Analysis of life cycle management leading to pharmaceutical process improvement by computer simulation

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Für meine Familie.

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List of Abbreviations

API	Active Pharmaceutical Ingredient
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CFD	Computational Fluid Dynamics
CMO	Contract Manufacturing Organization
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRO	Contract Researching Organization
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	Fixed Drug Combination
FIH	First-In-Human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HTS	High Throughput Screening
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
I-MR Chart	Individual Moving Range Chart
IND	Investigational New Drug
INDA	Investigational New Drug Appication
IPC	In-Process Control
IQWiG	Institute for Quality and Efficiency in Healthcare
LC	Life Cycle

LCM	Life Cycle Management
MAA	Marketing Authorization Application
MID 3	Model-Informed Drug Discovery and Development
MIT	Massachusetts Institute of Technology
NBE	New Biological Entity
NCE	New Chemical Entity
NDA	New Drug Application
NICE	National Institute of Health and Clinical Excellence
OHOP	Office of Hematology and Oncology Products
OHS	One-and-a-Half-shift System
OS	One-shift System
OTC	Over-The-Counter
PAT	Process Analytical Technology
P_{EMB}	Product Ethambutol
PhRMA	Pharmaceutical Research and Manufacturers of America
P_{INA}	Product Isoniazid
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Control
R&D	Research and Development
Rx	Prescription drug; from lat. Recipe
SD	Standard Deviation
TS	Two-shift System
U.S.	United States of America
WHO	World Health Organization
WT	Times for Weighing in

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Short Summary

The pharmaceutical industry participates in a highly changing environment with increasing demands and competition while being less innovative. The development of medicinal products and their value towards ordinary goods force the manufacturers to produce high quality products in the most cost-effective way. By analyzing the life cycle of medicinal products and its management, the present challenges as well as appropriate solutions were identified. One such solution is computer simulation, which is why two approved production processes of film-coated tablets were optimized by discrete-event simulations. Through this, a methodological approach was developed to build, verify, and validate models of the as-is productions. Afterwards, the models were modified into different optimization scenarios to challenge multiple shift systems. These shift systems were evaluated considering the campaign duration, the production costs as well as the capacity utilizations of employees and machines. The implemented model changes could bisect the campaign duration and reduce the production costs in a two-digit percentage share. Thus, process optimizations by computer simulations were proved to be one remarkable strategy in the life cycle management of medicinal products.

Kurzzusammenfassung

Die pharmazeutische Industrie partizipiert in einer sich stark verändernden Umgebung mit steigendenen Anforderungen sowie wachsender Konkurrenz und ist zugleich selbst weniger innovativ. Die Entwicklung von Arzneimitteln und deren Wert hin zu normalen Gütern zwingt die Hersteller möglichst kosteneffizient qualitativ hochwertige Produkte zu fertigen. Eine Analyse des Lebenszyklus von Arzneimitteln und dessen Management identifizierte sowohl die vorhandenen Herausforderungen als auch mögliche Lösungsansätze. Computer Simulationen stellen einen solchen Lösungsansatz dar, sodass zwei zugelassene Produktionsprozesse von Filmtabletten durch Simulationen optimiert wurden. Dafür wurde zuerst ein methodisches Vorgehen entwickelt um Modelle der Produktionsprozesse zu erstellen, sie zu verifizieren und zu validieren. Im Anschluss wurden diese Modelle in verschiedene Optimierungsszenarien abgewandelt um unterschiedliche Schichtsysteme zu prüfen. Deren Bewertung erfolgte anhand von Kampagnendauer, Produktionskosten sowie Mitarbeiter- und Maschinenauslastungen. Die implementierten Modelländerungen konnten die Dauer der Produktionskampagnen halbieren und die Produktionskosten um einen zweistelligen Prozentsatz senken. Somit wurde bewiesen, dass Prozessoptimierungen durch Computer Simulationen eine eindrucksvolle Strategie im Life Cycle Management von Arzenimitteln darstellen.

1. Thesis Introduction

1.1. Background and significance

The migration of pharmaceutical production processes towards emerging countries, especially China and India, has created strong dependencies for European countries. These dependencies, over 80% of the active pharmaceutical ingredients (API) are produced in Asia (1), have become highly relevant during the current COVID-19 pandemic. India for example, initially stopped the export of APIs and of finished medicinal products. Insecurities about the ongoing production capabilities caused the Indian government to prioritize the medical care of its own population (2). Such scenarios can risk a breakdown of the worldwide pharma supply chain for some indications.

Even before this pandemic, struggling supply chains have been an issue. Prominent examples are products containing hydrochlorothiazide, sulfamethoxazole, trimethoprim, propofol, and valsartan. The latter has even reached public awareness in 2018, when a so far not considered toxic by-product, N-Nitrosodimethylamine, provoked the market withdrawal of valsartan products. To decrease costs, their production was moved to China and India decades ago. There, changes of the synthesis process, while not adjusting the related analytics, led to the synthesis of N-Nitrosodimethylamine and further toxic by-products (3). Ever since, hypertonia patients struggle to receive the best medication as only few, foreign valsartan API manufacturers exist. Besides the named APIs being constantly out of stock, the German agency, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), listed 359 additional shortages in the supply of medicinal products in June 2020 (4).

The growing public interest is reflected in the media by special programs and official statements of politicians discussing the demand for European independence. A German non-profit association representing about 260 pharmaceutical companies encouraged the remigration of pharmaceutical productions. While the production of biologics and vaccines is more challenging and specialized knowhow is necessary, common medicinal products can be produced much more cost-effectively in Asian countries. Therefore, the association requests governmental support to provide enough financial incentives for relocating entire pharmaceutical productions (5).

Besides the described risks or even danger of abandoning European production sites, it is at least questionable whether it is indispensable. The increasing pressure on the pharmaceutical companies is unquestionable with the rising demands (6) and costs (7)

coupled with lower profit margins. Yet, other production-oriented industrial sectors, such as the automotive industry, have worked on strategies to maintain stable and sustainable productions within Europe. Why shouldn't the research orientated pharmaceutical industry also succeed?

1.2. Working hypotheses and aim

To address this issue, this work extensively investigates the occurring situation in the pharmaceutical industry, especially the associated life cycle management (LCM) of medicinal products. I hypothesize that successful LCM of medicinal products is possible and that it can assure the profitability of standard chemical medicinal products. Several different tools can optimize the life cycle (LC) of a medicinal product and I feel confident that computer simulations are one such tool for a practical application. Furthermore, I am even convinced that this method enables to significantly reduce costs and thereby safeguards profitable pharmaceutical productions in Europe.

The first aim of this thesis is to scrutinize the LC of medicinal products. This includes the present situation, challenging circumstances, and the current management strategies to overcome obstacles of each LC phase. The goal is to provide a profound overview about this topic in order to draw the link between different disciplines, such as engineering, management, and science to raise a deeper comprehension of complex interactions and of the participant's roles. This advanced understanding can subsequently contribute to a more sustainable, holistic, and successful LCM of medicinal products.

The second goal is derived from the above. The theoretical analysis of the prevailing strategies leads to applying one in reality. This demands industry cooperation to investigate actual products. A medium-sized contract manufacturer agreed to optimize the productions of two actually approved products by computer simulations. Both production processes represent a classic proceeding for film-coated tablets without any specialized or high-tech techniques. Hence, they are excellently suitable for a case study to increase the product profitability solely by production improvement. The computer models are built in the commercial software FlexSim, which is commonly used in different industry sectors to simulate material flows. Different optimization scenarios are developed and compared to identify the most profitable production process for both products. So, the ambition of this work is to demonstrate, based on a real case study, which optimization potential could be developed by means of computer simulation.

2. Chapter 1: Analyzing life cycle management of medicinal products

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2.1. Introduction

The pharmaceutical industry has undergone challenging economical and structural changes in the past 20 years. More than ever, research companies depend on successful new products to sustain profitability and prosperity. The development of new products requires more efforts (> €1 billion (8) and > 10 years (9)) nowadays than in the past. Despite these efforts, less new drugs become approved. Meanwhile, the industry faces increasingly pressurizing issues, such as higher regulatory demands (10-12), throughout the LC of a medicinal product, which decreases the profit margin. To increase the return on investment, companies need management strategies to become more effective as well as to maintain and strengthen pharmaceutical research.

The available management strategies have particular focuses and can be assigned to different LC phases of a medicinal product. A successful LC consists of four main phases: research and development (R&D), approval, commercialization, and market withdrawal. During R&D, different initial substances are explored and preclinically tested until the leading compound is identified (13). After the clinical trials have proved its quality, efficacy, and safety (14), the innovator can submit all collected documentation to the regulatory authorities to obtain the market approval (15). This allows the commercialization of the product. Initially, sales increase quickly until a plateau and the maturity stage is reached. Whenever unfavorable circumstances, such as adverse side effects (16) or economic factors (17-19), drastically lower the market share, the product is withdrawn from the market (20). During each of these phases, the pharmaceutical company faces specific issues, which must be assessed individually.

LCM intends to fulfill three different aspects. Firstly, the question whether the LC of a medicinal product is to continue or to end has to be reassessed constantly. Hence, decision makers need current knowledge about the product including market dynamics, engineering issues and changes in regulation or supply chain. The St. Gallen management model endorses this point of view stating that the individual environment and

organization condition the management efficacy (21). The second and third aspect of LCM depend on the LC phase. Until the approval of the medicinal product, the core question is how the time-to-market can be minimized. Afterwards, the intention is contrary with maximizing the time until market withdrawal. Figure 1 visualizes a schematic LC and the targets. After all, the management strategies aim to ensure the profitability of the existing product for the present and to finance future research. However, being confronted with much resource-intensive but unsuccessful research, the financial burden increases steadily.

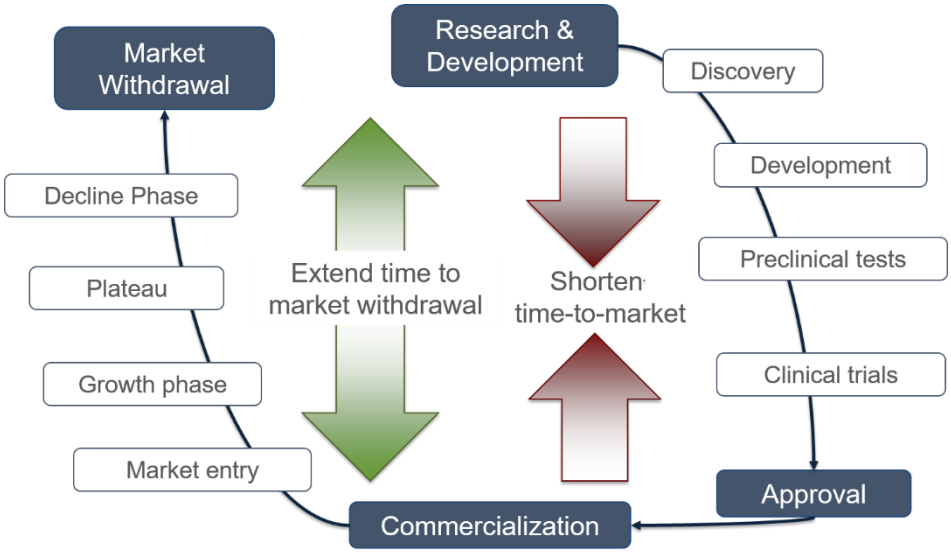

Figure 1: The life cycle of a medicinal product and the main management objectives. Reproduced from (22) with permission from Elsevier.

This topic concerns most participants of the health sector: researchers, health insurances with the reimbursements, regulatory agencies, and pharmaceutical companies. The latter can be divided into researching companies, generic companies, and in contract manufacturing organizations (CMO). Hence, there is variety of stakeholders with partly contrary interests. Usually, the participants have a limited, personal view on this topic without recognizing their own role in the overall system. Even inside a company, each department is focused on their own objectives. The scope and focus of this work are researching pharmaceutical companies which cover all phases of the LC in the global setting. The aim is to chronologically access the LC of medicinal products regarding the current state and demands along with LC phase specific issues. Additionally, the pending decisions and LCM strategies that offer the highest profitability from the product are introduced and evaluated.

2.2. Research and development

The first phase, R&D, lays the foundation for a medicinal product and can be subdivided into four parts: discovery, development, preclinical tests and clinical trials. This listing represents the chronological order; however, most parts can overlap in time, so does the development of the dosage form evolve constantly until some point in the clinical trials.

The necessary time-to-market and the required resources to bring a medicinal product to the market differ dramatically. Parameters, such as dosage form, indication, and characteristics of the API, whether it is a biological or a small molecule, influence R&D activities. The European Federation of Pharmaceutical Industries and Associations (EFPIA) name 12 to 13 years as the average R&D duration (23), while DiMasi indicated the cost to possibly reach up to US $1.4 billion until the approval (24). A cooperation of biological companies in the USA, called Pharmaceutical Research and Manufacturers of America (PhRMA), investigated the cost distribution (25):

- 21.1% preclinical tests
- 48.3% clinical trials
- 5.1% approval
- 16.6% pharmacovigilance
- 8.9% uncategorized

Even though the pharmaceutical industry invests these enormous resources, the chances of success are low. Only 1% of the compounds are actually tested in clinical trials (26) and 0.01 to 0.02% of the synthesized structures finally reach commercialization (23). The augmenting number of employees in R&D (23) also does not cushion the low productivity. A possible explanation is that most of them are neither involved in real research nor in development, but instead in the accompanying quality system. Regulatory authorities demand higher standards (10-12) resulting in higher investments because of new technologies and higher head count, while the R&D output diminishes.

The current intentions of R&D concentrate on finding treatments for four therapeutic areas: cardiovascular and central nervous system diseases, infections and oncological diseases making up over 50% of the overall efforts (27). The reasons can be found in the industry's motivation to do R&D. "Competition", "medical need", "potential market share", "prevalence of a disease", "research and development costs", and "technical feasibility" were named by Tamimi and Ellis as the main drivers (13). All of them are

comprehensible but underline the fact that R&D of new medication, and thereby a public interest, depend on an industry. The individual companies must ensure their own profitability and cannot be blamed for their entrepreneurial thinking which eventually raises the question of governmental responsibility.

