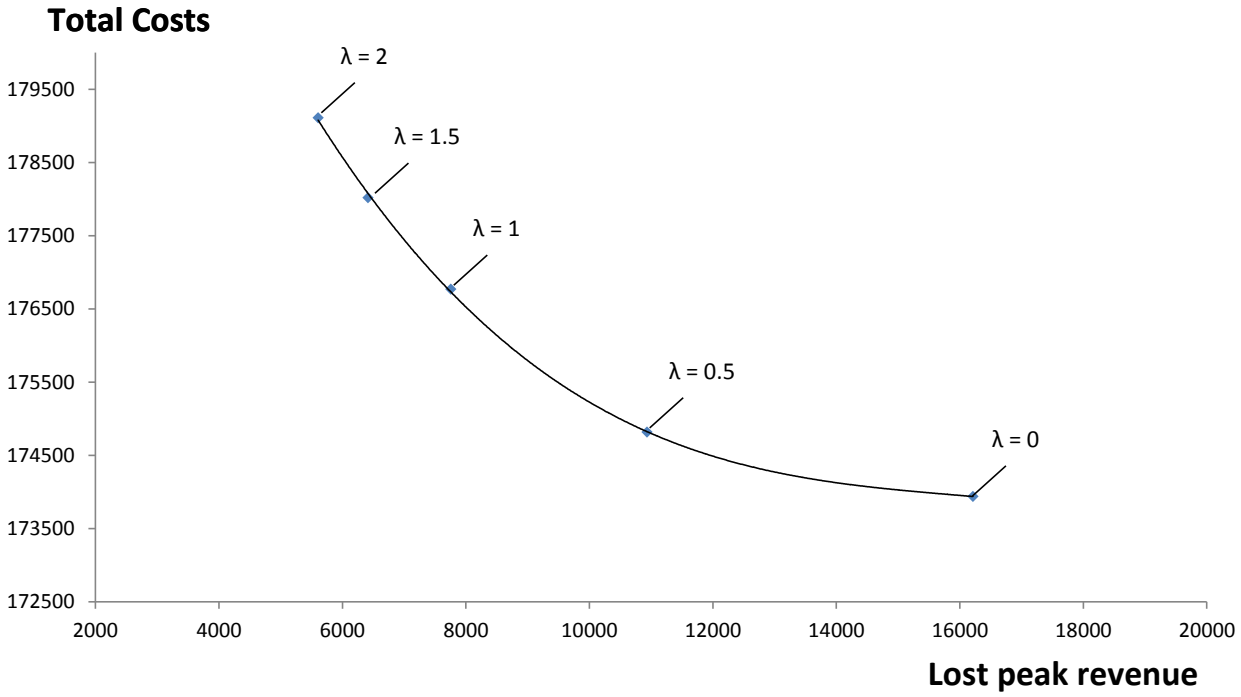

Figure 3.9: The Pareto curve.

Table 3.10: Numerical test for varying values of Lambda.

Lambda	*Exp. cost*	*Exp. shipped vol.*	*Scrap packaged vol.*	*UPM*	*Total risk packing*	*Expected delay in weeks*				
						A	B	C	D	E
λ = 0.0	100.00	100.00	100.00	100.00	100.00	0.29	2.00	0.51	0.33	0.35
λ = 0.5	100.50	101.09	101.04	71.19	100.69	0.21	1.25	0.35	0.25	0.22
λ = 1.0	101.63	101.73	104.50	52.45	103.35	0.76	0.16	0.57	0.03	0.07
λ = 1.5	102.34	102.07	108.76	44.52	106.56	0.15	0.64	0.21	0.22	0.13
λ = 2.0	102.97	102.28	108.95	39.70	106.99	0.15	0.47	0.18	0.19	0.13

3.8. Conclusion

Treating the topic of market launch planning of new pharmaceutical drugs, we identified three key risks or uncertainties; the uncertain duration of the authorization process, the risk of a forced label change and uncertain reimbursement levels. We developed a two-stage stochastic MILP model for addressing market launch planning. The key launch preparation decisions are the required API, PPM, CM, formulation and blister volumes and reservation of packaging capacity, which have to be planned up front (or here-and-now). All possible launch dates are found on a wait-and-see basis as they depend on the outcome of the authorization process. Additional wait-and-see decisions included packaging volumes and blistering inventories. As the uncertainties materialize at undetermined points in time due to the uncertain authorization date, non-anticipatory constraints are used for forcing decisions prior to the authorization to be identical. The model was reduced in size by using the problem structure to reduce the number of scenarios. A case study was created which reflects the reality of the industry and an extensive numerical test was carried out. Risk management was used as a more systematic approach to deal with TTM cost and opportunities.

In the numerical test it was possible to demonstrate the applicability of our modeling approach. In summary, our numerical analysis has led to the following managerial insights:

- Risk packaging is a consequence of limited capacity. In order to reduce TTM focus should be given to the larger markets as their size does not allow for a just-in-time production of the required volumes.
- Unavoidable market launch delays should be pushed to less profitable markets.
- Our modeling approach performs better than a strict risk packaging policy due to a better trade-off between cost and opportunities involved in reducing TTM.
- PPM suppliers should be chosen based on lead time performance rather than cost.
- There is a 14 % cost reduction to be gained from applying our model instead of using an overstocking rule for estimating the API supply volume as observed in the industry today.
- Overstocking API before market launch leads to more risk affine decision making (larger risk packaging volumes) which result in higher scrapping cost.
- Using robust optimization with the upper partial moment, we demonstrated that the lowering of the TTM goes along with only a modest increase in cost – if properly managed.

We also showed that our model in principle also is applicable for new products such as the fast growing group of biologics which have a higher sales price. However, the implications of the more demanding and costly API production process deserve further investigation. Our model does not suit generic manufacturers in its current form, as the forced demand fulfillment assumption is too strict and the problems with the reimbursement negotiations are much smaller.

There are several ways to expand the work presented in this paper. Capacity was here modeled in a standard way, but was shown to be the key for effective market launch. The main limitations that

go along with such a modeling approach come from a) the potential competition of the new product with other products for the production resources and b) from the limited initial skills of workers, which increase during ramp up as experience is gained. As identified in the literature review, contributions have already addressed the impact of introducing a new product into a multi-product pharmaceutical supply chain. Several studies have also covered ramp up of production. However, ramp up in multi-stage multi-site production such as often present in secondary pharmaceutical production seems to be largely untouched.

We assumed that the uncertainties are all independent. For the uncertain reimbursement level independence between markets is not completely accurate as reference pricing is used often used. Incorporating such interdependencies in our already complex structure of uncertainties is challenging, especially considering that the use and influence of reference prices is not transparent.

Though we have addressed inventory levels, we have not considered safety stock levels. The usual safety stock calculations neither consider ramp up of capacity nor the risks described here, which could be worth further investigations.

Chapter 4: Modeling ramp up for secondary pharmaceutical production

This chapter is based on an article submitted as:

Hansen, K. R. N., Grunow, M. (2013). *Modelling ramp up in the context of secondary pharmaceutical production*, submitted for International Journal of Production Research

Abstract

Ramp up is the term used to describe the increase in production capacity over time as experience with producing a new product is gained. Due to time-consuming demand diffusion, full utilization of production is not always the best production policy during ramp up. However, current ramp-up models all assume full utilization, which leads to an overestimation of the available production output during ramp-up. We therefore develop a methodology for capturing ramp up of effective capacity as a function of the cumulative production volume, which better reflects the experience gained with producing the new product. We demonstrate our more accurate and computationally effective method for the case of secondary pharmaceutical production. We develop a capacity planning model for a new pharmaceutical drug, which determines the number of new production lines and the build-up of inventory such that product availability at market launch is ensured. We apply our MILP model to a real industry case study using three empirically observed ramp-up functions to demonstrate its value as decision support tool. We also demonstrate the superiority of our ramp-up modelling approach over traditional time-dependent ramp-up functions and derive several insights into ramp up management.

4.1. Introduction

4.1.1. Ramp up and experience

Product life cycles are shortening and new products success is essential to companies continued profitability. Several studies have investigated which factors contribute to the success of new products (e.g. (Cooper and Kleinschmidt, 1995)), but little research has looked into how to manage product launch from an operations perspective (Bowersox et al., 1999). Achieving new product success requires that sufficient volume of the product can be produced, which is especially important in the early life of a new product, when it can typically be sold at a premium price such as seen in the electronics (Terwiesch and Bohn, 2001) and the pharmaceutical industry (Hansen and Grunow, 2010). Hence well-managed supply chain operations for product launch are important, but have been limited to focus on capabilities and forecasts in the literature (van Hoek and Chapman, 2006). The availability of the product in this phase is however often limited by the slow increase in production volume referred to as ramp up. Ramp up of production is becoming increasingly

important in industries such as automotive (Schuh et al., 2005) and electronics (Terwiesch and Bohn, 2001). Given the premium sales prices of new products, poor ramp-up performance and failing to meet demand has a very profound impact on a company's bottom line. When Apple introduced its iPhone 5 in late 2012, it was sold out in the opening weekend. Despite the apparent success, investors send the stock down 1.4 % as Apple missed out on selling an approximate 1 million units extra (Owens, 2012).

The ramp-up phase or simply production ramp up starts when a new product is introduced into production and finishes when the target capacity is reached. During this phase, managers and workers are gaining experience with producing the new product allowing them to extend the production capabilities. We refer to these production capabilities as effective capacity and the increase of effective capacity over time as production ramp up (Figure 4.1). The curve showing the increase in effective capacity is called the ramp-up curve. The effective capacity does however not have to be used. The actual production volume can be smaller than the effective capacity, leading to a capacity utilization smaller than one. These terms are illustrated in Figure 4.1. For the automotive industry, large demand leads to full utilization during ramp up (Schuh et al., 2005), but this does not hold for all industries.

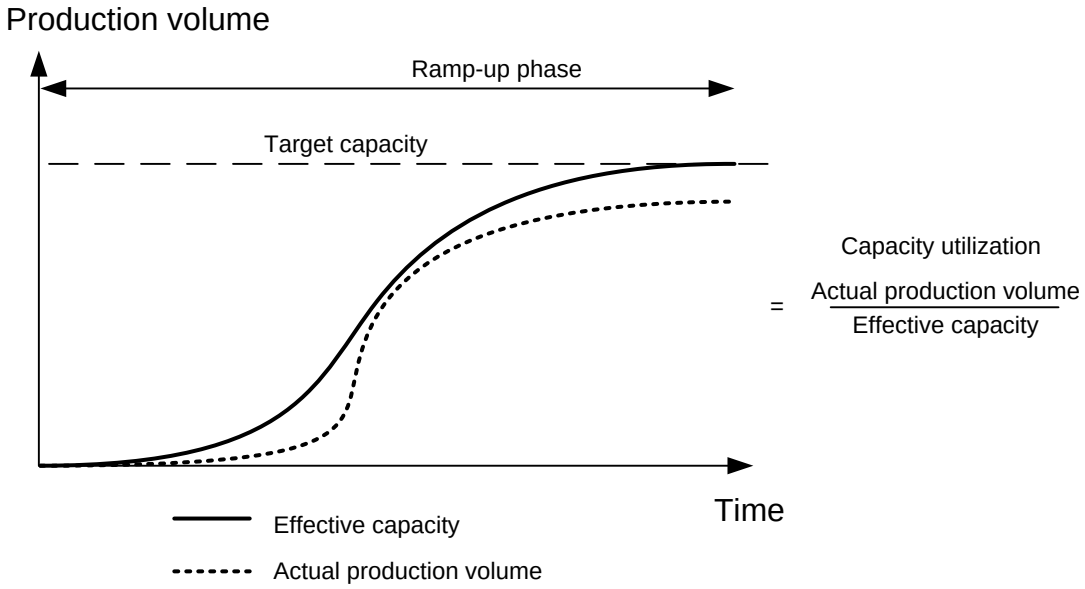

Figure 4.1: Illustration of the used terms in production ramp up.

Traditional models normally describe the increase in effective capacity over time. Such models however use the assumption that all the effective capacity is used i.e. that the utilization is always 1. This is only true if ample demand ensures everything can be sold (as is usually the case for example for new models in the automotive industry). For other industries, balancing supply and demand may result in a lower utilization at times. In this case, the full effective capacity found via traditional

models is misguiding, due to the shortfall in experience gained. The true experience gained is not captured and the measure of effective capacity is not accurate. A method in which the increase in effective capacity is captured as a function of cumulative production volume would instead provide a better expression for the true experience gained and hence be more accurate. The main focus of this paper is to develop exactly such a method.

To elucidate this problem, we consider secondary pharmaceutical production, which comprises the production stages involved in turning the active pharmaceutical ingredient [API] into pills or putting it into more advanced drug delivery systems before finally packaging it. Here we consider a new pharmaceutical drug, which requires new dedicated production equipment. Secondary pharmaceutical production displays significant ramp-up effects when production of a new product is started as the manufacturing processes resemble regular discrete part production in other industries. This is especially true for more advanced drug delivery systems, which are made up of mechanical components requiring assembly. In addition to manual operations such as assembly and material handling, strict regulations on documenting safety and traceability lead to extensive compulsory quality assurance and documentation processes, which also have to be learned by the employees. The following section provides background information on the case of secondary pharmaceutical production.

4.1.2. Ramp-up planning for secondary pharmaceutical production

Regulatory authorities such as the Food and Drug Administration [FDA] or European Medicines Agency [EMA] impose strict requirements on the performance of investigational new drugs during the clinical trials. If successful, the product is said to have been approved. However, if unsuccessful, the project is discarded and the investment in R&D is lost. An approved drug will enjoy the protection of a patent, which may be highly profitable. For this reason, pharmaceutical manufacturers manage ramp-up processes with strong focus on decreasing Time-to-Market [TTM] to have the drug in the market under patent protection for as long as possible. However patents, which are normally filed early in the R&D process, have often lost most of their protection period when the drug is launched (Laínez et al., 2012). When patents expire, competing drugs from generic off-patent pharmaceutical manufacturers quickly enter the market, leading to strongly reduced profit margins. In addition, increasingly hard reimbursement negotiations have to be carried out with the healthcare authorities to gain final market authorization, because the authorities are focusing on keeping expenditures down. These negotiations about price and reimbursement levels are further reducing the exclusivity period in the market. To keep TTM as low as possible, product availability at market launch is paramount and production managers have to guarantee they can deliver the required volumes of finished product (Pisano and Rossi, 1994). This challenge managers to improve operations further, and necessitates new planning methodologies (Hansen and Grunow, 2010).

With the construction of new factories and production lines lasting years, capacity planning for the API has to be made before the outcome of the clinical trials is known. New capacity is hence exposed to a considerable risk of a drug failing the clinical trials in which case the new product

would never reach production and the investment in capacity is lost. For capacity planning for the API, decisions on capacity expansion normally have to be made 4-5 years before launch as can be seen in Figure 4.2 (Papageorgiou et al., 2001, Gatica et al., 2003). The production of the API is referred to as primary production. In contrast, secondary production, consisting of bringing the API in a consumable form, is often simpler.

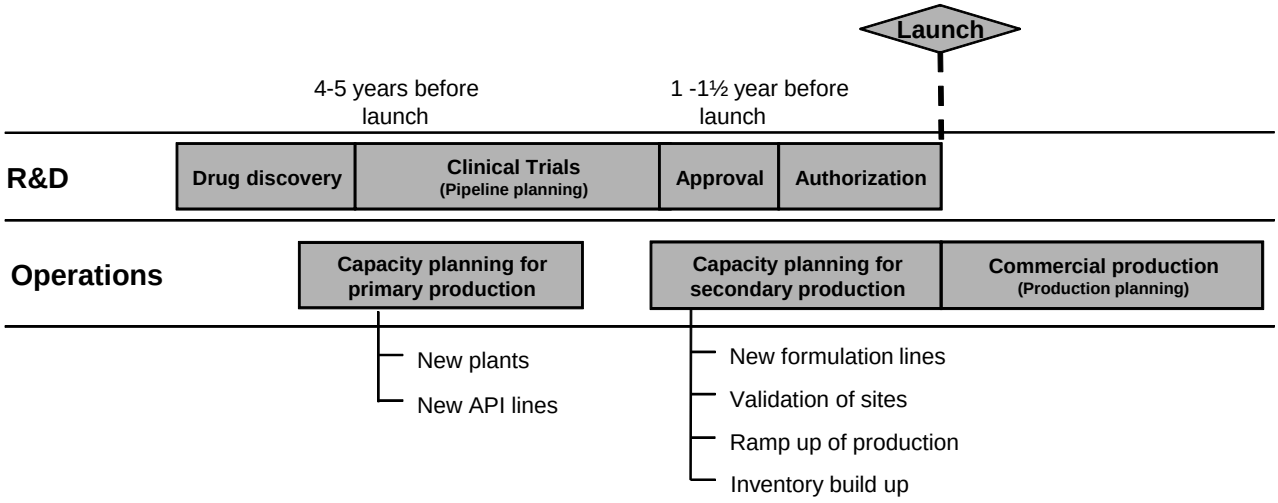

Figure 4.2: Overview of the tasks during new product introduction in the pharmaceutical industry.

The construction of new production lines in secondary production takes only around 3 months. This allows pharmaceutical companies to make decisions on secondary production capacity once the (preliminary) results of the clinical trials are looking so promising, that companies are confident the new product will get approved. Failure to obtain an approval is at this stage not considered anymore. Capacity expansion of secondary pharmaceutical production takes place in a short and well defined time frame close to market launch with capacity planning decision having to be made 1 to 1½ year before market launch as can be seen in Figure 4.2. This type of production displays significant ramp-up effects. Due to time-phased market launches and slow demand diffusion, production capacities are also frequently left unutilized. An effect further pronounced by the need to produce small volumes for process validation purposes long before market launch.

During the market launch phase, demand varies significantly. At market launch, companies have to have large volumes of finished products ready for filling the downstream supply chain, so the drug will be available in hospitals and pharmacies when patients needs it. We refer to this as the supply chain filling volume. Some companies are able to send out filled trucks with the new product within an hour after they receive the final market authorization. To cover this demand, production has to be ramped up and inventory built up without overinvesting in capacity. After market launch, the sales of a new drug follow a typical demand diffusion process as the drug gets used by more and

more patients (Cook, 2006). For pharmaceutical drugs this process often takes up to a year as patients are extraordinary loyal to their old (and less efficient) medication.

In order to sell products in a given market, the production of those products must first be validated by the authorities. Most authorities prescribe a set of guidelines referred to as Good Manufacturing Practices [GMP] for how pharmaceutical production equipment and utilities must be cleaned and handled to not put the patients at risk. To obtain a validation, the production of a minimum volume in a controlled and safe manner must be documented (FDA, 2011, EMA, 2012). Living up to these guidelines requires a significant investment in time and money to upgrade production and utilities and compiling the required documentation. It takes around six months for the authorities to finish reviewing the validation documents. A production site only has to be validated once, so the validation process does not have to be repeated for every production line. Though validation is required for selling the product, it is not required for producing it. This means that inventories can still be built up towards market launch before the authorities complete the validation process. The production process is normally validated as part of the approval application, but this is not strictly required.

The task of building and installing production lines is carried out by engineering firms with specialized engineers and technicians. When several production lines have to be installed, the number of specialist teams limits the number of lines constructed simultaneously. These limited resources in the construction of the production lines have to be considered.

Normally, the API is a stable compound, but when it is formulated, the drug starts to deteriorate. Though the actual shelf life is usually a couple of years, the effective shelf life available to the company is much smaller as a sufficient remaining shelf life is required, when the product is shipped out.

The uncertain duration of the reimbursement negotiations with the authorities increases the uncertainty about the earliest possible launch date. Demand uncertainty is high, as forecasts for the new drug build on estimates rather than historical data and are influenced by the uncertainty about price and about the health claims the company is allowed to make about the new drug. Nonetheless, due to the high profit margins of the drug, capacity planning for secondary production is done purely based on the scenario with the highest demand and earliest launch date. Addressing demand variations should be done in the following preparations for market launch, where decisions on required API volume and supply of packaging material must be made (Hansen and Grunow, 2014).

Secondary pharmaceutical production on dedicated lines is an excellent case in point of a production system for which capacity is not fully utilized during ramp-ups. As described above, demand diffusion for new products is slow, but at market launch, large quantities of the drug must be available to fill the downstream supply chain. As production must be ramped up to cover this, sufficient dedicated lines must be set up, but excess effective capacity is available after market launch. Full capacity utilization would lead to too high holding costs. In addition, due to limited shelf life, excess inventory would expire before reaching customers. Furthermore, production must be validated by the authorities well before market launch, leaving plenty of time until market launch

during which capacity utilization is low. These factors make it difficult to manage the ramp up as the experience cannot be described as a function of time. Instead it must be found as a function of the cumulative production volume.

The focus of this paper is to show how to capture production ramp up via cumulative production volume and to exemplify this modelling approach for the case of secondary pharmaceutical production. For a new pharmaceutical drug we find the right number of new production lines to open and the time of these investments, that allows balancing supply and demand over the entire market launch phase are the key decisions. The underlying trade-off is that of balancing holding cost and fixed production cost of producing large volumes far ahead of market launch with the investment cost of having multiple production lines available to cover demand.

4.1.3. Paper contributions and structure

In this paper, we develop a new method for capturing production ramp up better by relating the increase in effective capacity to the experiences gained in production. We show this in a model for capacity planning of secondary pharmaceutical production, which is able to find which production lines to open when, such that enough of the new product can be produced and inventory build-up before and during market launch. We contribute to ramp-up literature by:

- developing one of the first quantitative approaches to provide decision support in ramp up management,
- conceiving a computational effective method for relating effective capacity to cumulative production volume to capture the actual experience gained in production of a new product thereby modelling ramp up more accurately,
- demonstrating the value of our approach in the context of secondary pharmaceutical production,
- deriving several managerial insights into ramp-up management in the context of the case study.

In the next section we review of the scarce literature modelling ramp up and give an overview over capacity planning in the pharmaceutical industry. Thereafter follows a presentation of how we capture ramp up in section 3. The capacity planning model in which we use our method is presented in section 4. Section 5 contains the case study from the pharmaceutical industry in which the value of our way to model ramp up is presented. Concluding remarks and further research topics are presented in the final section.

4.2. Literature Review

The literature is inconsistent on how to define ramp up, but it generally refers to an increase in the effective capacity of the production over time starting from the first production until target capacity

has been reached (Ball et al., 2011). In Surbier et al. (2012), the literature on ramp up is classified according to keywords, industry and focus area. Challenges and research opportunities are outlined. The contributions reviewed are all empirical. The literature mainly treats the ramp up in the automotive and electronics industries and most literature focuses on how to organize the ramp up and to measure performance. In Clarke and Fujimoto (1991), the ramp up in the automotive industry is analysed and the strong link to the underlying learning process is clarified. Both Clarke and Fujimoto (1991) and Almgren (2000) find the ramp up of effective capacity in the automotive industry to follow an s-shaped curve over time. Risse (2003) shows the ramp up in the same industry to follow both an s-shaped and a power function. For the semi-conductor industry, Baud-Lavigne et al. (2010) show with a simulation model, that the ramp up follows an exponential curve, which is supported by the model developed earlier by Weber (2004). To the best of our knowledge, there is no study which considers the ramp up of secondary pharmaceutical production or medical devices.

Though the literature is full of empirical work on ramp-up management, only few contributions describe how to model ramp up in operations planning. Terwiesch and Bohn (2001) use the distinction between autonomous learning and learning by experiments introduced by Adler and Clark (1991). Learning through experiments creates a trade-off between how managers should use machine hours; either for regular production or for experiments which create extra capacity in subsequent time periods, but cost crucial capacity in the first periods after launch during which customers will pay a premium price. Matta et al. (2007) develop a closed expression to decide when and how many machines to ramp up using a Markov decision process. Their work is complemented by Niroomand et al. (2012), who focus on selecting either dedicated, flexible or reconfigurable manufacturing systems with different cost and ramp-up curves. Production ramp up is strongly linked to the underlying learning process where production workers gain proficiency with the process. Generally, learning is a vastly researched area. This has led to the development of several different learning functions, which all measure worker performance over time or cumulative production volume (Anzanello and Fogliatto, 2011). Ramp up and learning can however not be used interchangeably. While learning captures the increased proficiency gained by the individual worker in performing repetitive tasks (Biskup, 2008, Anzanello and Fogliatto, 2011), ramp up refers to an entire production system (Ball et al., 2011). Glock et al. (2012) consider dynamic planning and model ramp up in more detail. The authors use a given data set from an electronics manufacturer found in Badiru (1995) to find the ramp up and demand functions via regression. The ramp-up function is approximated with the constant time model from the learning literature. They develop a lot sizing model for finding the lengths of the production runs that match a steadily increasing demand, similar contributions to many other contributions which include learning effects in scheduling (cf. Biskup, 2008). Their approach to model production is not sufficient for considering a production network nor can it be used for finding the required capacity. Additionally, their model also only holds for a non-decreasing demand function, whereas we consider higher demand fluctuations from the supply chain filling effect and time-phased launches in different markets.