In the past two to three decades, many changes have stressed the western pharmaceutical industry (particularly European companies) (28), even if recent technological advances, such as virtual and high throughput screening (HTS), facilitate and strengthen innovation (13). Emerging countries challenge the former dominating companies causing lower growth rates and market values (1). The declining return on investment indicates further financial issues (15). The decreasing output of new chemical entities (NCE) (11) additionally weakens their position, albeit the pharmaceutical industry already invests the most in R&D (percentage of sales) in comparison to other industry sectors (1). Higher regulatory demands (6, 29) and augmenting costs for the quality system, quality control (QC), and quality assurance (QA) (29, 30), come together with limited sales prices because of reimbursement agencies (1). Furthermore, particular emphasis is put on individual medicine which leads to a more cost-intensive development (31) and the production of individual, small batch sizes. All these factors pressurize the industry as they cause decreasing margins (Figure 2).

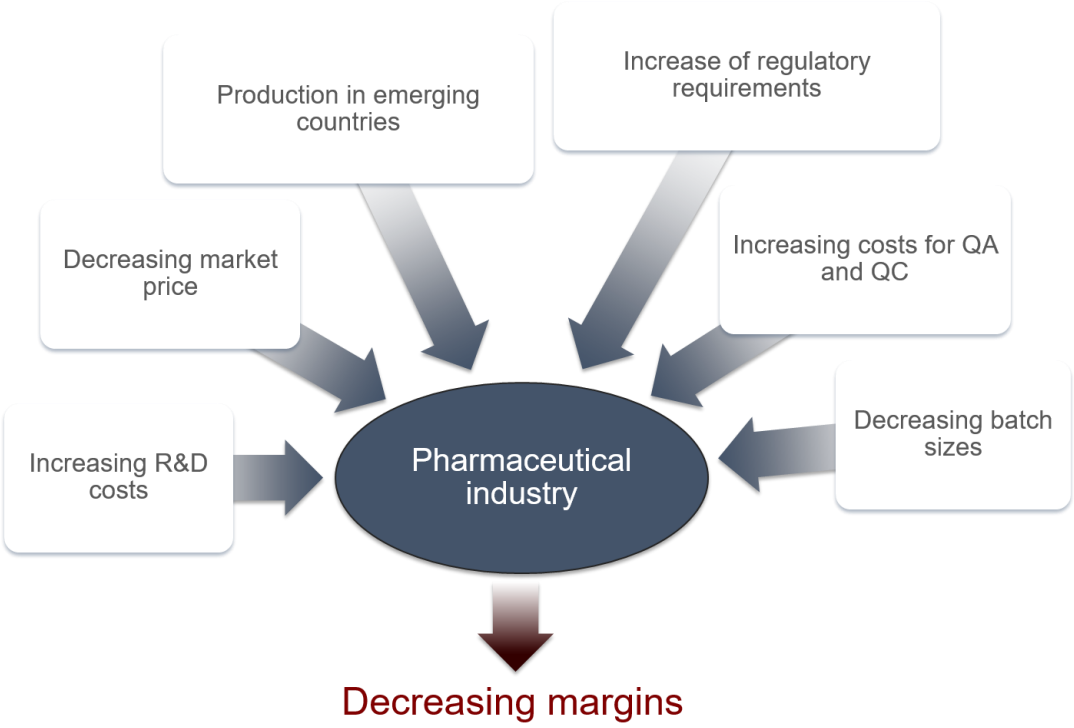

Figure 2: Summary of stress factors for the pharmaceutical industry causing decreasing margins. Reproduced from (22) with permission from Elsevier.

Most of these stress factors are difficult to address, as they depend on external triggers. Thus, it is even more important to identify reasons of internal issues. The inefficiency during R&D is at least partly caused by rising difficulties. Simple drug targets have already been examined, as more than 200 biologicals and over 3,000 (semi-) synthetic drugs have been developed until 2013 (1). The remaining areas are therefore neither obvious nor easy to access (28). Furthermore, the characteristics of the new molecules, being less soluble and less permeable (32), are more challenging for the development of the dosage forms.

At a later stage, communication issues between different departments hinder effective process development. The areal divisions and bloated bureaucracy in big companies cause “information silos” in different departments without having a cross-functional exchange of knowledge but instead a gap between development and production (6). Both would profit from the collaboration as R&D could directly consider tech transfer issues and the production system could gain a deeper product understanding.

A different reason for high attrition rates could be the wrong application of a research method. As an example, phenotypic and target-centric screenings are evidently important methods and contribute to successful R&D. However, the benefit of their application depends on the stage of the API development. While phenotypic screening is especially suitable for first-in-line drugs, the target-centric approach is better utilized for exploring follower drugs. It needs more given information like the molecular mechanism of action (33). Therefore, applying the wrong method would harm or even stop the R&D of a promising lead substance.

The migration of R&D and production capacities towards emerging countries is a well known risk for western pharmaceutical sites (23). The strict regulations in combination with a dissatisfaction of European and U.S. researchers can make emerging countries more attractive. There, the earned knowledge might provide these researchers with more freedom and a better standing. Nonetheless, the grown strict regulations established a high quality in Europe and in the USA (1). Not because of the quality, but because of the strong dependence on especially Chinese and Indian API productions, are these migrations of special interest. The COVID-19 pandemic demonstrates this dependence and the helplessness which might cause a rethinking. The German Medicines Manufcaturers’ Association claims to retract these migrations and to strengthen the European market (34).

2.2.1. Discovery and development

This initial R&D phase addresses the discovery of possibly interesting targets and molecules, helps to select the most promising ones, and focuses on the development of the best-suited dosage form for the intended application. For the identification of new substances, researchers can rely on different approaches. Natural materials can be the starting point as well as diverse screening methods. Receptor-targeted HTS, random HTS or virtual screens can be applied for a later targeted chemical synthesis of the identified molecules (13). These molecules can be classified into NCE and new biological entities (NBE). The identified lead structures run through in vitro tests to firstly analyze the selectivity and potency and to afterwards challenge their biochemical and toxicological characteristics (13). Besides research on the API, first attempts at developing a suitable dosage are made. Initially, simple forms like capsules or parenteral injections are sufficient. Later on, the pharmaceutical technologists work under immense pressure to improve and optimize the formulation whenever clinical trials are entered.

2.2.2. Preclinical studies

After a successful drug discovery and development phase, the pharmaceutical company applies for preclinical studies. In this phase, basis information must be collected and parameters specified to receive the approval of the regulatory authorities. Points of interest are employees and training, experiments, facilities, and the duration (35). The aim of preclinical tests is to understand the pharmacological-toxicological characteristics in order to find the initial doses for the later clinical trials in humans. Furthermore, toxic effects, toxic doses, and endangered organs are examined for the establishment of clinical monitoring. Genotoxicity, single and multiple doses toxicity, chronic and reproductive toxicity are investigated together with carcinogenicity (13, 36). The studies are conducted in vitro and in vivo whereby the animal studies must follow the principle of the 3Rs (reducing, refining, and replacing) according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH M3 (R2) guideline. Further regulatory requirements of preclinical tests are defined in ICH E8 (including general considerations for clinical trials) and the Directive 2001/20/EC for the European Union (36). Cevc stated that the costs for preclinical trials for one medicinal product are in the neighborhood of US $2.7–3.8 million (35). In contrast, DiMasi also considers the costs for all drop outs in his estimation and calculates

21.2% of US $1.4 billion making an investment of almost US $300 million for the determination of mostly toxicological characteristics (25). So far, the API was the main focus. However, new excipients are also introduced for some formulations. This requires additional preclinical tests and analysis regarding its physical and toxicological properties (37). Such an introduction must be balanced with the additional costs and durations.

2.2.3. Clinical trials

Before conducting the clinical trials, all information about the completed preclinical tests must be gathered and a concept must be worked out. The Clinical Trials Regulation EU No 536/2014 will repeal the Directive 2001/20/EC whenever the EU clinical trials portal and database are fully functional (38). They regulate good clinical practice (GCP) as well as the execution, ethics, and requirements for authorization. Within 60 days, the regulatory authorities must decide whether the application is approved or not (39). The U.S. agency, the Food and Drug Administration (FDA), grants an even faster decision with only 30 days. The content of the investigational new drug application (INDA) is similar to the European investigational medicinal product dossier (IMPD). Results of the preclinical tests, clinical protocols, the information about manufacturing of the new product, data from any prior human research, and investigator information are scrutinized (14). A summary of the different terms in the European Union and the USA are listed in Table 1. For the following text, the European versions are used.

Table 1: Terms and abbreviations during clinical trials in the EU and the U.S. Reproduced from (22) with permission from Elsevier.

Phase	**EU**	**Ref.**	**US**	**Ref.**
Clinical trials	Investigational Medicinal Product (IMP)	(40)	Investigational New Drug (IND)	(41)
Approval for clinical trials	Investigational Medicinal Product Dossier (IMPD)	(40)	Investigational New Drug Application (INDA)	(41)
Approval for marketing	Marketing Authorization Application (MAA)	(42)	New Drug Application (NDA)	(41)

Whenever regulatory standards are met and the approval is received, the clinical studies can start to prove quality, efficacy, and safety (38) of the investigational medicinal product (IMP) in three different phases. To begin, it enters Phase I studies, which are the first-in-human (FIH) tests on up to 100 healthy, male probands (43). The interaction

between IMP and body is investigated focusing on pharmacokinetics with the absorption, distribution, metabolism and elimination (44). Also, gradual dosage increase explores the tolerability (36). The FIH tests are conducted sequentially as a result of the antibody study TGN1412 2006 in London where six probands simultaneously received the antibody leading to severe life-threatening conditions for all of them (45). One further restriction is the skipping of Phase I studies in cases of cytotoxic drugs (13). In general, FIH tests are expected to take one to one and a half years until they are finished (43). The duration of the following proof-of-concept study generally amounts to < 24 months. This Phase II trial presents the treatment of patients for the first time. Hundreds of them receive the IMP to test its efficacy and safety (13), to determine its short-time side effects and the dose rates (43). The same aspects are furtherly investigated in the longest-lasting studies, the Phase III trials. Additionally, drug-drug interactions and human demographics are regarded. Thousands of patients usually participate in target randomized controlled trials in numerous countries all over the world. The field of participants is divided into one receiving “gold standard” medication and the other one receiving the IMP. This enables a comparison of the IMP to the current best treatment of the disease (43, 44). The overall time for clinical trials differs depending on the chosen literature. In general, seven to nine years are estimated (18, 35, 46, 47) having a probability of success of 21.5% for NCEs and 30.2% for NBEs (41). DiMasi summarized more information about R&D costs in 2016 (24). After investigating 1,422 cases between 1995 and 2007, he found out that the attrition rates sink from Phase I (39.9%) over Phase II (34.1%) to only 5.4% for Phase III studies. The approval was reached by 7.1% of the cases and the remaining 12.6% were neither abandoned nor had they reached an approval. Instead, they were still somewhere in between (24). There are multiple reasons for the discontinuation of an IMP. Firstly, the clinical trials can fail if one of the aims (quality, efficacy, and safety) is not met or if the IMP is not as effective as the gold standard. Secondly, disadvantageous characteristics concerning the half-life or the bioavailability can occur (13). Also, financial reasons can force a project stop. For different reasons, the company may have to cut costs and therefore prioritizes other projects due to the financial risk (1).

2.2.4. Pending decisions and further activities

More than the obvious activities are necessary as pending decisions for later stages of the life cycle need to be made. The protection of intellectual property is of central im-

portance. For patentability, the new product must fulfil three conditions. It must be unexpected, non-obvious, and useful (35). Processes, such as the discovery and the production, the indication, or the product formulation and deliveries are patentable (28). Later patent adjustments, like patent term restoration, trade marking or forming alliances to enforce intellectual property rights, are common part of LCM strategies for profit maximization (46). The exact timing is of great importance since the patent protection is limited to 20 years (10, 35). Whenever the patent is granted, the innovator can sell the product unrivalled for a more or less self-defined price. Applying too early therefore minimizes this protected, financially important time since competitive products can previously cut down the market share. On the contrary, a late patent application also favors competitors because some elements of the clinical trial documentation can be publicly accessed. Hence, at some time during preclinical tests, the innovator usually requests a patent (20) and a fast time-to-market must be achieved. This increases the pressure on preclinical and clinical trials to pass not only successfully but also quickly. Generally, the time-to-market takes 12 to 13 years of patent protection leaving only seven to eight years for unrivalled commercialization (35). The initial costs for patent application were presented by Cevc for both, Europe and the USA (35).

Other important questions arise during Phase II of the clinical studies. It must be decided how the production process of the new product can be realized best for the later commercialization. An existing production site can either be refitted or expanded, but also, a completely new site can be built (43, 48). The process design should be found during Phase II whereas the actual plant design happens during Phase III (44). Besides the above, further research is done. Long-term studies in animals are conducted to learn more about oncological/toxicological characteristics and market research is completed to estimate forthcoming sales (44). Also, follow-up indications are investigated to broaden the range of indications and to improve product protection. The supportive clinical studies usually start whenever the first trial has reached Phase II or III (13). The monoclonal antibody Adalimumab (Humira® by AbbVie) is a great example. It was first approved by the FDA in 2002 to battle rheumatoid arthritis. Only two, respectively three years later, two further indications followed (psoriatic arthritis, Crohn’s disease) (18) and in 2020, at total of eight therapeutic areas are listed on the European Medicines Agencies (EMA) homepage (49).

2.2.5. Life cycle management strategies

The just mentioned example, finding follow-up indications, also contributes to LCM strategies. It shows that from the very beginning of a medicinal product's LC, far-reaching decisions must be made. LCM strategies at different levels are of interest during R&D. Firstly, there are extensive strategies, such as computer simulations for pipeline management or creating attention for the disease of interest. Secondly, structural strategies, such as outsourcing activities or cooperation in open-source drug discovery, and thirdly, detailed research strategies, such as pharmacometrics, can be assigned. Also, the choice of the indication, researching on rare diseases in order to obtain an orphan drug status, can be part of the LCM strategies.

As early as 1999, Rotstein et al. highlighted the necessity of a management tool for decision-makers to choose the best approach for pipeline management. The chosen management tool must consider the following issues: the R&D costs, all possible results of clinical trials and the according probabilities, market questions, such as demand and price, and production issues (costs and capacities) (9). Based on these aspects, a variety of candidates is evaluated and prioritized among each other and the required resources must be allocated (50). Different computer models can be found in literature that address this complex topic (9, 44, 50). One such example is an interesting white paper of an EFPIA working group, called MID3, which discusses three different objectives and addressees. After explaining the basics of model-informed drug discovery and development (MID3), an extensive review of over 100 case studies is provided to highlight the benefits of MID 3 to decision-makers. Furthermore, MID3 specialists can use the given information to enhance their own capabilities and regulatory authorities are provided with sufficient material for the establishment of rules and guidelines (51).