The central tasks in planning for the pharmaceutical industry are first described by Shah (2004), who identifies the reduction of TTM as the key challenge for the whole industry. Six planning

domains are singled out of which the most important are pipeline planning, capacity planning and production planning. The work of Shah (2004) is followed by Laínez et al. (2012), who additionally introduce supply chain management, part of which is also to ensure the supply of the experimental drug for the test patients during clinical trials. Narayana (In press) reviews the entire literature on supply chain management for the pharmaceutical industry and illustrate the domains of literature. It concludes, that there is limited research covering the integration of supply chain management and new product introduction.

Capacity investments in primary production are strongly related to the uncertainty in the development of a new drug. If the drug is abandoned, the investments both in R&D expenditures spent on product development as well as new production equipment are lost. Capacity planning for primary production is well described by Pisano and Rossi (1994) based on a case study from Eli Lily. Rotstein et al. (1999) developed a model which can both identify the appropriate number of production lines to invest in, while selecting profitable candidate products and finding annual production volumes. The authors extend their work in Papageorgiou et al. (2001) to cover the full supply chain and to reflect the business structure of large pharmaceutical companies. However, due to the extension of the model, uncertainty is not accounted for. Gatica et al. (2003) subsequently develop a better model for addressing uncertainty. Not just originating from the clinical trials, but also from demand. Gatica et al. (2003) and Papageorgiou et al. (2001) are unified in Levis and Papageorgiou (2004), who develop a multisite model that also considers uncertainty. Tsang et al. (2007a) present another capacity planning model which in Tsang et al. (2007b) is supplemented by to a vast series of risk management techniques. Chambers et al. (2009) present a stochastic dynamic optimization model for deciding on whether to invest in flexible or dedicated production equipment. Finally, Sundaramoorthy et al. (2012a) consider the capacity planning for continuous pharmaceutical production and model capacity and production rate expansions in increments. They focus on better capturing the uncertainty of products getting the approval and include some of the latest developments in pipeline planning into their model. In the companion paper (Sundaramoorthy et al., 2012b) they address solving industry-sized problems.

While capturing the uncertainty of the approval, capacity planning for primary production does not fully capture the dynamics of the market launch phase. Due to the size of the time buckets in these long-horizon models, ramp-up of production is not captured. The scope of these models renders them inapplicable for determining the ramp up of secondary production. An approach dedicated for capacity planning of secondary production is therefore developed in this paper, which copes with large demand variations around market launch and significant ramp-up effects.

4.3. Modelling ramp up depending on cumulative production volumes

To better reflect the experience gained with the new production process in production, a method for linking the effective capacity to the cumulative production volume is needed. Our approach is inspired by the learning literature. We only consider learning-by-doing and neglect experiments as a source of effective capacity increase. With production not being interrupted for a long time,

forgetting can be ignored. We also do not consider the labour force or quality issues directly, but instead only focus on the relationship between experience and effective capacity.

Three principal ramp-up curves are observed in other industries (mainly automotive and semiconductor); a power curve, an s-shaped curve and an exponential curve, which we will represent via three archetypical functions. The power curve observed by Risse (2003) can be expressed by the power function as:

$$y = \alpha \cdot t^{\beta} \tag{1}$$

Where y is the effective capacity, t is time, α and β are parameters. This function obviously does not converge towards the target capacity, but target capacity would still limit the effective capacity. Risse (2003) also offers an expression for the s-shaped curve, which he describes through two different power functions. Instead, we model the s-shape through a sigmoid function, which has the more general form:

$$y = \frac{a}{(1 + c \cdot e^{-b \cdot t})} \tag{2}$$

For the sigmoid function, $a = 1$ represents the target capacity, while b and c are parameters that determine the slope of the curve.

Glock et al. (2012) found that the time constant function from the learning literature best resembled the observed ramp up of effective capacity in the electronic industry. The function is here given as:

$$y = y_s + y_n \cdot (1 - e^{-t/\varphi}) \tag{3}$$

y_s is the starting effective capacity, y_n the effective capacity increase rate and φ determines the rate of increase. Examples of the three introduced functions are shown in Figure 4.3. Though we here use these archetypical functions, managers do in practice have some influence over how effective capacity is ramped-up as they can control e.g. emphasis on quality (Terwiesch and Bohn, 2001) and number of product variants launched (Schuh et al., 2005).

The three selected functions can be rewritten to show effective capacity over cumulative production volume. First we see, that the cumulative production volume, x, can be expressed as the integral of the ramp-up function $x = \int_0^t f(\tau) d\tau$ as seen in Figure 4.4. In this expression, we can isolate t and insert it into our ramp-up function to get $y = f(\left[F^{-1}(x) \right]_0^t)$. We demonstrate these steps for the three functions in Appendix A. The curves of the resulting functions can be seen in Figure 4.5. All of these functions are concave, which enables piecewise linear approximation without the need for using binary variables in a MILP model. Hence the ramp up can be approximated as a series of linear capacity constraints.

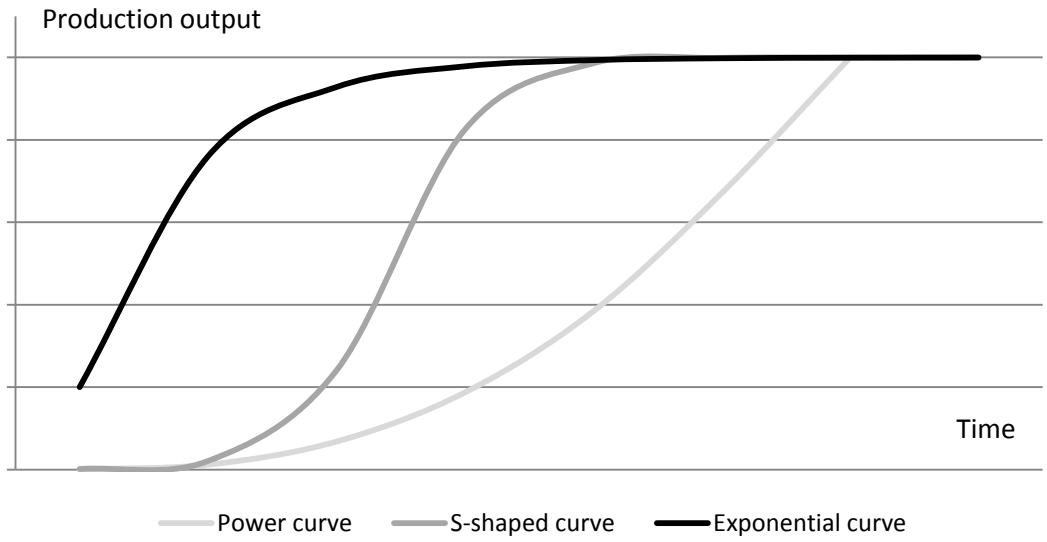

Figure 4.3: Three archetypical ramp-up curves observed in the empirical literature.

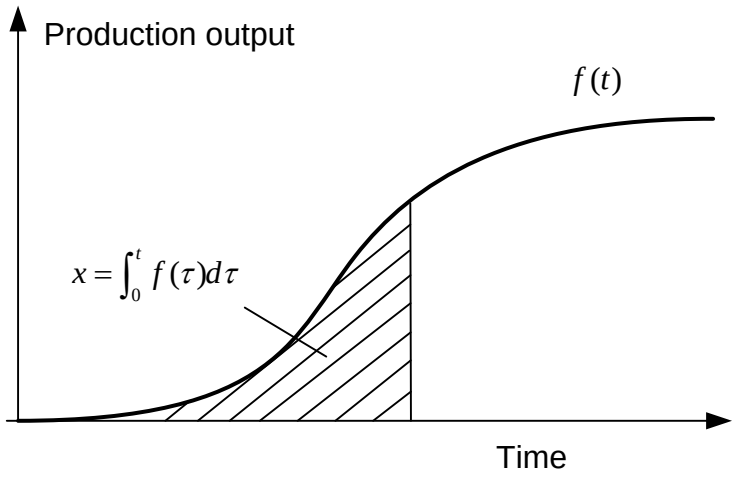

Figure 4.4: Illustration of the relation between time, effective capacity and cumulative production volume.

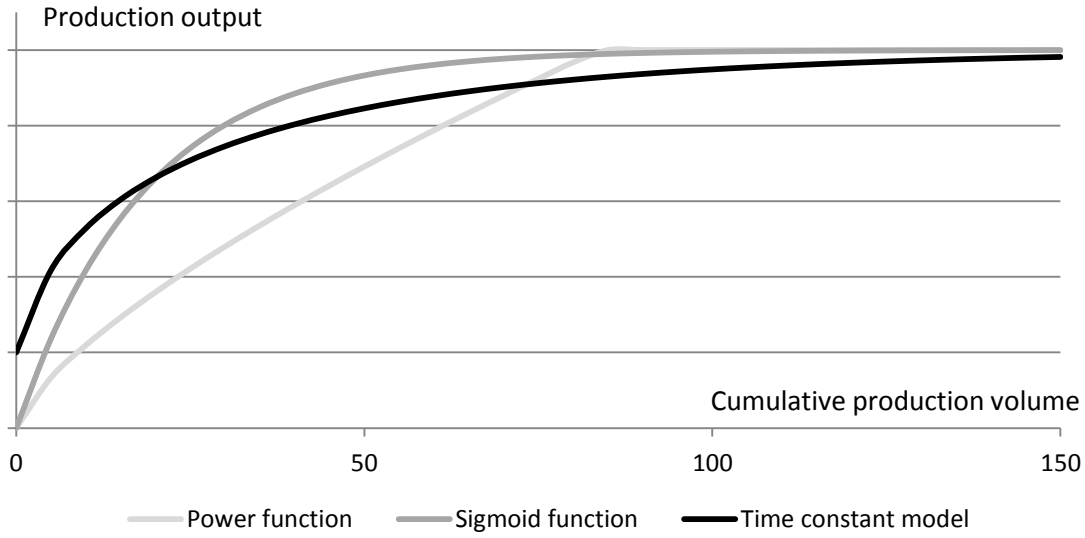

Figure 4.5: The three ramp-up curves showing effective capacity as a function of cumulative production volume.

The slope of the linear curves is denoted CR_r and the intersection with the y-axis is denoted CL_r for curve $r \in R$. Having effective capacity as a piecewise linear function over cumulative production volume, the effective capacity in a single period is illustrated in Figure 4.6. Given that the production on site *l*'s line *i* in period *t* is defined as $\rho_{i,t}^{l}$, capacity in the beginning of a period is given as $CR_r \cdot \sum_{t'<t} \rho_{i,t'}^{l} + CL_r$. During the production period, more experience is gained which should also be accounted for. It is clear to see, that this increase in effective capacity is on average $CR_r \cdot \rho_{i,t}^{l} / 2$ for the period. In this expression $\rho_{i,t}^{l}$ must however be replaced to avoid a circular reference in the capacity constraint. We approximate $\rho_{i,t}^{l}$ with $CR_r \cdot \sum_{t'<t} \rho_{i,t'}^{l} + CL_r$ and acknowledge that this approximation underestimates the actual effective capacity as $\rho_{i,t}^{l} \geq CR_r \cdot \sum_{t'<t} \rho_{i,t'}^{l} + CL_r$.

To the best of our knowledge, no empirical literature has looked into ramp up of secondary pharmaceutical production. With the wide range of different types of secondary production, the ramp-up curves would likely also vary depending primarily on the production process. The electronics industry, for which an exponential ramp-up curve is observed, is characterized by automated equipment that produces large numbers of each product. In comparison, the sigmoid and power functions are observed in the automotive industry, in which fewer units are produced and more manual labour per unit is required. If these are the determining factors, we expect the highly automated production of pills to exhibit an exponential shape ramp up just as seen in the electronics industry. The production of advanced drug delivery systems in contrast requires assembly and may therefore follow an s-shaped or a power curve as seen in the automotive industry. We consider this

relation probable as a connection between product complexity and ramp-up performance is established (Pufall et al., 2012).