Another important strategy during R&D is the creation of awareness for the disease and the related treatment. Usually, thought leaders try to influence the attention of these topics during the pre-launch phase by publishing and interactions (52). Several of them form an advisory board, which is accompanied by a physician relations manager and practicing physicians as key leaders (53).

Regarding structural strategies, the removal of internal “information silos” is comparatively easy and effective. By creating cross-functional teams, a knowledge transfer between different departments can bridge gaps. Creating a permanent, responsible position for the new product is recommendable (11).

A different strategy to lower the pressure on research, is the establishment of R&D centers and open source drug discovery (42). The pharmaceutical industry is a leader in academic cooperation (1) and expands these cooperation to other companies (11). The term “open innovation” describes the fusion of internal and external knowledge to further R&D (8) instead of the conservative isolation. The FDA supports testing combinations and co-developments in its Guidance for Industry on “Co-Development of Two or More New Investigational Drugs for Use in Combination” (28, 54). The advantage of such collaborations is obvious - costs and risks for basic research can be shared amongst all. Moors claims more public responsibility in R&D, because whenever research is publicly funded, free access to all information possible. This would lead to a fundamental change for the industry having only production and distribution left for competition (28). A different financing option for R&D are private foundations, such as the currently prominent one of Bill & Melinda Gates (55), or crowdsourcing (56).

Mergers and acquisitions of small, innovative research companies have been a common strategy for bigger, stiff companies. However, critics argue that the overall research activity is lowered and entire research sites had been closed in the past leading to failure (1). With the contrary strategy, the outsourcing of clinical trials, responsibility and complex internal activities are handed over to gain flexibility (6).

To investigate the pharmacokinetic and pharmacodynamic properties of NCE’s, pharmacometrics is an interesting tool. Mathematical computer models support dose findings and extrapolations from adult to pediatric patient data, for instance. Clinical trials can be tightened (42) and exposure of children reduced. Oxcarbazepine, topiramate and vigabatrin are examples for successful pediatric dose finding by pharmacometrics (15).

The last-mentioned LCM strategy during R&D is the fundamental choice “Which disease or treatment should be addressed?”. The main drivers have already been named earlier. Prevalence and potential market share are chief among them and therefore, it

would be expectable that the industry focusses only on widespread diseases. However, R&D on rare diseases have increased steadily over the past decades. In 1996, 15% of the newly approved products treated a rare disease. Ten years later, 20 to 25% and additionally ten years later, even 37% of the new products targeted rare diseases. The most investigated topic is oncology, as 30 to 50% of the novel drug approvals for rare diseases are Office of Hematology and Oncology (OHOP) products (7).

2.3. Approval

As soon as all necessary activities are finished, the pharmaceutical company must decide where the product will be launched. This can happen globally, meaning in multiple key regions at the same time (13) or in different markets over a timeframe of several years (44).

When the European market is of interest, the Directive 2001/83/EC must be followed (15). Three different options are possible. The company can seek approval in only one country, called a national procedure. Alternatively, in a decentralized procedure, it also applies for the approval in one country while considering, a mutual recognition for other European countries. The last option is to apply centrally at the EMA for an EU-wide marketing authorization application (MAA) (13). It takes on average 366 days until the approval is granted with a 96% probability of a definitive decision in the first round (35). The Section 505 of the U.S. Food, Drug and Cosmetics Act is the analogous regulation (15). The FDA is 44 days faster to approve the new product, however, only 68% of the decisions are definitive in the first round (35).

Possibilities to accelerate the approval process for the companies are quality by design (QbD) approaches, which will be explained later, the usage of electronic common technical documents or priority reviews (46). A priority review is granted for products with orphan drug status whenever less than 200,000 patients in the U.S. are affected (13). R&D is eased, regulatory support offered and market exclusivity granted for seven to ten years (depending on regulatory authority) (57). A striking example is the product MabThera® (rituximab, Roche) addressing cancer. In 2011 it yielded US $7 billion because of extended indications (1) and proves that orphan drugs can adopt pioneering positions (57). Here again, oncological indications are strongly represented: four out of the top ten orphan drugs are cancer related (1).

Furthermore, facility building, price negotiations, and promotions are continuously pursued (44) and extra positions for fast responses to regulatory queries are created (13).

One possible demand of the approval can be Phase IV studies, also called pharmacovigilance studies in the EU, which keep investigating side effects and product safety while challenging the according risk management (13).

According to Prajapati and Dureja, approval is the "most crucial phase", as the regulatory bodies pass their own, binding judgement (18). This statement is questionable, as the pharmaceutical companies have the possibility to get official guidance during R&D. The FDA, for example, supports clinical trial planning (28).

Later changes in the manufacturing process or in analytics are called post-approval changes, which again must be approved by the regulatory authorities (28). This makes them rigid, tedious (over 5 years in case of global changes) and costly. Meanwhile, authorities consider this issue, as for instance the FDA supports new attempts in modern methods (QbD, innovative manufacturing methods) easing the approval process (58).

2.4. Commercialization

As its name suggests, the pharmaceutical company finally starts earning money with the newly developed product during the LC phase of commercialization. The minimum goal must be to return the initial investments. In order to profit as much as possible, this phase is supposed to last as long as possible. It can be subdivided into three sections: one of fast market share growth in the beginning, one stable maturity stage (18) and a final declining stage. This behavior was nicely depicted by Schöffski et al. in a broad normal distribution seen in graph (20). The pending decisions and management strategies target two different aspects: some optimize the phase of commercialization and others prevent the next phase of market withdrawal. Table 2 provides a summary of all LC phases, the according LCM strategies, and their intention.

2.4.1. Strategies to shorten the time-to-market

There are four main strategies to shorten the time-to market: process design, marketing, simulations in supply chain management, and pricing strategies. The first strategy, **process design**, is not only essential but also extensive and therefore includes multiple tools which will be investigated as well (see also Commercialization in Table 2). It has also been addressed previously, during Phase II or III of the clinical studies (44). A fast implementation of the production site despite the steadily changing demands is essential and causes much pressure (59). Relevant issues besides the actual process are equipment and material flows (on-site and outward). Typically, the production of

medicinal products is realized in two steps. The API is produced during primary production at a special site. After testing and approving, it is transferred to the production

Table 2: Summary of the LCM strategies, their temporal classification, and aims. Modified from (22) with permission from Elsevier.

Phase		**LCM strategy**	**LCM Goal**
R&D		• Simulations for pipeline management • Rare diseases/orphan drug status • Open source drug discovery • Pharmacometrics	Shorten time-to-market
Approval			

Commercialization	Early	• Process design
		  • QbD and PAT
		  • Process intensification
		  • Modularization
		  • Pull production
		  • Continuous manufacturing
		• Marketing
		• Simulations in supply chain management
		• Pricing strategies
			Shorten time-to-market

	Late	• Pricing strategies
		• Own generic product
		• Patent settlements
		• Divestiture
		• Differentiation
		  • New formulations
		  • Indication expansion
		  • Fixed-dose-combinations
		• Rx-to-OTC switch
		• Maximizing brand loyalty
			Extend time to market withdrawal

Market withdrawal			

site for the manufacturing of the final dosage form, called secondary production (48). Those two steps are usually not only located at different sites, but are also run by different companies. 80% of the APIs are produced in India and China (1), while the secondary production is distributed more broadly. Whenever the process for a new product is implemented, it must be considered that the site also serves the manufacturing of other products (60). Hence, existing production lines can be used after retooling or a new, preferably flexible new production line is built. Behr et al. published a “catalogue of demands for technologies” which promotes amongst others dedicated equipment, the shortest possible production times and continuous manufacturing. Also, modularization could realize more flexibility for capacity changes during construction (59). For the complex establishment of a new, well-designed production line, much

specialist knowhow is necessary. Federsel exemplarily listed the different divisions process and analytical chemistry, process engineering, and quality departments (11). All of these approaches aim to create a profitable process. This is especially important since the production cost makes up to 30% of the overall costs (59). This information must be considered with caution as it is probably only true for average productions. The percentage depends on the product kind (biologicals, individualized medicines or high-tech products vs. blockbuster productions with chemical APIs) and the according analytical methods. Apart from being efficient, the processes are supposed to be more sustainable and “greener” in the future (61).

The above mentioned concept of QbD goes hand in hand with process analytical technology (PAT) and helps to encourage approval by the regulatory authorities (46). Together, they build an automated production, in which real-time analysis enables instant corrections and thus an optimization of the process. A design space, which is a specified surrounding, is defined along with critical quality attributes (CQA) and critical process parameters (CPP). A much deeper understanding of the process and all influential aspects is needed to create predictive models causing more efforts during R&D. However, these efforts are also advantageous for changes or validations (62, 63) and are a chance for safer, more efficiently produced products.

The following four trends aim to meet the requirements of an efficient production process. Process intensification simply describes a chemical engineering development to minimize and to create cleaner, more efficient processes. This is limited to the equipment and possible engineering attempts and does not cover chemical or inner process changes (64). During modularization, the design process, the building, and equipment are divided into single modules, e.g. a granulation module. This enables parallel work to be done on different aspects to reduce time and costs. Hence, qualification and validation work are simplified and the entire process is much more flexible. While less production capacities are needed during the beginning of commercialization, the demand increases whenever the majority stage is reached. Modularization facilitates adding, replacing, and removing of modules to adapt the production capacities to the market demand (59). This technique could potentially be a great candidate to evolve the current rigid productions to a pull production. At the moment, medicinal products are produced for stock causing high storage costs. The automotive industry is pioneering this agile production type which challenges production and supply chain in order to produce on demand (65). Continuous manufacturing is the last investigated trend.

Contrary to the common batch production, all process steps are performed without interruptions between sub steps (Figure 3).

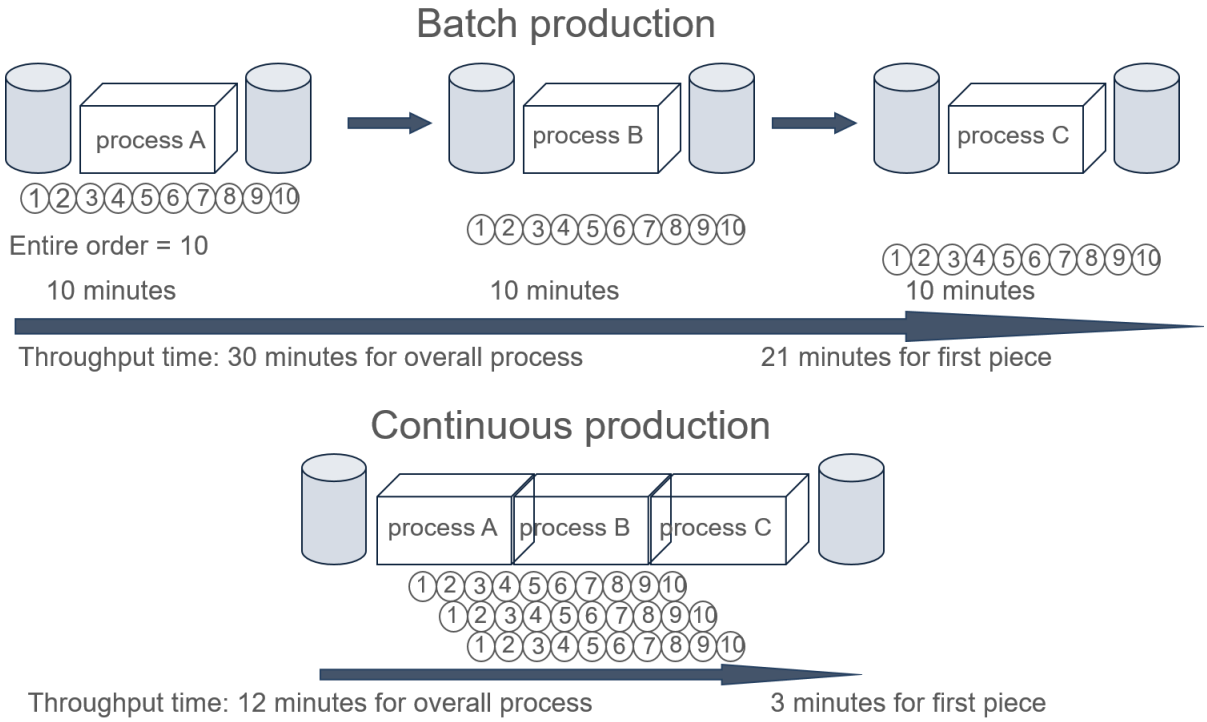

Figure 3: Comparison of classical and continuous batch productions.Ten pieces are to be produced in three process steps (A, B, C). While all pieces must be finished in the batch production before entering the following process step, this is not necessary in the continuous production. This way, the overall throughput time can be reduced from 30 to 12 minutes. Reproduced from (22) with permission from Elsevier.

Thus, there are no waiting periods between steps and all batch components are completed before entering into the next step. This trend allows smaller energy demands and lower costs. Another benefit is the ability to scale-up easier which shortens the time-to-market. The downsides of these benefits are more demanding process controls (66) and cleaning issues (67). The transformation of an existing batch production towards a continuous manufacturing process is possible but involves considerable time, efforts, and resources. It must be completely redesigned and needs a revalidation (67). A survey, conducted in 2012 with eight global pharmaceutical companies and one intermediate supplier, emphasized the importance of this concept. It stated that over 30% of the participants had already discussed this topic with regulatory authorities and 89% have been working on it, either in experiment or in production scale (68). This increases the responsibility of regulatory bodies to train their staff and keep them up-to-date on new techniques (69).

The described concepts are sometimes entangled and cannot be separated clearly in real-life. Some institutions have made efforts to alleviate this difficulty, for example, the Novartis-MIT Center for Continuous Manufacturing is one of the most prominent collaboration. The Massachusetts Institute of Technology (MIT) and the Swiss company investigated an integrated end-to-end pilot plant (48). The production from the raw material until the final tablets was realized by four different continuous productions on one site (48, 70). This enabled research on economic questions and capacity planning. Furthermore, simulations and process controls were examined (48, 66, 70-73). Another successful cooperation is “INVITE” between TU Dortmund University and Bayer Technology Services which focuses on modularization as well as on continuous manufacturing (61, 74). This is also the target of the related, EU funded program “F3 factory”, a flexible, fast and future factory (75).