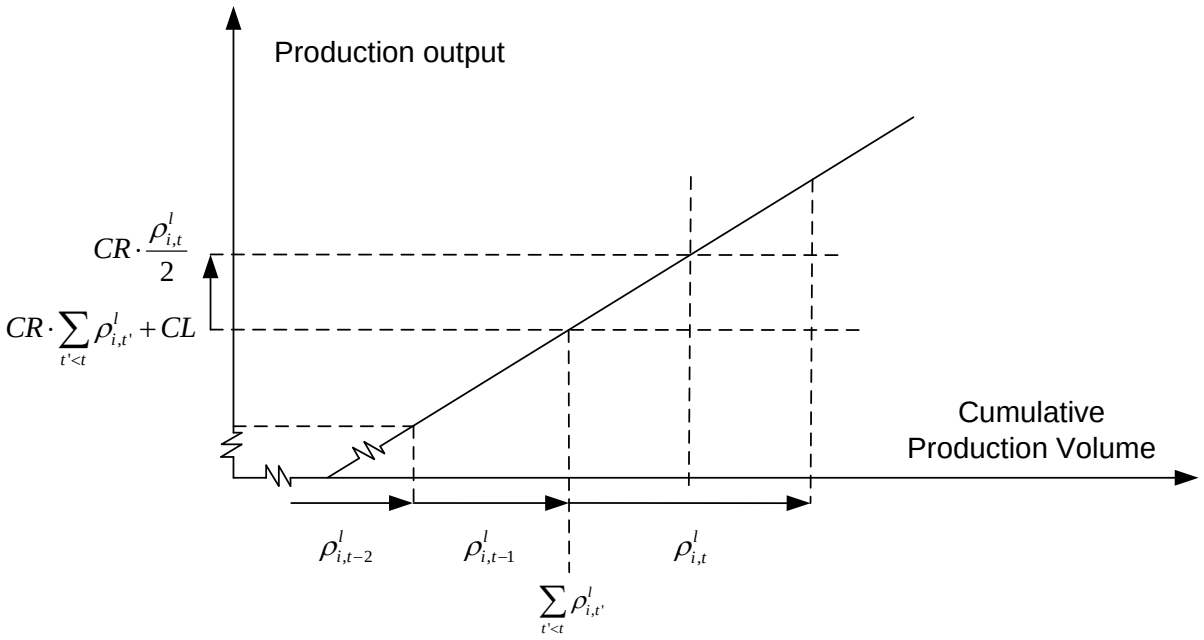

Figure 4.6: Illustration of the capacity in period t.

4.4. Development of a mathematical planning model for secondary pharmaceutical production ramp up

Pharmaceutical companies about to launch a new pharmaceutical drug have to have the product available at market launch to keep TTM down. To guarantee this, the right location and time for opening new dedicated secondary production lines must be determined. Here a model for providing decision support for this problem is described. As secondary production must be ramped up while having to leave production lines unutilized at times, effective capacity is modelled more accurately as described in the previous section.

4.4.1. Model description

A new product is introduced into different markets with different authorities $m \in M$. Since the new drug might be vital to patients, demand must always be fulfilled at this aggregation level. Figure 4.7 illustrates the simplified supply chain considered. A company has a number of sites $l \in L$. Each site can house $i \in I^l$ new production lines, which can be opened in any given month $t \in T$. Not every

site has to have a production line. The lines are assumed identical and we do not consider the need for utilities, laboratories or any other supporting functions. The effective capacity of the new production lines can be limited by a set of linear capacity constraints related to the cumulative volume, $r \in R$. The supply of API is neglected as the inventory of API is regularly sufficient to feed secondary production. Contract manufacturers, which are common in the industry, have not been considered. Each site has an inventory of finished formulation, which can be sent to all markets the site is validated for. Packaging of the final product takes place after the formulation. As it is a fast and flexible process with usually ample capacity, it can be neglected. Due to the considered time horizon, the limited shelf life of a formulated drug has to be accounted for. With the planning horizon spanning several years, the value of money over time needs to be included through the use of a discounting factor. We consider no other financial constraints.

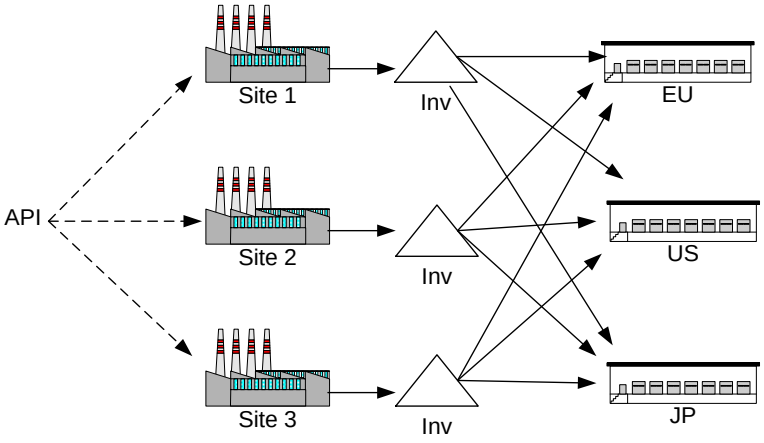

Figure 4.7: Overview of the considered supply chain.

4.4.2. Model formulation

Indices

t, t'	time periods.
l, l'	sites.
i, i'	production lines.
m	markets.
r	linear curves.

Sets

T	set of time periods.
L	set of potential production sites.
I^l	set of production lines in site l.
M	set of market.
R	set of linear curves.

Parameters

A_t^m	= 1, if the final market authorization has been given and market launch for market m is possible in time period t; 0, otherwise.
CAP	capacity of every production line
CL_r	initial effective capacity for linear curve r.
CR_r	rate of effective capacity increase for linear curve r.
CT	construction time of a new production line.
D_t^m	demand in market m, t periods into the launch.
K	sufficiently large number.
MC	maximum number of production lines under construction, simultaneously.
SFE_m	supply chain filling effect for market m.
SL	shelf life.
V	amount of product needed for validation.
VT	validation time.
D	discount rate.
GR^m	ross revenue for market m.
$APIC$	API cost.
F^l	construction cost of a production line in site l.

H holding cost for inventory per period per unit.

$O^{l,m}$ transport cost per unit from site *l* to market *m*.

Q^{l} running cost of a production line in site *l*.

$VC^{l,m}$ validation cost of enabling site *l* to produce and sell product for market *m*.

W scrap cost per unit.

Binary variables

α_t^m = 1, if the product is launched in market *m* in period *t*; 0, otherwise.

$\tau_{i,t}^{l}$ = 1, if in site *l's* line *i* is starting production in period *t*; 0, otherwise.

$\chi_t^{l,m}$ = 1, if validation of site *l* is conducted for market *m* in period *t*; 0, otherwise.

Continuous variables

$\eta_t^{l,m}$ volume of product delivered from site *l* to market *m* in period *t*.

ι_t^l volume of product on inventory at site *l* in period *t*.

$\rho_{i,t}^{l}$ volume of product produced in site *l* on line *i* in period *t*.

ω_t^l volume of product scraped from site *l* during period *t*.

Objective Function

$$\max \sum_t \frac{1}{(1+d)^t} \cdot \Big(\sum_l \sum_m (GR^m \cdot \eta_t^{l,m} - O^{l,m} \cdot \eta_t^{l,m} - VC^{l,m} \cdot \chi_t^{l,m}) - \sum_l (W \cdot \omega_t^l - H \cdot \iota_t^l) - \sum_l \sum_i (F^l \cdot \tau_{i,t-CT}^l - Q^l \cdot \sum_{t' \le t} \tau_{i,t'}^l - APIC \cdot \rho_{i,t}^l) \Big) \quad (5)$$

Subject to:

Sales Constraints

$$SFE_m \cdot \alpha_t^m + \sum_{t' \le t} D_{t-t'+1}^m \cdot \alpha_{t'}^m = \sum_l \eta_t^{l,m} \qquad \forall m \in M, t \in T \qquad (6)$$

$$\sum_t \alpha_t^m \le 1 \qquad \forall m \in M \qquad (7)$$

$$\alpha_t^m \le \sum_{t' \le t} A_{t'}^m \qquad \forall m \in M, t \in T \qquad (8)$$

$$\eta_t^{l,m} \le K \cdot \sum_{t' \le t-VT} \chi_{t'}^{l,m} \qquad \forall l \in L, m \in M, t \in T \qquad (9)$$

Material Balance

$$\iota_t^l = \iota_{t-1}^l + \sum_i \rho_{i,t}^l - \sum_m \eta_t^{l,m} - \omega_t^l \qquad \forall l \in L, t \in T \qquad (10)$$

Manufacturing Constraints

$$\rho_{i,t}^l \le (1 + \frac{CR_r}{2}) \cdot (CR_r \cdot \sum_{t' < t} \rho_{i,t'}^l + CL_r) \qquad \forall l \in L, i \in I^l, r \in R, t \in T \qquad (11)$$

$$\rho_{i,t}^l \le CAP \qquad \forall l \in L, i \in I^l, t \in T \qquad (12)$$

$$\rho_{i,t}^l \le K \cdot \sum_{t' \le t} \tau_{i,t'}^l \qquad \forall l \in L, i \in I^l, t \in T \qquad (13)$$

$$\sum_t \tau_{i,t}^l \le 1 \qquad \forall l \in L, i \in I^l \qquad (14)$$

$$\tau_{i,t}^l \le \sum_{t \le t'} \sum_{i' < i} \tau_{i',t'}^l \qquad \forall l \in L, i > 1, t \in T \qquad (15)$$

$$\sum_{t \le CT} \tau_{i,t'}^l = 0 \qquad \forall l \in L, i \in I^l \qquad (16)$$

$$\sum_{t-CT \le t' < t} \sum_l \sum_i \tau_{i,t'}^l \le MC \qquad \forall t \in T \qquad (17)$$

Shelf life Constraint

$$\omega_t^l \geq \sum_{t' \leq t-SL} \sum_i \rho_{i,t'}^l - \sum_{t' \leq t} \sum_m \eta_{t'}^{l,m} \qquad \forall l \in L, t \in T \qquad (18)$$

Validation Constraint

$$\sum_{t' \leq t} \sum_i \rho_{i,t'}^l \geq V \cdot \chi_t^{l,m} \qquad \forall l \in L, m \in M, t \in T \qquad (19)$$

$$\sum_t \chi_t^{l,m} \leq 1 \qquad \forall l \in L, m \in M \qquad (20)$$

Bounds

$$\alpha_t^m \in \{0;1\} \qquad \forall m \in M, t \in T \qquad (21)$$

$$\tau_{i,t}^l \in \{0;1\} \qquad \forall l \in L, i \in I^l, t \in T \qquad (22)$$

$$\chi_t^{l,m} \in \{0;1\} \qquad \forall l \in L, m \in M, t \in T \qquad (23)$$

$$\eta_t^{l,m} \geq 0 \qquad \forall l \in L, m \in M, t \in T \qquad (24)$$

$$\iota_t^l, \omega_t^l \geq 0 \qquad \forall l \in L, t \in T \qquad (25)$$

$$\rho_{i,t}^l \geq 0 \qquad \forall l \in L, i \in I^l, t \in T \qquad (26)$$

In the objective function in Eq. (5), the net present value of the market launch phase is maximized. The first term represents the gross revenue from which transportation, validation, scrap, holding, construction, fixed production cost of each line and API cost are deducted, respectively. In Eq. (6), the volume of finished product shipped to each market in each period is determined and demand fulfilment is enforced. Note here the addition of the supply chain filling effect, which is only considered in the period with market launch. Market launches are governed by Eq. (7) and (8), in that market launches can only take place once and only after the authorization has been given. The option of delaying market launch ensures feasibility. Furthermore, the validation of the production process has to be completed, before the product can be shipped to the individual markets, which is ensured by Eq. (9). Eq. (10) is the inventory balance. In Eq. (11) the piecewise linear approximation of the ramp-up function based on the cumulative production volume is modelled as described above. Effective capacity is set lower than target capacity through Eq. (12). Eq. (13) ensures that production only takes place on open lines, and lines can only be opened once

(Eq. (14)). Eq. (15) orders the opening of production lines so the numerical lowest production lines are selected first to reduce computational degeneracy. Lines cannot be opened before they have been constructed (Eq. (16)) and construction is limited to only *MC* lines at a time to represent limited resources of the construction team (Eq. (17)). Shelf life is limited by assuming a FIFO stock keeping principle and not allowing the inventory level to be higher than cumulative difference between production and shipped volume for the length of the shelf life (Eq. (18)). Eq. (19) ensures that sufficient volume is produced for validation. Eq. (20) prescribe that a site is validated only once for each market. Eq. (21) through (26) define the variable domains.

4.5. Case study

For this case study, data from a real pharmaceutical company has been changed for confidentiality purposes. The supply chain in Figure 4.7 with three production sites and three markets EU, US and Japan is considered. The new product is launched (first) in these markets, due to their profitability. The introduction into other markets is often postponed as lower profit margins make these countries less interesting. With an obligation for mutual recognition for EMA's member states, Europe can be treated as one market. For each production site, two dedicated production lines can be constructed. The planning horizon is set to three years divided into months i.e. 36 time periods. The parameters in Table 4.1 come from the case company. The maximum number of lines simultaneously under construction is given by the chosen contractor and each line takes 3 months to construct. The target capacity of a new line is 500,000 units per month. The validation volume is set to 100,000 units for all markets. Validation time is usually 6 months. The total shelf life of a formulated drug is two years, but given that a significant remaining shelf life is needed further downstream, shelf life is here set to 12 months. The discount rate is 0.5 % per month. The holding cost is set to 0.2 per unit per month mainly reflecting the perishability of the drug and the API cost is set to 2 € per unit. Construction, production, transportation and validation costs are found in Table 4.2. Typically, validation costs are higher for sites in less developed countries where production costs are lower.