With regard to its investments, **marketing** is another important part of LCM. It is reported that the industry spends only half of the marketing investments on R&D (1), yet hopefully, investment does not equal importance. In efforts to market appropriately and to increase the market share of the product, professionals (such as nurses or physicians), health insurance providers, and sometimes also patients must be addressed (18). Since each stakeholder has diverse intentions, knowledge, and needs, different, individual approaches are pursued. To reach patients, companies aim to be trustworthy and transparent, following high ethical standards. Thus, the companies established self-regulation as seen in the code of practice of the International Federation of Pharmaceutical Manufacturers and Associations “Promotion must be ethical, accurate, balanced and must not be misleading. Information in promotional materials must support proper assessment of the risks and benefits of the product and its appropriate use” (76). Such direct customer advertising is not always possible in Europe since it is limited to over-the-counter (OTC) drugs (10). In terms of marketing to physicians, common strategies are sometimes tangible (free samples, small gifts like pens containing the product name) and sometimes more non-tangible in nature (thought leaders, direct contacting, supportive clinical trials, visits) (1, 77). All these described marketing elements are part of the product strategy concentrating on the image and branding of the product. Besides the product strategy, a company strategy focuses on the culture and company direction and a market strategy deals with competitors and launch topics (44). Those three groups form the overall product launch strategy (78).

The purpose of **supply chain management** is to provide information, services, and wares to the pharmaceutical company and its associates (53). Therefore, logistic flows, internal and external communication channels to physicians or suppliers are essential. Since many multinational companies outsource some activities, the supply chain management has become even more complex. Computer simulations regarding costs, timing of stocking, manufacturing and transportation have been used to optimize supply chain management (60, 65) and to establish a functional market supply.

Pricing strategy: The next consideration when marketing a new product is the price. It depends on diverse aspects, differs throughout the LC and from market to market. The first aspect to consider is the current treatment price as an approximate value (30). Secondly, it is important to include knowhow about the competitors. What are their follow-up products and line extensions (10)? The producer must also consider future competitors from the generic market and therefore, possibly shrink the attractiveness of their product by lowering the own prices (52). The fourth aspect for approval, the cost effectiveness, is sometimes named the “fourth hurdle” alongside quality, safety and efficacy (40). An increasing number of reimbursement agencies, such as the Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany, evaluate costs and benefits of a new product in comparison with the current best treatment. In the UK, the National Institute of Health and Clinical Excellence (NICE), denied amongst others the reimbursements of Inlyta® (Pfizer), Yervoy® (BMS) and Zelboraf® (Roche) (1). Such exclusions combined with varying patent expiry dates caused different pricing strategies (52). These strategies also differ depending on the timing in commercialization. While it is important for increasing sales to have a low-price during the introduction, it can be raised whenever the sales are growing because of product improvements. In the subsequent maturity stage, the price is lowered again (18). The pricing strategies for prolonging market withdrawal will be further explained.

The moment of **patent expiry** can be the end point in the LC of the medicinal product. When this happens, the product not only competes with new innovative products but also with generics (18). These generic products cost only about 10% of the initial product causing a dramatic drop in sales and market share (42). Singulair® (Merck) is a classic example losing 87% of sales in 2012 (1). The attractiveness for generic products not only depends on the price but also on the difficulties during manufacturing and analysis: medicinal products containing chemical APIs are much more likely to be copied than biologicals. Nevertheless, as early as in 2013, Remisma® (Celltrion

Healthcare) was approved by the EMA as a biological generic of Remicade® (infliximab, MSD). Afterwards, the earlier mentioned MabThera® (rituximab, Roche) had to face the competition with Truxima® (Celltrion Healthcare) in 2017. It took the FDA three extra years to approve Remisma®, however MVASI® (Amgen) was already introduced to the American market as a biosimilar of Avastin® (bevacizumab, Roche) in 2017. These examples emphasize the importance of good patent and LC prolonging strategies for chemical and biological products.

2.4.2. Strategies to extend the time to market withdrawal

For a successful **LCM prolongation**, companies need a global and internally transparent approach (10). The following tactics address different issues and can be combined and applied at other phases of the LC (41).

As already stated, **pricing strategies** are also important at the end of commercialization and they depend on reimbursement strategies and patent durations. Lowering the price before the patent expiry can establish strong loyalty with all participants (52) and decrease the interest of competitors. Whenever the patent protection is over, the innovator must decide whether he wants to increase, maintain or decrease the price. Increasing the price leads to higher earnings for a limited time (10) and identifies more price-insensitive patients. The risk of losing market share is also given when there is no change in the price policy. With a decreasing price, the companies try to stay competitive with each other and with generics (17).

Instead of competing with the original product, the innovator company can also produce its **own generic** version. Bringing the first generic to market guarantees a market exclusivity for additional 180 days in the USA (79). Also, the originator does not have to invest enormous resources into product development, process design or building up a supply chain. This is why researching companies often hold subsidiary generic companies, like Sandoz which is owned by Novartis (10). This growing market has become increasingly interesting for researching companies and might be the cause of their longing for market control on generics (1).

Another approach dealing with generics is contracting them or even **divesting** the own product. The latter can become relevant whenever the product does no longer match the portfolio of the company, which is usually at the end of the LC (80). **Patent settlements** on the other side, include the transfer of knowhow against fees. Four out of ten

researching companies have set patent settlements for their products. This astonishingly high incidence is underlined by 7th Report on the Monitoring of Patent settlements of the European Commission. The number of such settlements increased from 24 (early 2000's) towards 183 (2008) and continued high with 125 in 2015 (81).

While the above strategies are more management based, **differentiation** is research driven. This happens when the existing molecule is refined to improve patient comfort and safety, to widen the therapeutic area or to reduce costs through a follow-up product. The possibility to introduce a reformulation, a new formulation with other synthesis techniques, a modified release, drug delivery or simply other doses are relatively easy to implement but also the least protective. Fixed drug combinations (FDC) on the other hand, are more expensive to develop (42). However, patients benefit from synergic effects while reducing the number of intakes. This can lead to lower doses and minimized therapeutic risks. A further profiteer is the healthcare system because co-payments and administrative costs decline (15). This is reflected by an FDA Guidance for Industry "New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products" (54). The option of addressing new indications was already mentioned as early as during clinical trials; it is a resource- and time-intensive strategy and yet the most protective one. These three attempts aim to reach a secondary patent ensuring further market exclusivity (42). Sometimes however, the question about possible misusage, called evergreening, by patenting too many different attributes must be raised (46).

Rx-to-OTC switch: Switching from a prescription (Rx) to an OTC product gives the opportunity to extend the market share as direct customer advertising is forbidden for Rx products in the EU. It is however required that the ailment is self-diagnosable and that the potential for abuse is low. One aspect to consider, however, is the lower price, which requires an extensive market share. Since OTC products are paid directly by the patients, they must be well established. This works best whenever the product is still under patent protection (80). Cases out of the therapeutic groups of antacids and antihistamines are successful examples for such Rx-to-OTC switches (10).

In these cases, brand loyalty is extremely important. Depending on the severity of the ailment, patients are either willing to change from a well-known and well tolerated product to a generic one or not (80). The innovator company can **maximize brand loyalty**

by promoting scientific facts to increase the confidence in the original product and to weaken the confidence in generics even more (10).

The multinational pharmaceutical company Bayer AG demonstrated rewarding LCM with its product Adalat® (nifedipine, Bayer). After being launched in 1975, the first patent expired ten years later in 1985. Diverse strategies to prolong the LC of Adalat® were applied, including pricing strategies, patent settlements, differentiation and maximizing brand loyalty (52). Their successful application enables Bayer AG to still sell Adalat® in 2021.

2.5. Market withdrawal

Reasons for the final market withdrawal can be categorized into safety issues or serious side-effects on the one hand and commercial reasons on the other hand. Those happen when all LC prolonging strategies were exploited to their full potential and sales are decreasing (16). Once this occurs, the price is increased to maximize profit and to persuade patients to change to other treatment remedies later on. Whenever various similar products are on the market, the weakest is withdrawn and promotions are modified for the remaining core product (18).

2.6. Closing comments and future prospects

The urgency for an improved strategic proceeding during the LC of a medicinal product was condensed in this chapter. Figure 4 summarizes the according findings: The LC is pictured on a horizontal axis and divided into R&D, approval, commercialization, and market withdrawal.

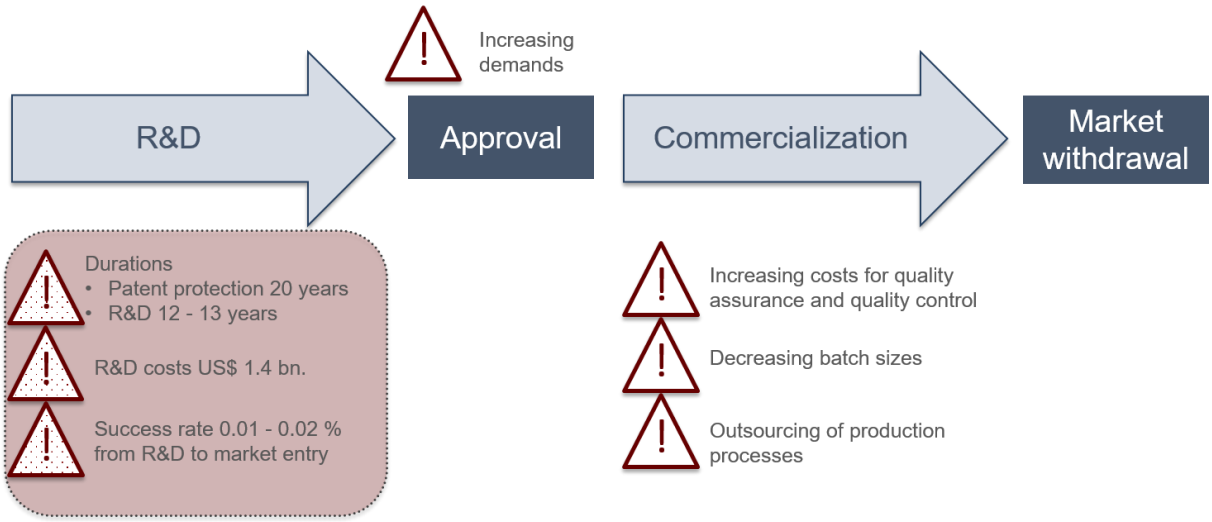

Figure 4: Common challenges of a medicinal product assigned to the according LC phase. The ones during R&D are most influenceable and therefore highlighted in red. Reproduced from (22) with permission from Elsevier.

Along the time axis, the occurring challenges and obstacles are assigned. While rising regulatory demands, for instance during clinical trials or production, increase investments throughout the entire LC, the success rate to bring a new medicinal product on the market has shrunk dramatically. The industry can only eliminate the internal causes during R&D (highlighted by the red colored box in Figure 4) but not influence external ones as seen by the results of the FIH study with TGN1412. So, most of the LCM strategies only aim to treat the symptoms. On top, production processes become less profitable. Distributors and individualized medicines demand for smaller purchase quantities more often, causing batch sizes to decrease. However, quality and fixed costs remain the same whilst less product is produced. Such rising costs are one of many factors that cause companies to outsource their productions and European production sites to be even less attractive. It is therefore of great interest to identify and implement more holistic approaches in LCM instead of having some of the above mentioned, piecewise compensations. For this reason, computer simulations have been introduced as part of R&D as well as of supply chain management. The extension of computer models towards other parts of the LC can support management decisions by providing profound knowhow about different strategic scenarios before implementing them.

3. Chapter 2: Computer simulations of pharmaceutical production processes

Parts of this chapter were published in:

Hering S., Schäuble N., Buck T. M., Loretz B., Rillmann T., Stieneker F., Lehr C.-M. Analysis and Optimization of Two Film-Coated Tablet Production Processes by Computer Simulation: A Case Study. Processes. 2021;9(1):67

3.1. Introduction

The pharmaceutical industry acts in a complex business world, which will become even more pressurized in the future. The need for new strategies and procedures throughout the entire LC of medicinal products is unquestionable. As previously mentioned, computer simulations are one valuable tool with plenty of applications that can improve the LC of a product (Chapter 1: Analyzing life cycle management of medicinal products). For the experimental part of this thesis, a case study with computer simulations of two real, approved production processes was conducted. The case study examined the efforts and chances of optimizing the production processes with discrete-event simulations. Therefore, data was acquired to create representing models of the production processes. These models, which were initially verified and validated, were finally used to successfully debottleneck and optimize the capacity utilizations of the original production processes.

3.1.1. Computer simulations of production processes

The use of computer simulations during LCM was already extensively investigated in the first chapter of the thesis. It was conducted that they can represent a complex system while covering not only the relations between different aspects but also the mutual influences. They go beyond statistical methods and make multidimensional issues analyzable.

A simulation model was described as an imitation of a process to strengthen the control, the prediction or the understanding of its conduct (82). Whenever such a model is used to produce a result, it is called a simulation (83). Alternative definitions and further background information are well summarized by Banks (84). Possible tasks during the model development of production simulations can be the performance of material and energy balances, the calculation of the necessary demands, an assessment of production times, or carrying out cost analyzes (85). Another characteristic of a simulation is that changes of production parameters can be scrutinized without performing any

experiment on the actual production site saving time and money. The regular production is not interrupted and no other quality activities, such as risk analyzes or additional cleaning validations, are necessary. On the contrary, preventive actions can be taken to minimize risks and to avoid failures. Process and product knowledge increase during modeling which creates an excellent starting position to improve efficiency and quality. Furthermore, computer simulations can support process control to predict the impact of changes in a system on other process steps (86).

Simulations can mimic individual or multiple steps of a process. Single process steps simulations are often based on computational fluid dynamics (CFD) to investigate fluid flow or heat-transfer behavior. This makes those simulations interesting for mixing or separation processes, pneumatic transports of solids, drying, and filling steps (87). One published example of a CFD simulation showed its feasibility to predict scaling effects on fluidized beds (88). A more extensive approach was a flowsheet model, which investigated API purification steps and the later mixing during manufacturing. The purification dependent API characteristics influenced the API concentration in the mixed powder, as well as the crystal size distribution. All of this had a direct impact on the tablet properties (67). The MIT even developed a model for the process control of a continuous end-to-end tablet production. It covers all process steps and the associated mass and energy balances as well as the reaction kinetics (71). The company Aspen Technology is a successful, well-established partner for chemical and pharmaceutical companies to optimize, schedule, and control processes in real-time over entire production sites. With the acquisition of SolidSim engineering GmbH in 2012, capabilities for solid simulations were also added (89). These examples show that the pharmaceutical industry has started to apply different production simulations and that meanwhile, simulations have become a common part of process development and process optimization.

Another simulation type are discrete-event simulations. This is when changes of variables happen due to defined events, rather than due to constant changes over time. This approach covers different aspects, as Habibifar et al. summarized. Research of eleven publications (2007–2019) deal with mathematical modeling, with simulations or statistical techniques (90). Here again, the optimization of single process steps (91) was seen alongside with more holistic questions (92). Other recent discrete-event modeling research focused on hospital room occupancies (92), a flow shop (93), and

manufacturing scheduling (94). The wide range of software and simulation types indicates, that there is not one single correct way to optimize pharmaceutical production processes. Instead, a detailed view of the given process, the circumstances and the simulation goal must be considered when choosing the software. Due to the constraints of a small head count and limited resources, a user-friendly, practice-oriented solution was pursued.

3.1.2. Case Study: Two approved film-coated tablet productions

The process owner is a middle-sized pharma company producing about 20 different bulk products followed by primary and secondary packaging. Most of the products are tablets which can be furtherly differentiated into being produced by two different production ways. In consultation with the process owner, two similar bulk production processes were chosen. Some ingredients and product properties, such as the tablet size, differ. This causes slightly different procedures, for example different cleaning and processing times because of other punch sizes. Nevertheless, complexity, equipment and operations are similar. If this similarity causes similar study results, a transfer of the gained knowledge to other similar processes is possible.

The processes represent classical film-coated tablet productions consisting of twelve main production steps with up to seven sub steps. In total 47 steps are necessary from the setting up of scales until the final bulk packaging. Figure 5 visualizes the main steps (boxes on the left) with sub steps (boxes in the middle) and some machines whenever necessary (boxes on the right).

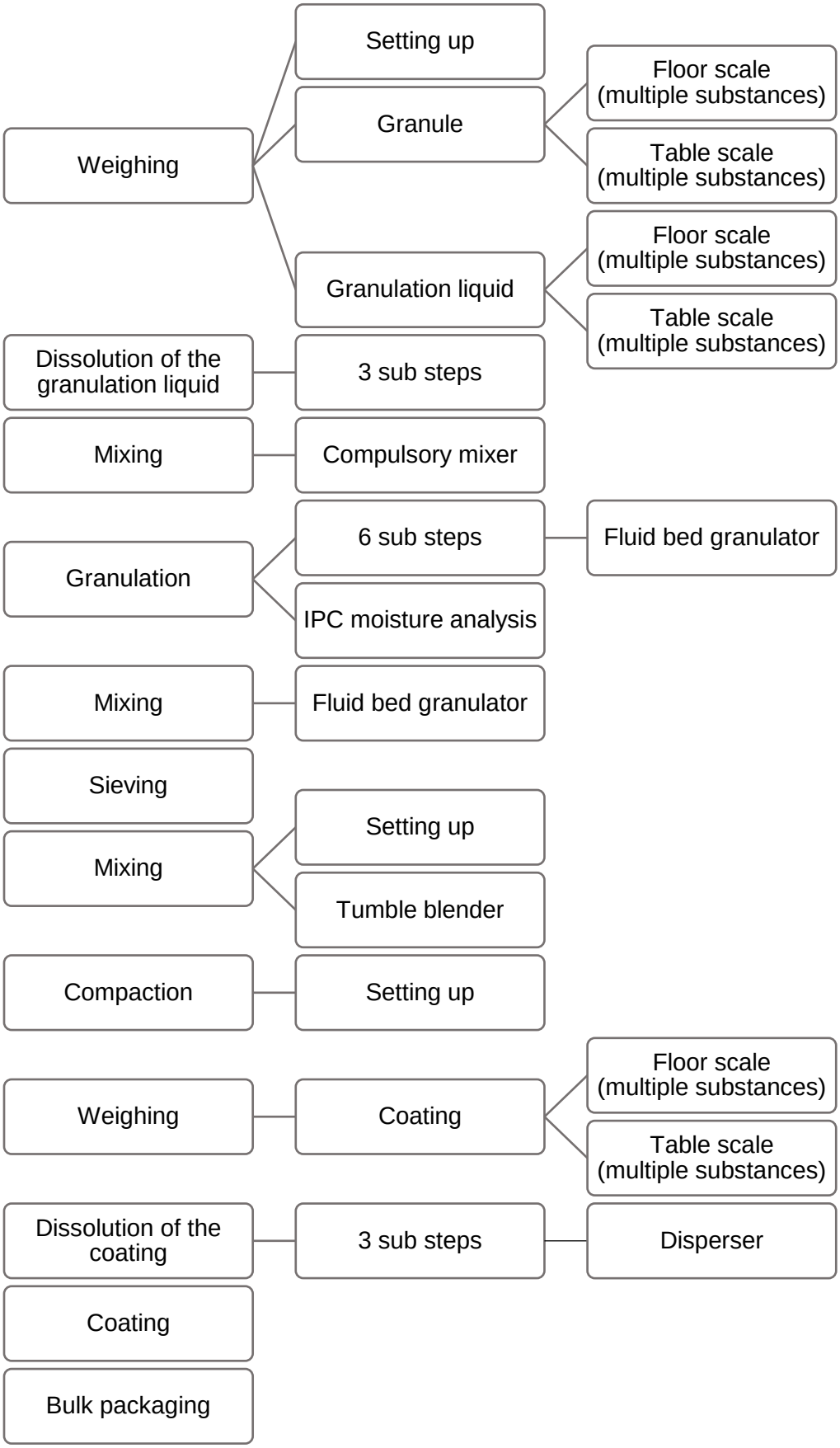

Figure 5: Chronological order of the time intensive process steps of film-coated tablet productions including the according machinery.

For the later simulation models, not all of these steps were essential. Some could be joined, excluded, or even prioritized (for more details see 3.3.2). The remaining steps for the simulation models are the following ones:

- Setting up scales
- Weighing granule and granulation liquid
- Dissolution of the solid components to finish the granulation liquid
- Compulsory mixing
- Fluid bed granulation
- In-process controls (IPC)
- Sieving
- Tumble blending
- Compaction
- Weighing the coating
- Dissolution of the solid components to finish the coating
- Coating
- Bulk packaging.

The production equipment is mostly operated manually as it is about 25 years old on average. The investigated products are produced in production campaigns by four employees with varying numbers of batches (normally 3 to 18 batches). In order to represent their average campaigns, the campaign sizes in the simulations cover four batches for the first product, called P_{INA}, and ten for the second product, P_{EMB}.

Other products with the same APIs and resembling production processes, e. g. similar products with different doses, exist. Even though they are not subject to any additional analysis, they still influence the cleaning and setting up of equipment. Whenever analogous products contain the same APIs and excipients, lower efforts are necessary. Thus, only directly batch related setting up times as well as product-independent daily routine cleaning times are regarded. Furthermore, any historical data being correlated to deviations, such as machine breakdowns, personnel shortages, or human failures were excluded. Also, outlier tests were performed to identify and exclude deviating historical batch data. This way, the simulation models only describe standard production campaigns.

Both products treat tuberculosis, an illness which has latently infected about one-quarter of the word population in 2020. In South-East Asia, in Africa and in the Western Pacific, 87% of all tuberculosis cases occur. By 2030, this epidemic is supposed to end as it is one of the Sustainable Development Goals of the World Health Organization (WHO). Recently, the incidences decreased about 2% a year. Most of the infections

are caused by the *Mycobacterium tuberculosis* attacking the lungs. The treatment is based on a combination of different drugs (standard: four antimicrobial drugs over six months) which can completely cure patients (95). The first-line drugs are in alphabetical order ethambutol, isoniazid, pyrazinamide, and rifampicin (96). The first product contains the API isoniazid and is therefore named P_{INA}. For the second product, ethambutol is naming for P_{EMB}.

This case study was pursued with one main aim. The overall production processes of P_{INA} and P_{EMB} were to be optimized. Therefore, their virtual reproductions (as-is models) had to be implemented in the first place. The chosen software was FlexSim enabling a holistic reproduction of all process steps in one discrete-event simulation. The user-friendliness supported this decision. Based on the established as-is models, six different optimization scenarios were built for each product. The process owner was especially interested in optimizations caused by organizational changes as the production processes are part of the market authorization. Hence, essential changes in the production process would cause costly post-approval changes. The implemented scenarios represent three different shift systems with a varying head count. This way, the results of this scientific case study can directly influence management strategies of the process owner and therefore support a local, middle-sized company.

3.2. Materials and Methods

No standardized procedure could be found in literature for conducting a case study with these conditions: having discrete-event simulations to optimize two film-coated tablet productions. So, an intuitive approach was developed and implemented and is displayed in Figure 6.

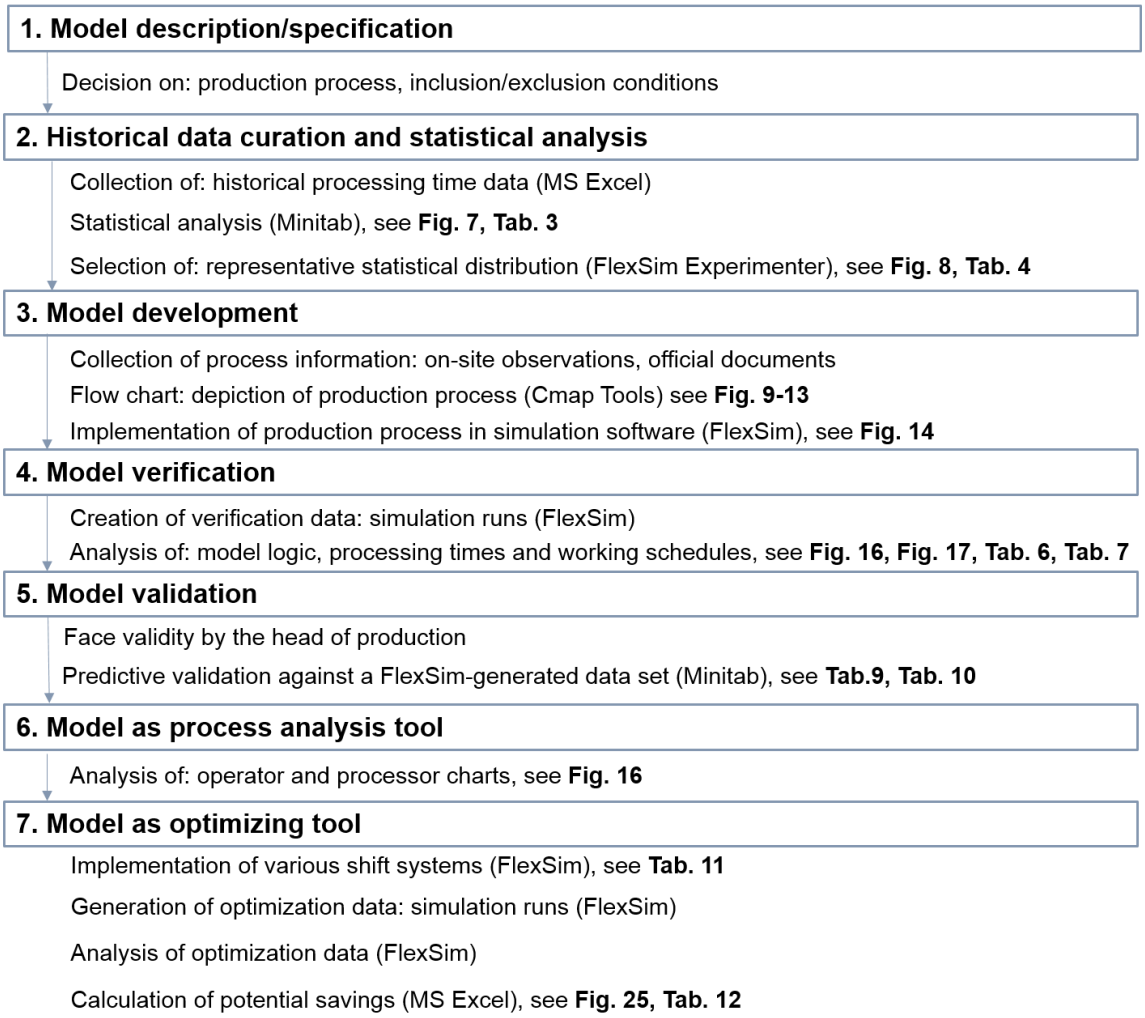

Figure 6: Methodological approach of the case study from model description until its application as optimizing tool.The seven steps are highlighted in blue boxes, while their accodring sub steps and cross-references are listed underneath. Adapted from (97).

Initially, it was decided what was to include and exclude during model description. Then, historical batch data, on site observations, official validation and qualification documents of the process owner, and work experiences were acquired and analyzed. This acquired information was divided into numerical and logical threads. The numerical thread, including for instance processing times, was statistically analyzed. The logical thread served the process of model development, especially for creating model logic. Both threads were used to develop as-is models of the bulk productions. Afterwards, these models were verified and validated. Finally, they were used for process analysis and optimization.

3.2.1. Materials: Employed software

Four different software were used: Microsoft® Excel and Minitab®, well reputed for data handling and statistical analysis, together with Cmap Tools and FlexSim for the visualization of the process flows.

Microsoft® Excel (Microsoft, Seattle, USA) enabled collecting processing times and deviations in the beginning and later on, during model verification, validation as well as during model application, it enabled the comparison of different data. Additionally, it was used for simple analysis, such as calculations of medians, arithmetic means, standard deviations, or minimum and maximum values.

More extensive statistical questions were handled with **Minitab®** (Minitab GmbH, Munich, Germany). Boxplots and individual moving charts for graphical evaluation were created and different hypothesis tests were performed with the statistical analysis program. Some of these are common parts of the Six Sigma method (98), which aims to describe, measure, analyze, improve, and control (DMAIC) processes (99).