Market data can be found in Table 4.3. The market diffusion of the new drug is modelled with an s-shaped function as described in Cook (2006), which reaches peak demand after 10 months while 50 % of peak sales are reached after 5 months. Note that full demand for all markets corresponds to full utilization of the effective capacity for four production lines. The demand represents the best possible demand scenario, which supply should cover. The supply chain filling effect is given as 3 months peak demand. The authorization dates are provided by the authorities.

Table 4.1: Scalar parameters.

Parameter	*Abbr.*	*Value*	*Unit*
Construction time	CT	3	Months
Cost per production line	F	2500	k€
Max # of lines under construction	MC	2	-
Capacity per line	CAP	500.000	Units
Validation volume	V	100.000	Units
Validation time	VL	6	Months
Shelf life	SL	12	Months
Discount rate	D	0.5	% per month
Holding cost	H	0.2	€ per unit per month
Scrap cost	W	0.5	€ per unit
API cost	APIC	2	€ per unit

Table 4.2: Production site specific parameters.

Production site	*Production cost per period [k€]*	*Transportation costs to market per unit [€]*			*Validation costs to market [k€]*		
		US	EU	JP	US	EU	JP
1	1000	1.1	1.8	2.2	750	1750	1500
2	1100	1.5	1.2	1.4	1500	1250	1250
3	850	2.5	2.8	1.2	2000	1500	1750

To model ramp up, the three functions introduced in section 3 are used with ramp ups lasting 6 months if the lines were fully utilized (to within 99.7 % of the target capacity for the sigmoid and time constant function). We demonstrate how we find the linear approximation curves in Appendix B.

These problem instances have 540 binary and 871 continuous variables and 2550 constraints. The model takes up to 100 seconds to solve to optimality with CPLEX v.12.5 on a Dell Latitude E6400 with an Intel Core 2 P8400 2.27 GHz processor and 4 GB ram.

Table 4.3: Market parameters.

Markets	*Contribution margin [€ per unit]*	*Peak demand [units]*	*Authorization date [Month]*
US	66	750,000	12
EU	60	750,000	13
JP	54	500,000	16

4.5.1. The model as decision support tool

To illustrate how the model can be used for decision support, a Gantt chart representation of which lines to open in which sites is given in Figure 4.8. Here construction and ramp phases for the individual lines are shown. The period in which a site submits the validation material is represented by the circled market abbreviations. Lines are opened when needed either to obtain validation before market authorization or to cover the increasing demand. The underutilization of lines is reflected in the long time required for completing the ramp up in some sites.

The operations plan produced by the model which shows target and effective capacity, production volume, inventory and shipping profiles as well as market launch dates is shown in Figure 4.9 for the sigmoid ramp-up function. Only the first 24 months are shown as the system has already reached steady state at this point. It is clearly seen how production is ramped up with each line following an s-shaped curve. Prior to each market launch, inventory is build up to cover the supply chain filling effect. Inventory is also used to postpone the opening of the last line. The substantial amount of unused effective capacity and the resulting longer ramp-up lengths in Figure 4.8 and Figure 4.9 illustrate the necessity to model ramp up based on cumulative production volume rather than time.

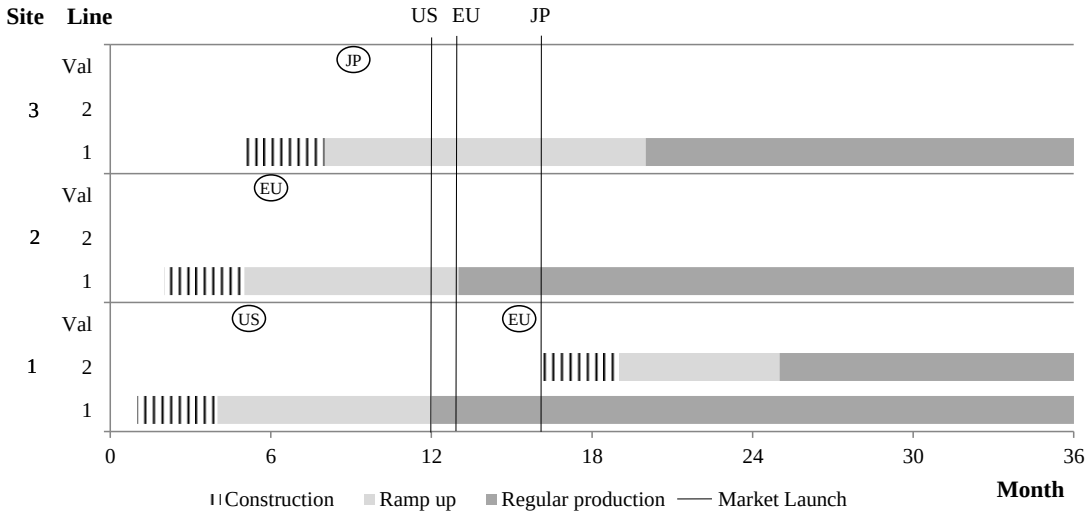

Figure 4.8: Overview of market validations, construction and ramp-up phases for each line and site.

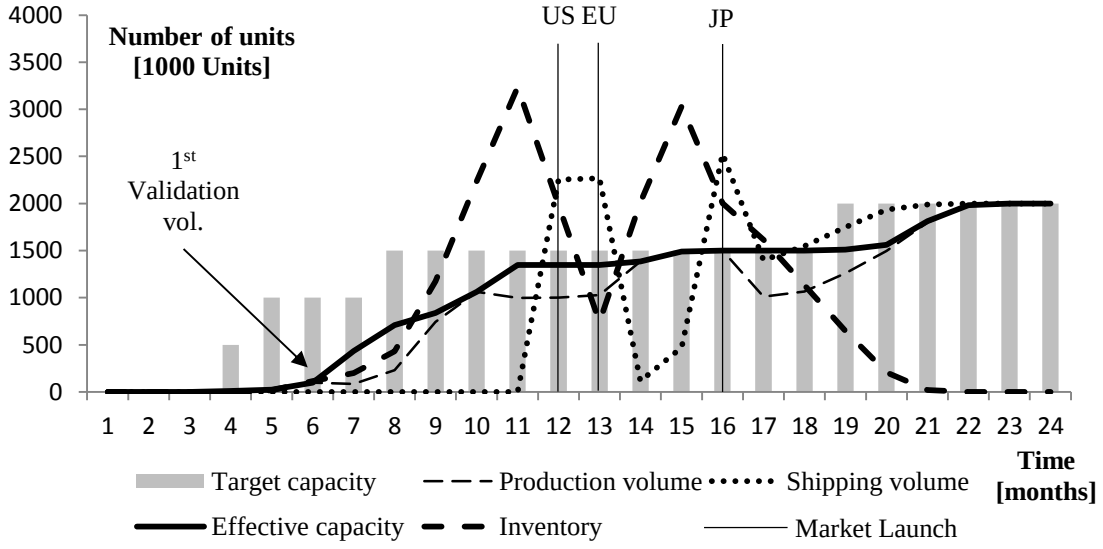

Figure 4.9: Target and effective capacity, inventory and shipping profiles over the planning horizon using the sigmoid function for modelling ramp up.

The model solution can also be compared to the current approach prevalent in the industry. Capacity expansion is often done via one project with a single company responsible for constructing the new lines and completing the project within a year. When we add a constraint which does not allow the construction of new lines after month 12 to mimic this operational policy, we obtain the solution shown in Figure 4.10. Here the length of ramp up is much longer. The additional cost lead

to a 7 million € drop in the company's profits showing the value of postponing the opening of some lines.

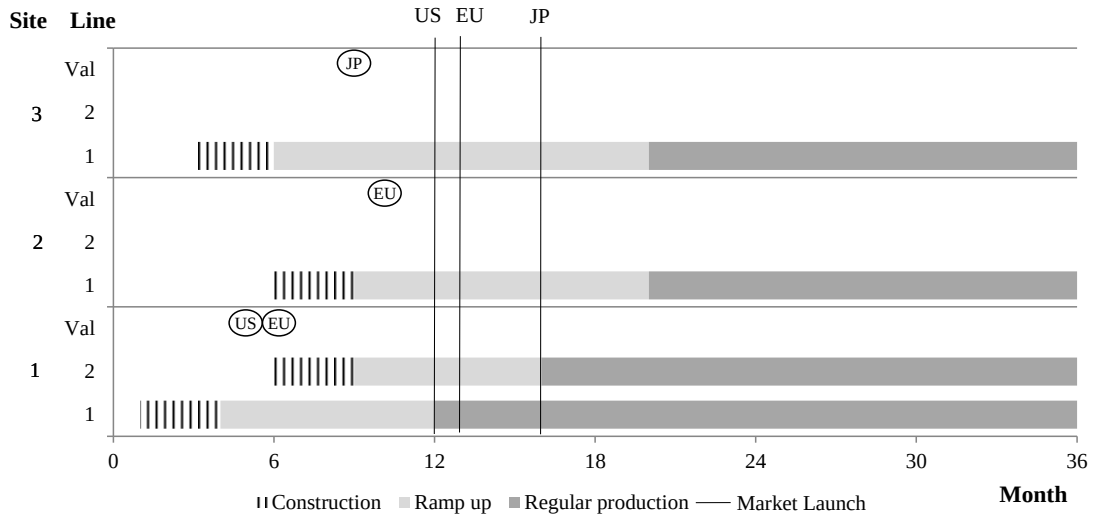

Figure 4.10: Comparison to the current industry approach.

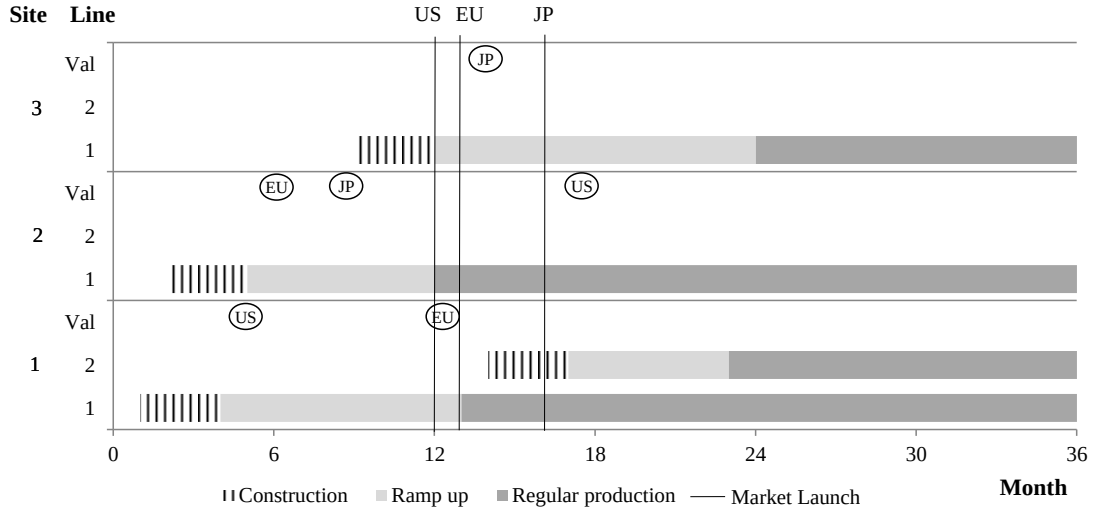

Figure 4.11: Market validations, construction and ramp-up phases for each line and site, if two validations per market are enforced.

As a decision support tool, the model allows managers to quickly perform what-if analyses. Managers in the pharmaceutical industry are for example often interested in the impact of having multiple sites validated for each market. This is often done to reduce the risk of supply shortage, if

production in one site is temporarily disrupted. Figure 4.11 shows the result when we enforce two validations per market. Site 2 is validated for Japan before Site 3, allowing the construction of the line in site 3 to be postponed by 4 months.

Table 4.4: Analysis of reducing the effective shelf life.

	Effective shelf life length [months]						
	8	*7*	*6*	*5*	*4*	*3*	*2*
Profit [m$]	2249	2249	2249	2249	2247	2242	2238
Scrap [1000 units]	0	2.4	46.80	231.2	669.4	661.2	1601
Inventory [1000 units]	20810	20810	20920	18760	17290	13550	9604

Companies might want to or have to deliver products with a longer remaining shelf life to customers, effectively reducing the shelf life available to them. Table 4.4 shows the results for different lengths of effective shelf life. Here profits drop consistently. Scrap increases as some production for validation and ramp up is necessary, which afterwards have to be thrown out. For 3 months of effective shelf life, the solution structure changes, causing higher production and transportation cost and lower profit without increasing scrap.

4.5.2. Comparison between time-dependent and volume-dependent ramp up

Having shown that our approach leads to longer ramp ups than the 6 months needed under full utilization, we now demonstrate why this is a better approach to modelling ramp up. For this we compare our modelling approach referred to as volume-dependent ramp up with the common time-dependent ramp up. For time-dependent ramp up, Eq. (11), (12) and (13) are replaced with $\rho_{i,t}^{l} \le \sum_{t' \le t} CAP_{t-t'+1} \cdot \tau_{i,t'}^{l} \quad \forall l,i,t$. Let ϕ_i^l be the time period in which line *i* in site *l* is opened i.e. $\phi_i^l = t$ if $\tau_{i,t}^{l} = 1$ and let σ_i^l be the time period in which line *i* in site *l* reaches target capacity. Then the vectors describing line openings and last ramp-up period in Table 4.5 are given as $[\phi_1^1, \phi_2^1, ..., \phi_2^3]$ and $[\sigma_1^1, \sigma_2^1, ..., \sigma_2^3]$. Table 4.5 shows a comparison between time-dependent and volume-dependent ramp up for the power function.

Table 4.5: Comparison between volume- and time-dependent ramp up.

	Solution		*Total capacity over the planning horizon*	*Average utilization*
	Line opening	*Last ramp-up period*		
Volume-dependent	[4,17,5,0,8,0]	[9,22,10,0,15,0]	48,019,175	93.86 %
Time-dependent	[4,18,5,0,8,0]	[9,23,10,0,13,0]	49,143,528	88.03 %

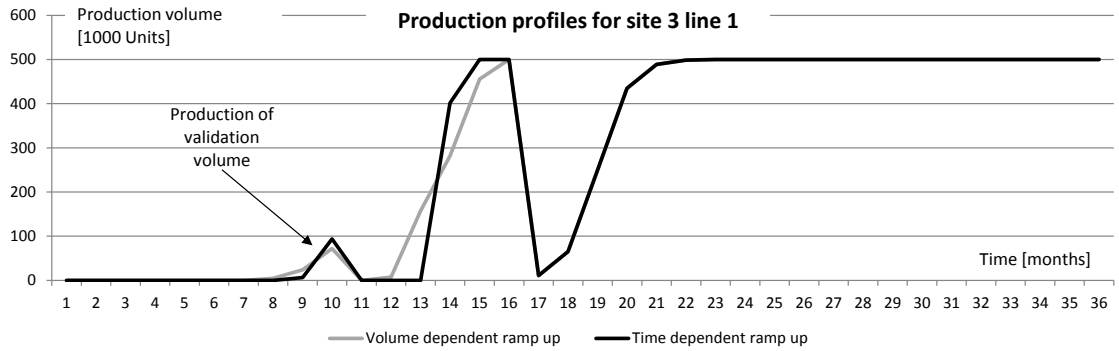

Figure 4.12: Illustration of the problem with modelling ramp up as time dependent.

As can be seen in Table 4.5, time-dependent ramp up provides more capacity over the planning horizon than volume-dependent. The difference is caused by the predefined effective capacity increase of time-dependent ramp up, which does not require any production. In practice this leads to large jumps in planned production volumes as illustrated in Figure 4.12. Here, Site 3's production steadily increases for volume-dependent ramp up, while production volume goes from 0 to 400,000 units in one month for time-dependent ramp up. This corresponds to leaving production lines unused and then producing large production volumes right before market launch. This would not be possible in reality. For this site, ramp up is faster than product diffusion, requiring only smaller volumes to be produced, which explains why the ramp up last 8 months.

4.5.3. Influence of the ramp-up functions

The influence of the shape of the ramp-up functions is shown in Table 4.6, which compares the three functions used here. As both the sigmoid and the time constant function reach a relatively high effective capacity faster, lines can be opened up later than for the power function and the ramp-up period can be extended. This is shown in Figure 4.13, in which the shape of each ramp-up function is clearly visible. Though lines are opened later, the model with the time constant function still creates a higher total effective capacity for the entire planning horizon. Clearly, the ramp-up

function has a direct impact on the profit of the market launch. The results illustrate the importance of using the correct ramp-up function for planning ramp up. If used incorrectly, the time constant function would lead to lines that are opened too late, whereas the power function loses money on unnecessary early openings. To avoid delayed market launch or premature investments, the ramp-up capabilities of the company should be thoroughly investigated, before planning is undertaken.

Table 4.6: Results for the different volume- and time-dependent ramp-up functions.

Ramp-up function	*Solution*		*Total effective capacity over the planning horizon*	*Profit [m€]*
	Line opening	*Last ramp-up period*		
Power function	[4,17,5,0,8,0]	[9,22,10,0,15,0]	48,019,175	2247.7
Sigmoid function	[4,19,5,0,8,0]	[11,24,12,0,19,0]	49,457,912	2249.4
Time constant model	[6,20,7,0,10,0]	[13,25,14,0,21,0]	49,904,495	2256.5

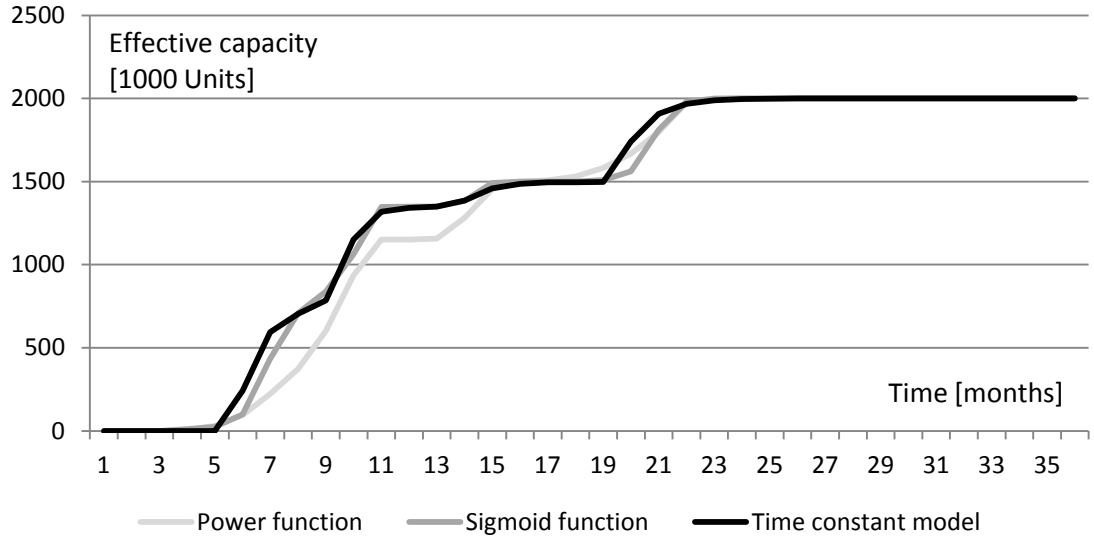

Figure 4.13: Ramp up of effective capacity for all volume-dependent ramp-up functions.

4.5.4. Length of ramp ups and the value of shortening ramp ups

In addition to the shape of the ramp-up curve, the length of the ramp-up process is important as it directly affects the opening decisions. This is shown in Table 4.7, which shows the results for different ramp-up lengths. The value of the lengths refers to the duration required if the line is fully utilized. Smaller profits result for larger ramp-up lengths. The decision of when to open lines also

changes, indicating that an underestimation of how long ramp up takes would lead to lines being constructed too late. The solutions for the different ramp-up functions converge as the length is reduced. However, the decisions on when to open the lines continue to be different.

The preparation of production for a new ramp up is important for how fast the ramp up can be completed (Schuh et al., 2005). Investing in e.g. training of personnel or process improvements can help reduce the ramp-up length. Table 4.7 illustrates, that shortening the ramp-up process has a direct value as investments could be postponed. Reducing the ramp-up length of e.g. the power function from 4 to 3 months would generate an extra 3 mill € in profit, which forms a strong argument for investing ramp-up preparation measures.

Table 4.7: Results for the different ramp-up functions with different ramp-up lengths.

Ramp-up function	*Ramp-up length = 2 months*		*Ramp-up length = 3 months*		*Ramp-up length = 4 months*		*Ramp-up length = 6 months*	
	Profit [m€]	Line openings	Profit [m€]	Line openings	Profit [m€]	Line openings	Profit [m€]	Line openings
Power function	2253	[5,19,6,17,0,0]	2253	[5,19,6,0,9,0]	2249	[4,18,5,0,8,0]	2248	[4,17,5,0,8,0]
Sigmoid function	2257	[6,21,7,0,10,0]	2254	[5,20,6,17,0,0]	2253	[5,19,6,17,0,0]	2249	[4,19,5,0,8,0]
Time constant model	2258	[6,21,7,18,0,0]	2258	[6,20,7,19,0,0]	2258	[6,20,7,19,0,0]	2256	[6,20,7,0,10,0]

4.6. Conclusion and further research

In recognition of the fact that production systems are frequently not fully utilized during ramp up, this paper focuses on capturing the effective capacity during ramp up better. Ramping up a new process represents a learning process in which experience is gained as more units are produced. For not fully utilized manufacturing systems, a time-dependent ramp function would overestimate the effective capacity available. Instead we suggest a method for linking effective capacity to cumulative production volume. We illustrate the value of this methodology by developing a computationally effective model for making capacity expansion decisions for secondary pharmaceutical production. Here slow demand diffusion, time-phased market launch and early production for validation leaves new production lines temporarily unutilized. We propose a MILP model, which also considers industry aspects such as process validation and limited shelf life.

In an industrial case study the model is used as a decision support tool with three different ramp-up functions. The results are compared to the current approach in the industry, showing the value of postponing the construction of production lines. The model allows managers to perform what-if analyses such as enforcing multiple validations for each market and reducing the effective shelf life, which both cause changes in the opening decisions. It is demonstrated how time-dependent ramp up leads to an overestimation of effective capacity and can generate capacity expansion plans, which make on-time market launch impossible. The different ramp-up functions are compared, showing the importance of investigating the ramp-up capability of a company before planning any ramp ups. Reducing the length of the ramp-up process leads to significant savings. This is also indicative of the value of possible investments in ramp-up preparation measures.

The method for capturing effective capacity as a function of cumulative production volume is demonstrated for secondary pharmaceutical production. The number of advanced drug delivery systems is growing (Sezer, 2012), so we expect the methodology developed here to become even more relevant for the industry. However, our modelling approach is also suitable for describing ramp up in other demand-driven industries with slow demand diffusion.

Two extensions to the work presented in this paper will be subject of our future research. The first relates to a more advanced representation of learning. The second to the consideration of uncertainties inherent in the market launch phase. By having several new production lines in a network starting up in succession, companies are normally able to transfer knowledge from line to line or site to site to shorten the ramp up. Though these effects have been reported in the literature, no work has tried to quantify it or use it in a planning methodology. Especially for lines in the same production site, knowledge transfer plays a significant role.

The current trends in the pharmaceutical sector lead towards more uncertainty in market authorization dates, in allowed prices and in approved claims. An inclusion of these uncertainties is crucial in planning for effective market launches.

Chapter 5: Conclusion and future research

In this dissertation, the new product introduction process in the pharmaceutical industry is treated. Focus is given to large pharmaceutical companies that both develop and manufacture novel pharmaceutical products. Several trends challenging the industry are identified, and the increasing difficulty of bringing new drugs to market faster or even at the same pace is singled out as the key problem for the industry. Attention is given to the management of companies' supply chain operations, which has so far not prioritized the crucial operations around market launch, even though this directly impacts TTM. Developing new planning methodologies for operations in this part of the new product introduction process is the main aim of the thesis.

In this chapter, we conclude by revisiting the research questions posed at the beginning of this thesis. A summary and the main findings of the previous chapters are here used to answer each question in turn.

5.1. Conclusion

RQ1: What are the challenges facing the pharmaceutical industry during the new product introduction process in reducing time-to-market?