With **Cmap Tools** (Florida Institute for Human and Machine Cognition, Pensacola, Florida, USA), detailed flow charts were generated to depict all process steps and the according relations. Its handling with drag and drop is user-friendly (100) and facilitates process understanding.

The most complex task of creating computer models was fulfilled in **FlexSim** (FlexSim Deutschland - Ingenieurbüro für Simulationsdienstleistung Ralf Gruber, Kirchlengern, Germany). It is a tool to run discrete-event simulations of production and logistic processes to represent information and material flows. Through FlexSim, process changes like different plant design, other product flows, or alternative utilizations of resources can be analyzed and compared in advance. After functionally mapping the dynamic process flow, a 3D representation is built which can be directly analyzed within the program. This makes the entire process tangible and multilayer situations can be understood easily; also, for non-experts. Hence, it is a common, commercially available software to support management and strategic decisions.

The process is captured object-oriented, meaning that all process components (machinery, staff, logistics) are implemented as objects. According attributes are assigned for characterization and methods (procedural function) are implemented for manipulating the overall system. To represent the process as realistic as possible, connections, relations in between, critical parameters, and logics (set-up times, head count, priorities, working schedules) are also implemented. The metrics of interest, such as capacity utilization, state statistics, or transport time, must be defined and suitable display items for their statistics must be chosen.

These models are built by user-friendly clicking and dragging as well as by programming with C++. The latter is of interest for more complex demands, like inserting model logic or check points. Furthermore, different views and representations can be applied. Also, FlexSim offers multiple additional modules such as for debugging, experimenting or data fitting (101).

3.2.2. Methods: Statistical data processing

The methodical pursuit can be divided into data preparation, model building, model verification and model validation. This division and the according processing are based on personal estimations as no fully standardized procedure is available. The campaign durations are defined as one major outcome of this case study making processing times the most important data. Therefore, it was crucial to only include data of relevant standard production campaigns. It was hence assessed whether deviations influenced the historical processing times and outlier test were performed to exclude such data. This way, the resulting data pool represented only standard processing times without any machine breakdowns, personnel shortages or operating errors. If the production equipment was modern enough, the production could have been tracked and thereby, processing times could have been generated automatically. In this study, data was gathered by hand. The processing times of the different process steps were determined by subtracting start and stop times out of historical batch documentations by hand, afterwards they were transferred into digitally workable Microsoft® Excel files. Figure 7 summarizes the statistical processing from data preparation until model verification.

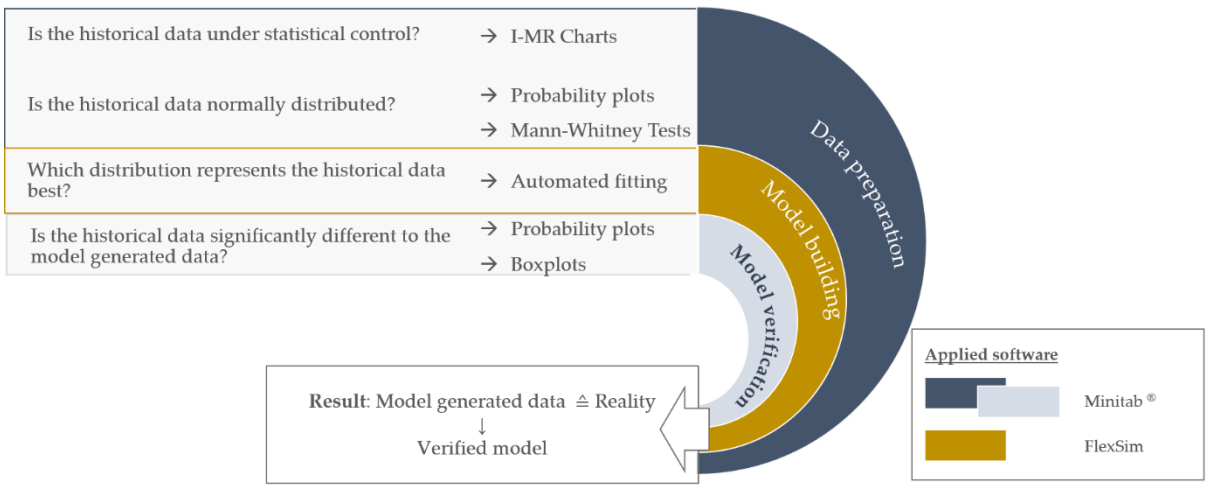

Figure 7: Chronological, statistical workflow from data preparation until model verification. Minitab® was used to analyze and to compare all different data. Furthermore, the distributions representing the historical data the best were determined in the module ExpertFit of Flexim. Reproduced from (97).

Data preparation, following some parts of Six Sigma with Minitab®, was the first step whenever all necessary data was collected. Initially, it was tested if processing times were under statistical control by individual moving range charts (I-MR chart). Their original intent is to monitor continuous, normally distributed process data in order to identify and correct process instabilities (102). In this study, I-MR charts allowed to find shifts, trends or process variations as well. Afterwards, the data pool from each process step was tested to see if it is normally distributed with probability plots. This was essential for further data handling, such as applying the correct hypothesis tests. Additionally, Minitab® was used to visualize and test data pooling opportunities.

During **model building,** the best fitting distribution to represent the historical batch data of each process step was identified and implemented. To accomplish this, a module of FlexSim, called ExpertFit, was used. The raw data was copied into ExpertFit and an automated fitting was started. During this process, the module differentiates between discrete and continuous distributions. The latter are further partitioned into bounded, unbounded and non-negative distributions. A detailed listing of all available distributions can be found in the supplementary material (Supplementary table 1). After fitting the historical data, the distributions and their respective parameters are evaluated and accordingly listed. Each of these evaluations was controlled by checking different graphical comparisons (Density-Histogram Plot, Frequency-Comparison Plot, Distribution-Function-Differences Plot or P-P Plot).

Whenever data cannot be fitted congruently with any distribution, one is encouraged to use an empirical table instead. This way, the values of the raw data are listed in a table and FlexSim randomly picks values. In any case, the chosen distribution or the empirical table must be transferred into FlexSim and linked to the correct process step. Since these statistical distributions and no fixed values are implemented to represent processing times, the model outcome varies from run to run.

Figure 8 exemplarily visualizes a cut out of the graphical comparison for packaging of P_{EMB} with three chosen distributions (Density-Histogram Plot; Log-Logistic, Log-Logistic (E) and Erlang (E)).

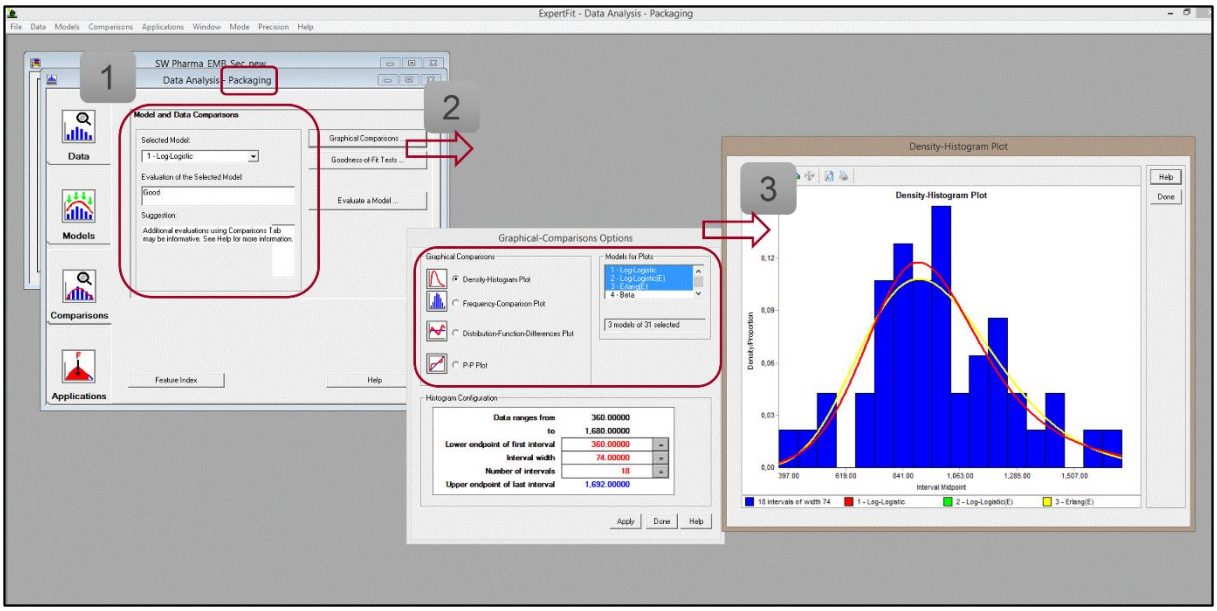

Figure 8: Cutout of a graphical comparison in ExpertFit for the process step packaging. (1) Selection of the statistical model of interest with the according evaluation for the implemented raw data of packaging. (2) Selection of the desired graphical comparison type and the models of interest. (3) Visual display of the chosen graphical comparison.

Data handling during **model verification** started with the transfer of FlexSim- generated raw data into Minitab®. It was copied out of FlexSim reports into the statistical analysis program with which Mann-Whitney tests were conducted to compare the newly generated data with the historical batch data (confidence interval 0.95; significance level 0.05). It was already proven during data preparation that the majority of the historical processing times are not normally distributed.

Model validation proceeded similarly to model verification. Again, the FlexSim-generated data was compared in Minitab®. This time, it was compared to new, real life validation batch data. Boxplots were generated to visually approximate the possible differences. Afterwards, Mann-Whitney tests compared FlexSim-generated data with the new validation data. It was also tested with Mann-Whitney tests if the new validation data differs to the historical batch data. Additional interval plots and I-MR charts were created to substantiate the results.

3.3. Results

3.3.1. Necessary input for computer simulations

From the very beginning of this dissertation, carrying out a case study with FlexSim was intended. However, it was hard to find companies, which were willing to share their knowhow and sensible production data. Multinational companies were especially protective, while smaller companies were more open-minded. The latter prioritized the

benefit of a collaboration to optimize their production processes with computer simulations over the risks of divulging internal matters to an external person. Two further projects were started but could not be finished. The reasons for their discontinuation however indicated essential necessities for a successful implementation of pharmaceutical production simulations with FlexSim.

The first project dealt with the API synthesis of an IMP for a dermal application. The process owner and -innovator was a start-up with a non-pharmaceutical background, troubling collaboration and mutual understanding. The Good Manufacturing Practice (GMP) knowhow and resulting requirements were not available. The synthesis process was not strictly defined but had multiple complex decision points. So far, only two experienced chemists were able to perform it. Furthermore, only few replications of the synthesis were performed in the final batch size and none with the final production equipment. Different starting points were investigated to define the process and to set specifications. However, the intention of the project was not to create a stable process but to optimize an existing one with FlexSim. These issues were topped by legal disagreements between the participating parties, which finally stopped all cooperation.

The second project was the production of pain killing tablets containing nanoparticles. The process owner wanted to compare two production processes for film-coated tablets. One process included a standard formulation with inner and outer phase while the other process included an API embedded in nanoparticles. Preceding the first project, both production processes were defined, established, and specified. Thus, their process flows were captured and depictured in Cmap Tools. However, the process owner did not produce the product himself but had a CMO for the only rarely happening productions. It was therefore not clear when, or if at all, an observation on site was possible. This and the fact that only general information about the process was given hindered deeper process knowledge. Additionally, the process owner did not provide historical batch data. As one of the major study outcomes is the process time, the statistical distributions must represent the process times as realistic as possible. Rough estimates based on experiences of one person are not sufficient. The missing raw data and the insecurity about having the chance to generate them combined with limited process understanding led to project discontinuation.

Both failed projects emphasized the importance of defined, specified processes, of deep process understanding and of the availability of sufficient raw data. All of these

preconditions were given in the third project, the production of film-coated tablets against tuberculosis.

3.3.2. Model design and building

The first step of **model design** was investigating the processes of interest to found a basis and to build a detailed process understanding. These experiences were used afterwards to create an extensive flow chart in Cmap Tools. The representative one of P_{EMB} is depicted in the following figures (Figure 9 to Figure 13). It contains all process steps and sub-steps, the processors with the present operators as well as the average processing times. Additionally, the connections between all steps are displayed revealing some dependencies.

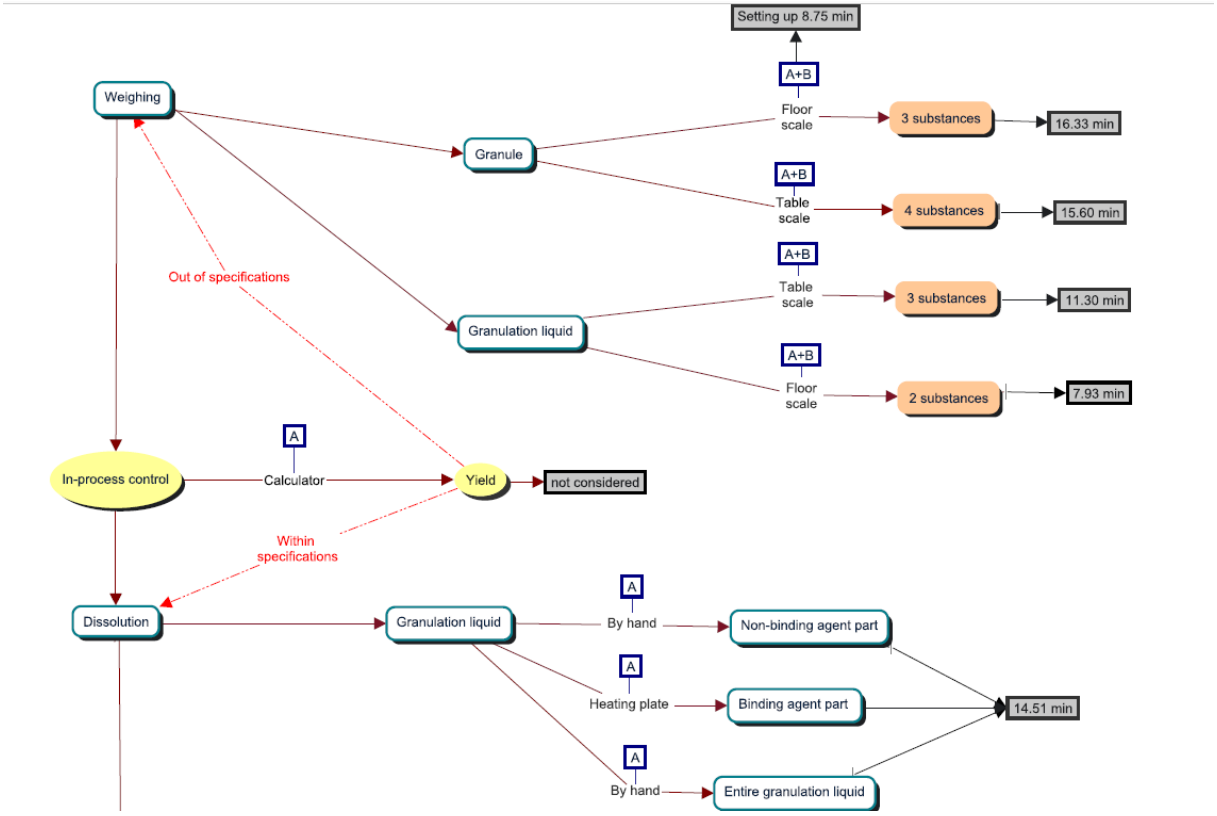

Figure 9: Flow chart cutout of the weighing and dissolution process for P_{EMB}.

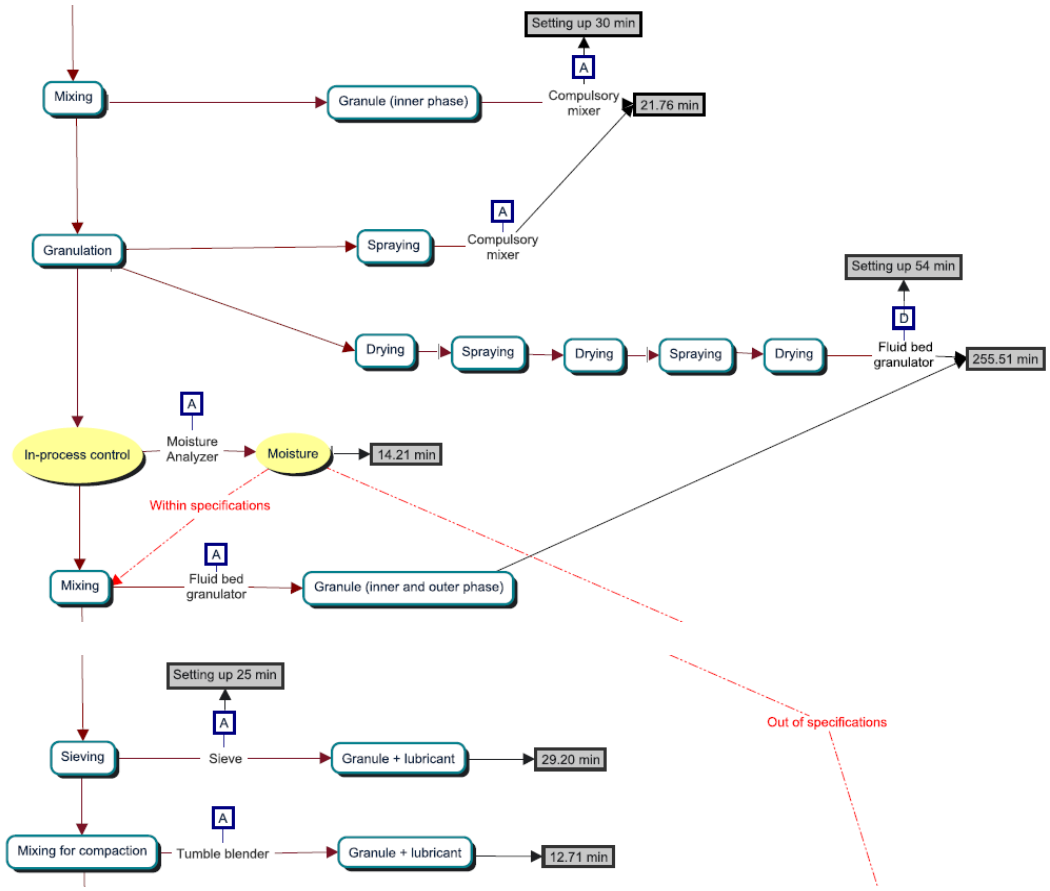

Figure 10: Flow chart cutout of the granulation process for P_{EMB}.

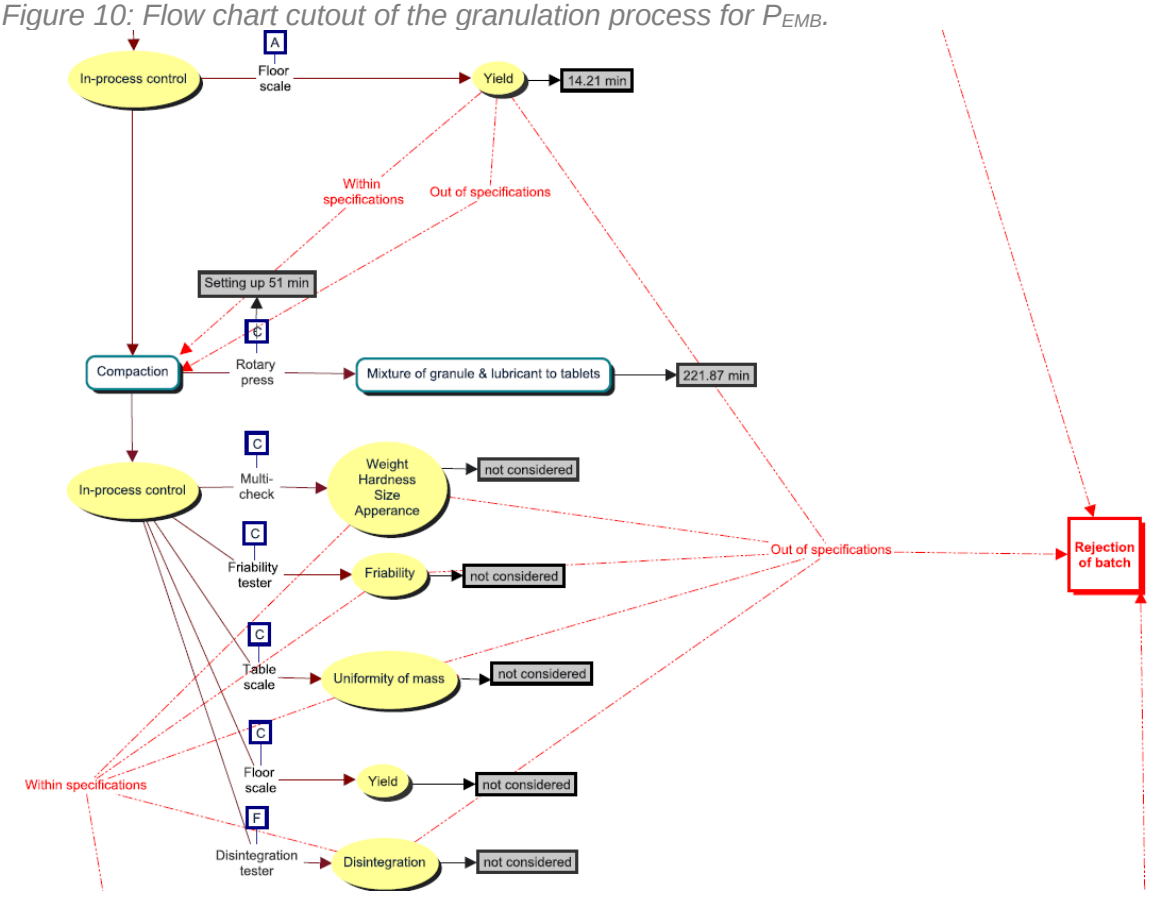

Figure 11: Flow chart cutout of the compaction process of P_{EMB}.

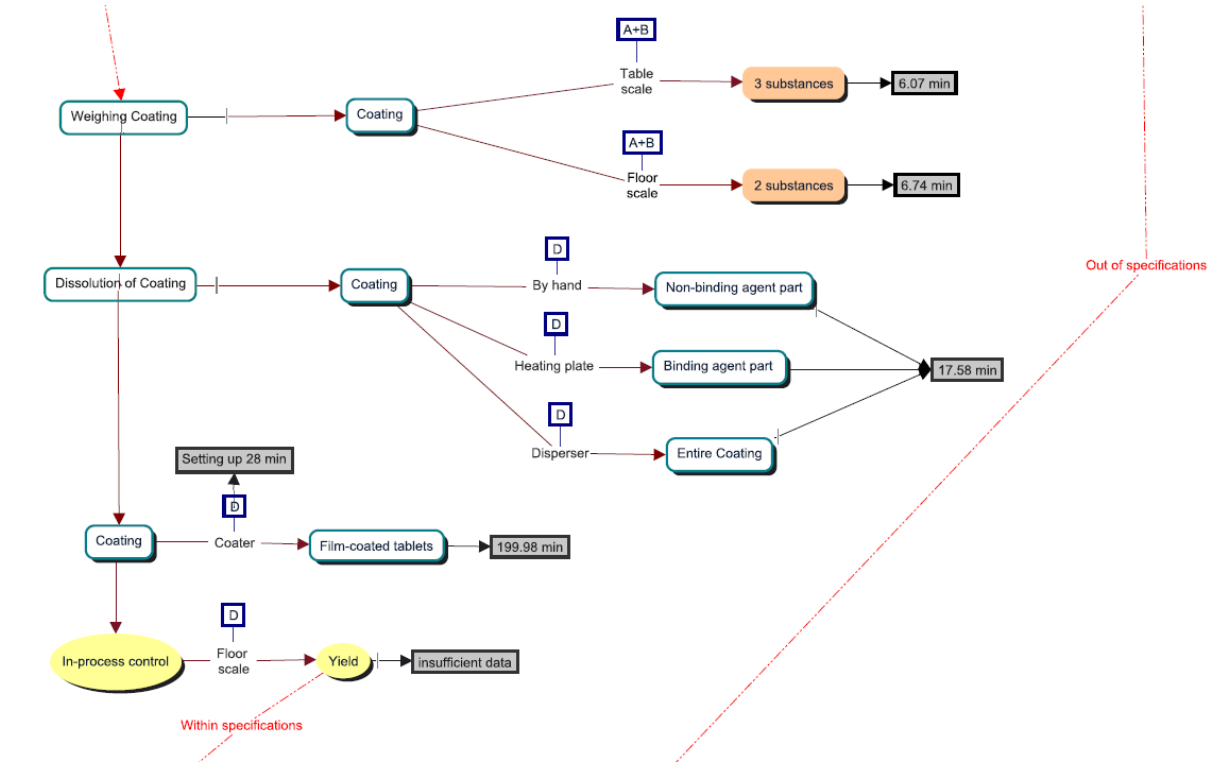

Figure 12: Flow chart cutout of the coating process of P_{EMB}.

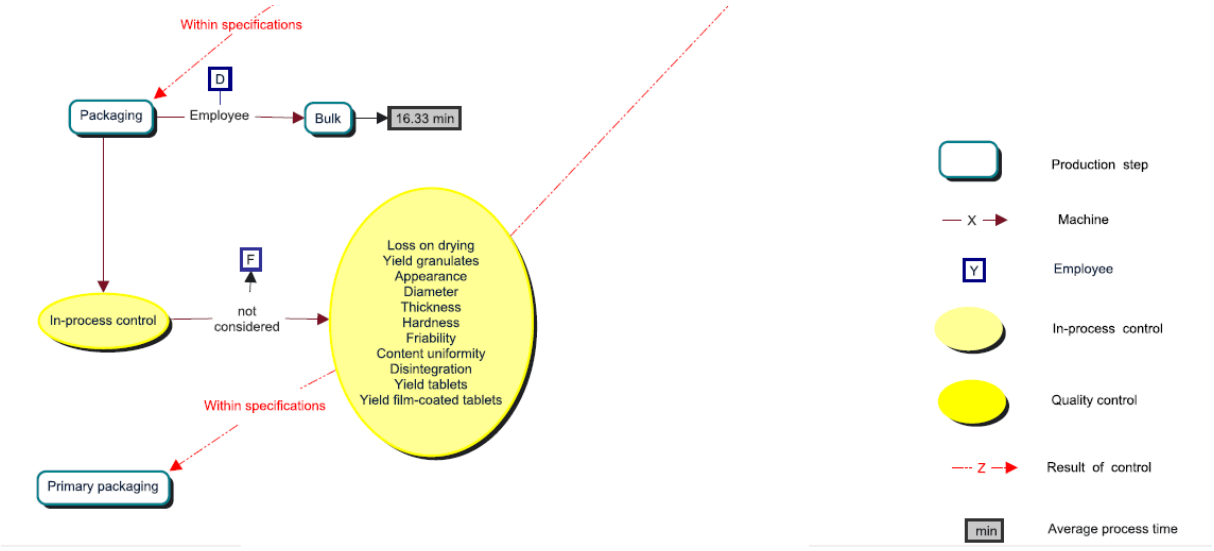

Figure 13: Flow chart cutout of the packaging process for P_{EMB} including captions.

By approving the correctness of the flow chart, the head of production confirmed the conceptual model. After merging all information, it was evaluated which process steps could be combined or eliminated in order to simplify the later model logic for the FlexSim models. The gained knowledge and findings were transferred from Cmap Tools to FlexSim without any interface.

Two principles were followed during **model building** in FlexSim**.** The models were built as simple as possible and only the most important attributes were integrated. This processing reflects a general practice in computer modeling (103). Furthermore, deviations, special events, and machine breakdowns were excluded from the simulations.

The actual building process in FlexSim is summarized in Figure 14, in which the building order is visualized by numbered circles.