The new product introduction process is analyzed in chapter 2. In a case study from a pharmaceutical company, managers from all functions are interviewed on their role in the new product introduction process and their relation to other functions. From the interviews, key tasks and their interrelationships are identified from which a project network representation and a precedence relationship between tasks of the new product introduction process are constructed. The discussions with the managers also help in forming observations on the central challenges facing the industry. Several companies are used for validation, confirming the findings and adding further insights. Through literature review of the planning challenges in the new product introduction process, several planning areas are subsequently identified. The identified planning areas consider a fairly aggregate decision level and most contributions are confined to these areas, attempting only to propose different model formulations or improve decision techniques rather than expand the range of decisions supported. Five observations about the remaining challenges in new product introduction are identified, which could lead to shorter TTM. The first observation is that companies are slow to implement the advanced planning methodologies found in the literature, whereas the next two observations relates to expansion of the planning domain for pipeline management. These extensions are difficult due to the complexity and lack of transparency in the system of approvals with a multi-

tude of authorities. The two remaining observations appear to be more fruitful lines of research as they point to the lack of a planning methodology for planning operations up to market launch. Surprisingly, no well-defined techniques are found to help determine production volumes or inventory levels. These decisions are getting harder to make due to rising uncertainty and they will require more attention in the future if companies are to cover demand at market launch. On the supply-side, ramp-up effects present in the introduction of new drug delivery systems are making capacity planning of secondary pharmaceutical production more complex, requiring more attention if TTM should be kept low. These two observations form the direction for the next research questions.

RQ2: How can pharmaceutical companies better plan operation in preparation of market launches while considering some of the unique uncertainties present around the launch?

Planning of operations for market launch of new pharmaceutical drugs is treated in chapter 3. Three key uncertainties from the market authorization process are identified; the length of the process, the risk of a forced label change and uncertain reimbursement levels, which is handled through demand uncertainty. These uncertainties are captured in a two-stage stochastic MILP model, which encompasses all stages of secondary pharmaceutical production. Several launch preparation decisions, which have to be made up front, are found through the model. We demonstrate how the structure of the problem can be used for modeling the scenarios in a very effective way and how uncertainty over time can be resolved without the need for multi-stage programming. Based on a case study from a typical pharmaceutical company, an extensive numerical test of 100 different instances is investigated.

The expected delay of a market launch represents TTM, as expected delays reflect the lost peak revenue of a longer TTM. Trading off this with several other costs, the model supports decision making for the launch preparation decisions such as required API volume, volume outsourced to a CM and the PPM volume purchased. Our model prioritizes resources such that market launch delays predominantly take place in less profitable markets. Considering all instances, delays are however unavoidable. Furthermore, we find that risk packaging, i.e. having market-specific finished product on inventory prior to market authorization, is only needed for large markets, when capacity restricts covering the market in one period.

Further insights are gathered by changing the supply chain configurations and testing several operations policies. We found, that PPM suppliers should be found based on their speed rather than cost, as lead time was found to have a far greater impact on expected delay and total cost than supplier cost. By changing the sales price to reflect drugs with higher development cost and higher benefit for the patients, it was found that drugs with a higher price such as e.g. the fast growing group of biologics can also be described with this model. Additionally, our model outperforms any strict risk packaging policies as it better reflect how much of the product should be risk packaged.

The real benefit of our approach is demonstrated by a comparison with the current industry approach. Currently managers estimate the needed API volume through a worst case rule which leads to overstocking. The amount of API found by our approach is significantly smaller, and our approach leads to a 14 % lower cost due to lower API production costs, holding costs and scrapping cost. Furthermore, our results indicate that oversizing the API inventory, which the industry has done excessively, leads to more risk affine managers in terms of higher risk packaging. Expected delays of market launch are however shorter for the industry approach.

Finally, we demonstrate how robust optimization can be used to balance TTM and total cost. Since any delay has a high cost, a delay in just one scenario leads to a cost significantly higher than that of other scenarios. This difference leads to large variations in the total expected cost. By using robust optimization with the first order upper partial mean to reduce this variation, a consistent reduction of the expected delay i.e. TTM at a limited increase in cost without necessarily overstocking API is found. With this Pareto relationship between total cost and lost peak revenue, managers can find their acceptable TTM and cost combination.

RQ3: How should pharmaceutical companies plan secondary production capacity to reflect ramp up of effective capacity on underutilized production lines such that product availability at at market launch is ensured?

The fourth chapter focuses on improving modeling of ramp up in capacity planning for secondary pharmaceutical production. For demand-driven industries, full utilization is not always required, but lowering production also reduces the experience gained with the new product and the projected increase in effective capacity is not attained. This leads to an overestimation of the ramp-up effect in current time-dependent ramp-up models. Instead, an effective method for capturing ramp up as a function of the cumulative production volume is presented. It is demonstrated on secondary pharmaceutical production, which due to slow demand diffusion and the required production of a validation volume ahead of market launch, sees equipment utilization lowered at times. The planning model using the improved ramp-up modeling is used to ensure product availability as new production lines have to be constructed and ramped up prior to market launch. Industry specific characteristics such as validation of production for each market and limited shelf life are also considered in the model.

A case study from the industry is presented, and the model is shown to provide both capacity expansion plans as well as production and inventory profiles over the market launch phase. To assure product availability, planning is based on the highest demand scenario. Results clearly show both the original shape of the used ramp-up function as well as the extended ramp-up length due to underutilization. A comparison with the current practice of building all lines within the first year demonstrates the value of a more nuanced approach to capacity planning, which allows the postponement of several line openings. Different what-if analyses can be carried out such as enforcing

multiple validations for each market to ensure supply in case of disturbances. Experiments with different effective shelf lives also show the model's functionality as a decision support tool.

Several insights into ramp-up management are also gathered. The overestimation of the often-used time-dependent ramp up is demonstrated and it is likely that on-time market launch with this representation is not possible. As secondary production ranges from production of pills to syringes or even more complex drug delivery systems, three different ramp-up curves found in the empirical literature are compared; the power curve, the s-shaped curve and the exponential curve. Faster ramp ups (exponential curve) allow for the opening of new lines to be delayed compared to slower ramp ups (power curve). This effect is less pronounced if the ramp-up length is reduced, but a difference in the expansion plan is still evident, demonstrating the value of faster ramp up. By reducing the length of ramp ups, the value of investing in ramp up preparations is shown. Assuming that the different types of secondary production resembles equivalent production in other industries, we suspect that the highly automated production of pills will exhibit an exponential ramp-up curve, whereas more advanced drug delivery systems would resemble the s-shaped ramp-up curve of the labor intensive automotive assembly.

In this thesis, the current planning methodology for new product introduction in the pharmaceutical industry is expanded by including two models into the planning hierarchy shown in Figure 1.3. The first model for supporting a series of launch preparation decisions while considering 3 different uncertainties is presented in chapter 3. As seen in Figure 5.1, this model would support decision making for aggregate production volumes which are send to the subsequent MRP process based on input from capacity and demand planning. Capacity planning is extended in chapter 4, where a far more accurate model for capacity in secondary production is developed (cf. Figure 5.1). The model focuses on capacity planning for introduction of a new drug delivery system and captures ramp up of effective capacity better, while considering validation and limited shelf life. With better capacity planning, the quality of the launch preparation model is increased. Central for both models is the use of industry-specific characteristics to better capture problems. The lower planning levels of MRP, production and demand fulfillment remain unchanged.

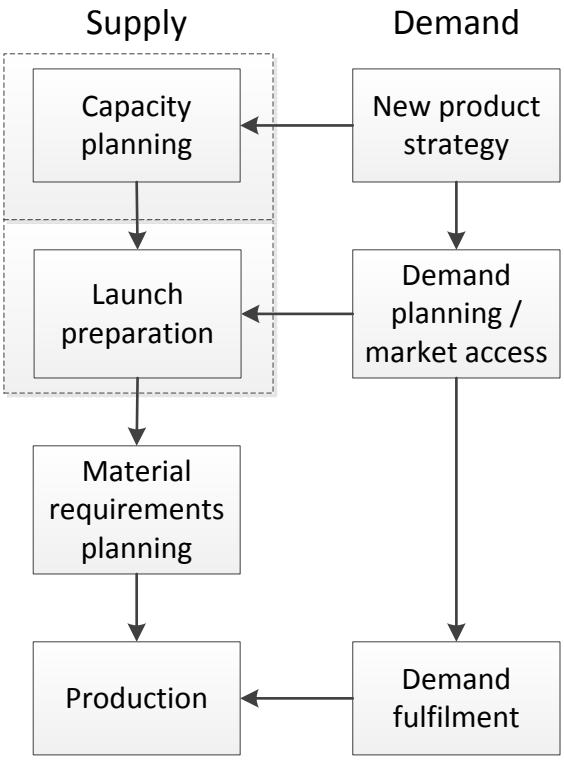

Figure 5.1: Overview over the contributions of this thesis to operations prior to market launch.

5.2. Future research

In this final section, possible future research is outlined both to the present case of planning operations in the last stage of new product introduction in the pharmaceutical industry and more general to research topics in operations management and planning. With new trends leading to a more complex and uncertain end phase of the new product introduction process, the old paradigm of excessive production to inventory based on loose estimates should be replaced by more complex methodologies, which consider both dynamics of market launch and industry-specific characteristics. In this thesis, two contributions to this area are presented, but there are still many possibilities for expanding this work.

The need for planning of operations in the last phase of new product introduction to ensure product availability at market launch and keep TTM low is clearly demonstrated by our results in chapter 3. Our approach was demonstrated for several different instances and supply chain configurations. Expanding the supply chain to consider a larger network with multiple PPM suppliers and CMs in more detail would allow for better uncovering of their role in operations prior to market launch. Further insights into which stage(s) should be outsourced up to market launch and how multiple suppliers should be managed could still offer more insight into managing operations before and during market launch. The impact of introducing a new product into an existing multi-product pharmaceutical supply chain has already been investigated (cf. chapter 2 and 3). However, these contributions do not capture the uncertainty of market launch and can hence only give an aggregat-

ed picture of the impact of a new product in the supply chain. For larger cases, computational speed may become an issue requiring new solution procedures. Here, hierarchical modeling could be a good way to split the problem up in e.g. a pre-launch model and a launch model, similar to Özer and Uncu (2013). One simple approach of cautiously estimating the required API volume was treated in chapter 3, but more elaborate heuristics might also be developed to cover more of the launch preparation decisions.

By using the structure of the problem, we were able to capture three separate uncertainties in one model and still have an acceptable computational complexity. This shows that there are still a lot of opportunities to develop new methodologies for modeling several uncertainties in a tractable way, rather than just focusing on a single source of uncertainty. When considering more uncertainties simultaneously, the correlation between the outcomes of these uncertainties is obviously a central point. In chapter 3, independence was assumed between the uncertainties. We believe this is a fair assumption, but certain interdependence cannot completely be ruled out. Interdependence between e.g. the reimbursement levels in different markets is very likely as reference pricing is used. As discussed in chapter 2, this is however difficult to capture due to the lack of transparency and data. Other interdependencies and correlations can also be difficult to identify and hence model. Robust optimization was used as a risk management approach in chapter 3 as a way of trading off TTM and total cost. Other risk management techniques such as conditional-value-at-risk could not be implemented due to our modeling approach for the scenarios. For a system with several risks, there is generally much research left to both find ways to model it and ways to manage it.

The value of better capturing industry characteristics such as improved modeling of production ramp up, validation and shelf life are demonstrated in chapter 4. It is possible to add further aspects of pharmaceutical production to models. Validation volumes could be more detailed if enough information about the new drug is available to calculate the exact required amounts. As distribution of a drug takes varying length of time for different market and thereby consume different amounts of the shelf life, market dependent shelf life should perhaps be considered. Russian reports of drugs being six months in transit show that distribution time can sometime be a significant length of time. Lower planning levels could also consider document flows and lead times directly as these often at this level are determining the lead time of pharmaceutical production. Several possible expansions of our approach to model ramp up could also be interesting. With several new identical production lines, knowledge transfer is an obvious way to reduce the ramp up length. Currently this is already being practiced in the industry. After ramp up of the first line, the production team from that line is sent to other lines to teach other teams about the new processes, i.e. a one-way transfer of knowledge. This could lead to the creation of lead- and follow-plants as seen in the automotive industry. Two-sided knowledge transfer could also be considered for two lines being ramped up simultaneously in the same plant. If knowledge is transferred, their combined experience i.e. combined cumulative production volume could potentially be used to describe the ramp-up process. A completely different way to shorten ramp up, when several identical lines are considered is to instigate friendly competition between plants for who can produce the most. Finally, the contractor team building the lines might also gain experience leading to shorter construction time of new lines.

Throughout the thesis buildup of inventory prior to market launch is discussed. However, we have thereby only considered inventory as a buffer to balance supply and demand over the planning horizon. Since demand uncertainty of new pharmaceutical products is high due to the lack of historic data to base forecasts on, safety stocks are usually carried to buffer against short term demand variations. Safety stock placement has already been covered in the literature and can also cope with non-stationary demand (cf. Graves and Willems, (2008). Safety stock placement however only considers lead times, service level and pooling effects. This leaves room for further research of how additional uncertainties or limited shelf life might influence such models.

With high profit margins on new pharmaceutical drugs and increasing uncertainty, further investigation into the use of flexibility for the pharmaceutical industry could be very interesting as an alternative to risk management. The industry is already embracing several methods of creating flexibility such as e.g. contract manufacturing. Recently, the industry has also been trying to expand the range of measures to create flexibility by e.g. improving production planning, increasing labor flexibility and integrating suppliers (McKinsey, 2011). There is however not enough research on how to use flexibility in operations planning and especially how to best comprise an appropriate mix of different flexibility measures. Several of our contact companies are e.g. considering using postponement to gain flexibility around packaging. Some are considering using partial packaging of products in combination with keeping multiple versions of the labels on-hand before the final market authorization. They can then use the label which is authorized. This will keep TTM low while still giving them the possibility of getting stronger claims authorized. But it is also a costly approach.

Where it is clear that good planning can help keeping TTM down, only new technologies in combination with adapted regulatory guidelines seems to be able to provide significant reductions in TTM. Such technologies, which could also help shorten clinical trials, could be improved computer analyses to provide predictive toxicology of new chemical compounds or development of biomarkers to better prove a drugs effect statistically (FDA, 2004). Another initiative that might impact manufacturing significantly is the immergence of continuous production to replace the current batch production. Continuous production, enabled through safe continuous process monitoring, could lead to faster process design and smaller dedicated production facilities without the need for lengthy setups and hence reduce throughput times of the API dramatically. Though these new technologies could cut TTM significantly, their development is slow and it seems that large reductions in TTM are not imminent. Until then it therefore seems that incremental improvements in e.g. supply chain planning as demonstrated in this thesis is the most viable option for shortening new product introductions in the pharmaceutical industry.

Appendix A

In this appendix, we show how the ramp-up curves describing effective capacity as a function of time can be re-written to a function of effective capacity over cumulative production volume. This better represents the underlying learning process and captures the experience gained.

Power function

For the power function, the effective capacity (y) as presented in Risse (2003) can be expressed as a function of time (t):

$$y = \alpha \cdot t^{\beta} \tag{A1}$$

To obtain capacity as an expression of the cumulative production volume, an expression for the cumulative production volume (x) as a function of time is first found by integrating (A1) from 0 to t to find the cumulative production volume given as an expression of time.

$$x = \int_0^t \alpha \cdot \tau^{\beta} d\tau = \frac{\alpha}{\beta+1} \cdot t^{\beta+1} \tag{A2}$$

In this expression we can isolate t:

$$t = \left(\frac{(\beta+1)x}{\alpha} \right)^{\frac{1}{(\beta+1)}} \tag{A3}$$

and find the effective capacity as a function of cumulative production volume by:

$$y(x) = \alpha \cdot \left(\frac{(\beta+1)x}{\alpha} \right)^{\frac{\beta}{(\beta+1)}} \tag{A4}$$

Sigmoid function

For the sigmoid function, the effective capacity (y) can be expressed as a function of time (t):

$$y = \frac{a}{(1 + c \cdot e^{(-b \cdot t)})} \tag{A5}$$

To obtain capacity as an expression of the cumulative production volume, an expression for the cumulative production volume (x) as a function of time is first found by integrating (A5) from 0 to t as above.

$$x = \int_0^t \frac{a}{(1 + c \cdot e^{(-b \cdot \tau)})} d\tau = \left[\frac{a \cdot \ln(c + e^{b\tau})}{b} \right]_0^t = \frac{a \cdot (\ln(c + e^{bt}) - \ln(c+1))}{b} = \frac{a \cdot \ln(\frac{c + e^{bt}}{c+1})}{b} \tag{A6}$$

To obtain the capacity as a function of the cumulative production volume, we first isolate *t*

$$y = \frac{a \cdot \ln(\frac{c + e^{bt}}{c+1})}{b} \Leftrightarrow \frac{b}{a} \cdot x = \ln(\frac{c + e^{bt}}{c+1})$$

$$\Leftrightarrow \frac{c + e^{bt}}{c+1} = e^{\frac{b}{a}x} \Leftrightarrow (c+1) \cdot e^{\frac{b}{a}x} - c = e^{bt} \Leftrightarrow t = \frac{\ln((c+1) \cdot e^{\frac{b}{a}x} - c)}{b} \quad \text{(A7)}$$

and insert the expression into (A5)

$$y(x) = \frac{a}{(1 + c \cdot e^{(-b \cdot \frac{\ln((c+1) \cdot e^{\frac{b}{a}x} - c)}{b})})} = \frac{a}{(1 + c \cdot ((c+1) \cdot e^{\frac{b}{a}x} - c)^{-1})} = \frac{a}{1 + \frac{1}{(\frac{c+1}{c}) \cdot e^{\frac{b}{a}x} - 1}}$$

$$= \frac{a \cdot ((\frac{c+1}{c}) \cdot e^{\frac{b}{a}x} - 1)}{(\frac{c+1}{c}) \cdot e^{\frac{b}{a}x}} = a \cdot (1 - \frac{1}{(\frac{c+1}{c}) \cdot e^{\frac{b}{a}x}}) \quad \text{(A8)}$$

For large values of c, $\frac{c+1}{c} \approx 1$, so

$$y(x) = a \cdot (1 - \frac{1}{(\frac{c+1}{c}) \cdot e^{\frac{b}{a}x}}) \approx a \cdot (1 - e^{-\frac{b}{a}x}) \quad \text{(A9)}$$

Time constant model

For the time constant function, it is not possible to find an analytical expression as we cannot isolate *t* in $x = k \cdot t + r \cdot (t + e^{-t} - 1)$. Instead we use the Newton-Raphson method to numerically approximate the curve as described in both Atkinson (1989) and Jensen and Bard (2003). Here *t* values can be found by iteratively approach the true value through the step size:

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)} \qquad n \geq 0 \quad \text{(A10)}$$

With this, we can approximate our function for any value. Illustrations of the resulting function are based on 200 different points.

Appendix B

Finding a piecewise linear curve to approximate the functions is a fitting problem. We instead simply approximate the curve with a number of tangents, which suffices as only a few function values will ultimately be used in the model. This approach, however, leads to a slight overestimation. For each function, we first find the cumulative volume at which target capacity is reached. The tangent and respective cumulative volume $\bar{x}$ crossing this point are then found. Hereafter seven points are found within the interval $[0;\bar{x}]$ given as $x_r = \{0;0.1;0.2;0.3;0.4;0.6;1.0\} \cdot \bar{x}$. This distribution is chosen since the derivatives change substantially in the first part of the curve. With the points determined in this way, the maximum overestimation is small. As the curves are used as linear constraints in the model, adding additional points adds little to the complexity, but also adds little in terms of solution accuracy. The slope, denoted CR_r, is found as $CR_r = \partial y(x_r)/\partial x$ and the intersect with the vertical axis denoted CL_r is given as $CL_r = y(x_r) - CR_r \cdot x_r$. As the tangents to the origin for the power and sigmoid functions would have $CL_1 = 0$, we use an x_1 slightly larger than zero to obtain an effective capacity in period 1 which is larger than zero. The parameters for the linear curves approximating the ramp-up functions are found in Table B.1, while the linear curves used as well as the piecewise linear curves approximating the ramp-up functions are shown in Figure B.1.

Table B.1: Parameters for the linear approximation of the ramp-up functions.

Curve	*Power function*		*Sigmoid function*		*Time constant model*	
	CR	*CL*	*CR*	*CL*	*CR*	*CL*
1	1.949	3,200	2.344	4,600	2.429	109,400
2	0.817	28,100	0.875	155,300	0.415	250,300
3	0.674	45,400	0.327	311,600	0.192	327,000
4	0.601	60,400	0.122	407,400	0.104	378,100
5	0.554	74,000	0.046	457,100	0.060	414,100
6	0.494	98,700	0.006	491,700	0.022	457,900
7	0.427	141,900	0.000	499,700	0.003	490,600

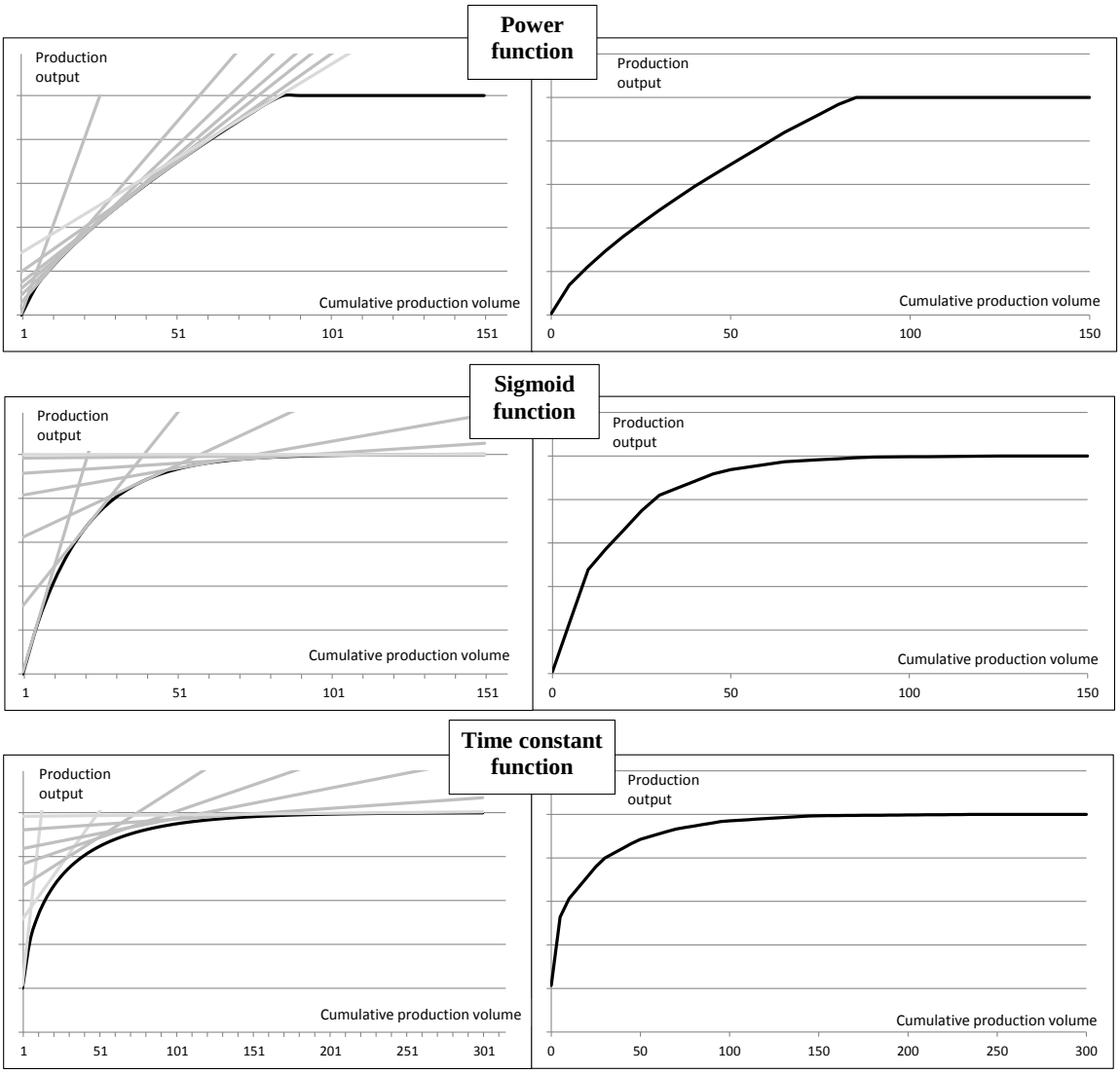

Figure B.1: Linear tangents approximating of the volume-dependent ramp-up curve for the power, sigmoid and time constant functions (left) and the resulting piecewise linear curve (right).

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List of Abbreviations

API	Active Pharmaceutical Ingredient
C1-4	Clinical trial, number 1-4
CM	Contract Manufacturer
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
IND	Investigational New Drug application
MILP	Mixed Integer Linear Program
MRP	Material Requirements Planning
NDA	New Drug Application
PC	Pre-Clinical trials
PPM	Printed Packaging Material
RQ	Research Question
RFID	Radio-frequency identification
SME	Small and Medium-sized Enterprises
TTM	Time-to-Market