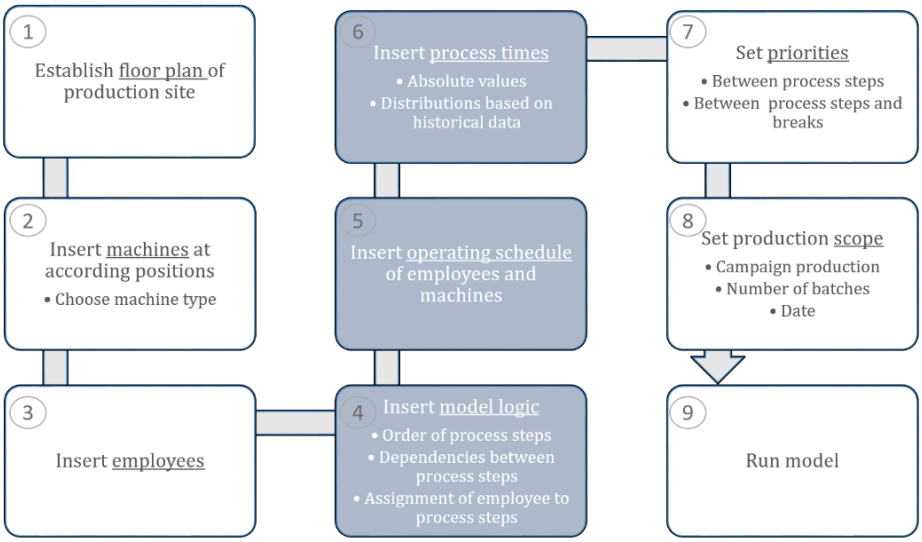

Figure 14: Steps of model building in FlexSim. In the beginning, the foundation for the model is laid. The following blue colored boxes represent the most critical steps of inserting the model logic, the operating schedule, and the processing times, which must be verified and validated. In the last third, final settings are made. Reproduced from (97).

It starts with the establishment of a floor plan of the production site ①. The process owner provided all necessary information to rebuild the site in-silico as close to reality as possible, including rooms, locks, and transportation routes (Figure 15).

② Afterwards the machines were integrated at the correct locations (blue boxes in Figure 15). In FlexSim, the machines are called processors of which three different types are available. The normal processor type simply processes items, which in this case study are starting materials becoming film-coated tablets throughout the process. The next processor type is a combiner, for instance a compulsory mixer combining granulation liquid with granule mass. The last processor type, a separator, on the contrary, makes multiple items out of one. This type was chosen to represent the process step of packaging: One batch is packed into eight separate bulk packages by hand.

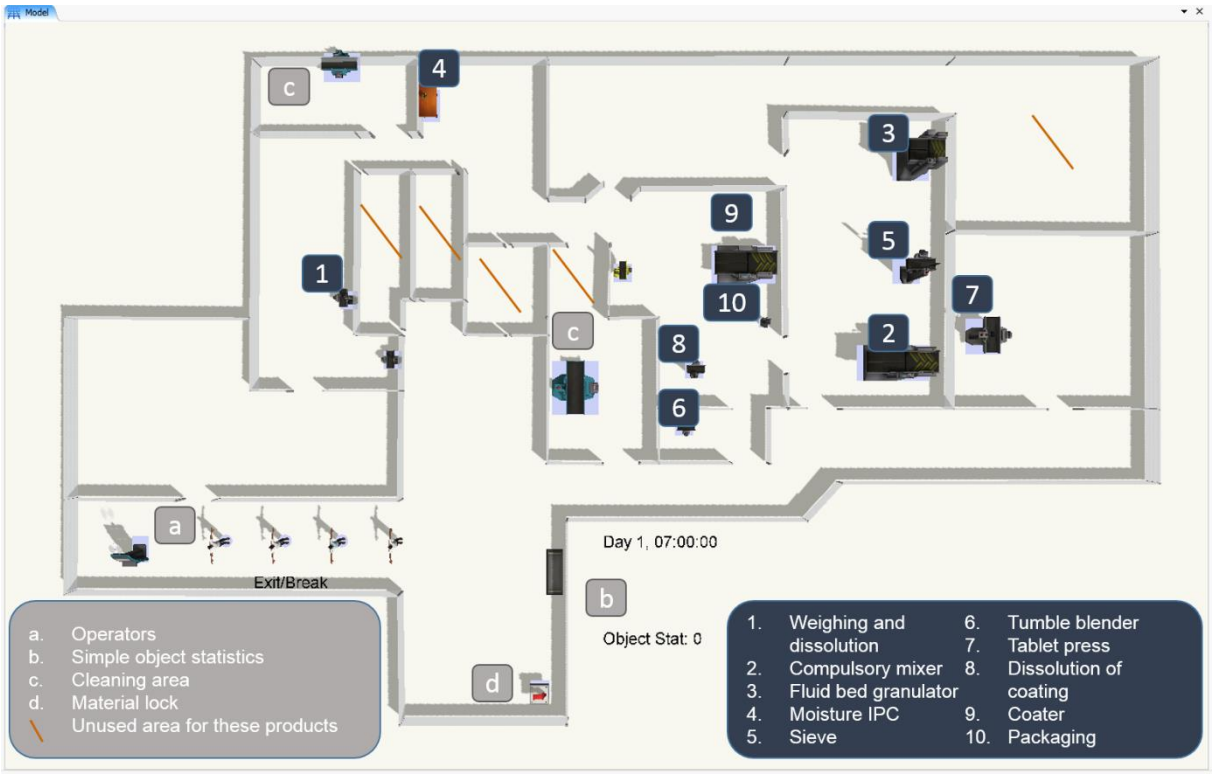

Figure 15: Floor plan of the production site in FlexSim containing operators, processors, and the most important elements. Reproduced from (97).

③ In order to operate the processors, employees are needed. The so-called operators represent the actual headcount of the production. Besides processors and operators, FlexSim models also include sources, queues, and sinks. Items are generated by sources and cleared by sinks. Queues are necessary to create waiting spaces for flow items for a later continuation of the processing.

The next three steps of model building are highlighted in Figure 14. They are more complicated and need to be verified and validated. The first of these steps is the insertion of model logic ④. The sources, queues, processors, and sinks are connected to establish the item flow. The chronological order of the process steps is thereby defined based on batch documentation and on official validation reports. Besides easy chronological orders, more complex logic is needed if some steps depend on certain events. As an example, holding times of the items must be taken into consideration. It is therefore not wanted to start certain process steps until an instantaneous processing is granted, even if processors and operators would have the capacities. Such further logic is implemented with triggers, such as sending messages whenever certain events happen. One exemplary integrated rule is that only weighted substances for one batch can be prepared for hold. Therefore, the queue for finished weighted substances has the

capacity for one batch. Whenever an operator collects these weighted substances, the empty queue has the trigger to send a message to the sources. The sources are programmed to not release any new items (open ports) until such a message is received. Another way of controlling the process is to place information on all items. This way, processors can differentiate between items, which allows amongst other things to apply different statistical distributions (processing times) according to the item type (scales apply different processing times for granule, granulation liquid, and coating).

The predefined operating schedules (7:00 to 3:45 p.m.) were integrated for all operators and processors ⑤. Furthermore, the needed presence of the operators at the processors and the operator breaks (9:15 to 9:30 a.m. and 12:15 to 12:45 a.m.) were entered. While some processors can stop their process step over night, others cannot (sieving, coating). Hence, different operating schedules were established for these ones.

The last critical step is the implementation of the processing times ⑥. Finding the best fitting distributions was already explained in 3.2.2. Additionally, Mann-Whitney tests and two-sample t-tests were performed to compare the processing times of P_{INA} and P_{EMB} whenever the production step was not product dependent (Table 3). The tests indicated, that the historical processing times for the set-up of scales, the weighing of granulation liquid (both scales), the dissolution of granulation liquid, tumble blending and weighing of coating (both scales) could be pooled. This increased the sample size and harmonized the models for both products.

Table 3: Testing for pooling historical batch data of P_{INA} and P_{EMB}.

Process step	Product dependent	P_{INA} normally distributed	P_{EMB} normally distributed	Applied test	*p*-value	Pooling
Set-up scales (once daily)	✗	✗	✗	Mann-Whitney	0.169	✓
Weighing granule floor scale	✓					✗
Weighing granule table scale	✓					✗
Weighing granulation liquid floor scale	✗	✓	✓	two-sample t-test	0.387	✓
Weighing granulation liquid table scale	✗	✓	✓	two-sample t-test	0.149	✓
Dissolution of granulation liquid	✗	✓	✗	Mann-Whitney	0.203	✓
Compulsory mixer (mixing)	✗	✓	✗	Mann-Whitney	0.013	✗
Fluid bed granulation	✓					✗
IPC moisture analysis	✓					✗
Sieving	✓					✗
Tumble blender (mixing)	✗	✗	✗	Mann-Whitney	0.200	✓
Compaction	✗	✓	✗	Mann-Whitney	0.000	✗
Weighing coating floor scale	✗	✗	✓	Mann-Whitney	0.202	✓
Weighing coating table scale	✗	✗	✗	Mann-Whitney	0.254	✓
Dissolution of coating (disperser)	✗	✓	✗	Mann-Whitney	0.035	✗
Coating	✓					✗
Packaging	✓					✗

Table 4 shows the chosen, best fitting distributions for all process steps. Interestingly, a normal distribution was never the best choice for any of the process steps.

*Table 4: Listing of the in FlexSim integrated process steps with the best fitting distributions according to ExpertFit. * pooled process steps. Reproduced from (97).*

Process step	**Statistical distribution**	
	P_{INA}	**P_{EMB}**
Set-up scales (once daily)	Empirical table*	Empirical table*
Weighing granule floor scale	Log-Logistic	Pearson type VI
Weighing granule table scale	Gamma	Pearson type VI
Weighing granulation liquid floor scale	Beta*	Beta*
Weighing granulation liquid table scale	Log-Logistic*	Log-Logistic*
Dissolution of granulation liquid	Log-Logistic*	Log-Logistic*
Compulsory mixer (mixing)	Weibull	Beta
Fluid bed granulation	Log Laplace	Beta
IPC moisture analysis	Log Logistic	Johnson bounded
Sieving	Erlang	Weibull
Tumble blender (mixing)	Pearson type V*	Pearson type V*
Compaction	Log Laplace	Log Logistic
IPC weighing floor scale	Johnson bounded	Pearson type VI
Weighing coating floor scale	Beta*	Beta*
Weighing coating table scale	Johnson bounded*	Johnson bounded*
Dissolution of coating (disperser)	Beta	Pearson type VI
Coating	Log Logistic	Beta
Packaging	Log Logistic	Beta

The listed distributions cover the most important, batch dependent process steps. However, more routine work, such as cleaning or documentation, must be integrated since they diminish working capacities. As these times could not be extracted from any official documents, all operators quantified their experiences and the arithmetic mean was chosen as standard value for all models (Table 5).

Table 5: Additional production steps with their according duration based on operator experience.Reproduced from (97).

Process step	**Duration [min]**
Starting of all systems	20
Cleaning of weighing equipment	65
Cleaning of other equipment	56
Weighing after tumble blending	1
Dissolution of coating (Heating plate)	11
Documentation	15
Set-up for compaction	51

Whenever all components, their connections, and the correct processing durations were entered, it had to be prioritized between the different production steps as well as between breaks and production steps ⑦. Coating as an example, is a production step that cannot be stopped and needs the permanent attendance of an operator. Therefore, it has a higher priority than the breakfast break.

The last step of model building is the definition of the model scope ⑧. The process owner favors campaign productions with order-dependent sizes. Common campaign sizes were chosen for the simulation models (P_{INA}: four batches; P_{EMB}: ten batches).

In addition to the basic model building, extra checkpoints and workarounds were created to ensure a profound model verification. Model verification does not always investigate the same model components since every model is unique. There are therefore only a few pre-created packages in FlexSim. For this case study, the model logic, the operating schedules and the processing times were identified to be the most critical parts. Thus, it was chosen to install information stickers on all flow items. Parts of the analysis module were linked to those information stickers in order to track and analyze them. This required more than using drag and drop options, namely some individual programming in C++.

⑨ The finished model can be run by manual starts and stops in the menu bar. This is comfortable for checking certain events or the behavior of the model. The speed can be adjusted and it is possible to predefine stops. However, when evaluable data is

necessary, multiple runs must be performed with the Experimenter module. It is determined how many replications will be performed and which statistics are tracked.

3.3.3. Model verification

The scope of this case study's model verification was to confirm the correct implementation of the model logic, of the operating schedules, and of the processing times and to thereby confirm the entire model. It was chosen to perform as many model runs with the Experimenter module as numbers of historical batch documentation were available (P_{INA}: 25 runs; P_{EMB}: 45 runs). When running the Experimenter, no parameters were changed. The different outcomes of each run are based on the processing times, which are no fixed values but statistical distributions. Two kinds of reports were exported to receive all necessary information: a performance measure report and an interactive report. Their content and further usage is listed in Table 6.

The performance measure report contains a summary, a replication plot, and a frequency histogram. Also, the single value of each replication is listed for every process step. The content is completely predefined and no adjustments can be made. All single values were transferred into Minitab® to analyze and to verify the processing times of all steps. The interactive report is, as the name implies, interactive. Multiple drag and drop options can be used to display different information. For this study, the selection of the process step and of different dashboard charts was sufficient. One chart always represents the data of one replication for one process step. The states charts of the processors and operators were used to confirm the operating schedules, while Item Trace Gantt charts were used to verify the model logic. They were additionally used during model application to evaluate the campaign duration.

Table 6: Content and usage of the FlexSim reports "performance measure report" and "interactive report".

	Performance Measure Report	**Interactive Report**
General information	Predefined content Number of replications	Interactive handling of report Selection of • Performance measures (process step) • Dashboard (chart type, replication number)
Content	Summary • Mean (90% Confidence) • Std. Dev. • Min. value • Max. value Replications Plot Frequency Histogram All Single values	Charts • States Processors • States Operators • Item Trace Gantt ⇨ One chart always includes data of only one replication
Further processing	Transfer of single values into Minitab® Statistical analysis (Mann-Whitney tests)	States Processors and States Operators chart • Transfer of times and states Item trace Gantt • Extraction of the **campaign duration**
Verification of	Single values ⇨ **Processing times**	States Processors and States Operators charts • Test order • Identify bottlenecks ⇨ **Operating schedules** Item trace Gantt chart • Order of process steps • Dependencies between different process steps ⇨ **Model logic**

As already mentioned, the **model logic** was verified by extracting information of the Item Trace Gantt charts of the interactive report. Hence, information stickers (labels, type tracked variable) were installed on all items after model building. Furthermore, the

processors were programmed to leave the desired information on the stickers. Whenever one item was processed, the entering and the leaving time for this processor were recorded. This provided the pure processing times on one hand and on the other hand, the process order was tracked. Figure 16 displays a schematic, simplified Item Trace Gantt chart for one batch.

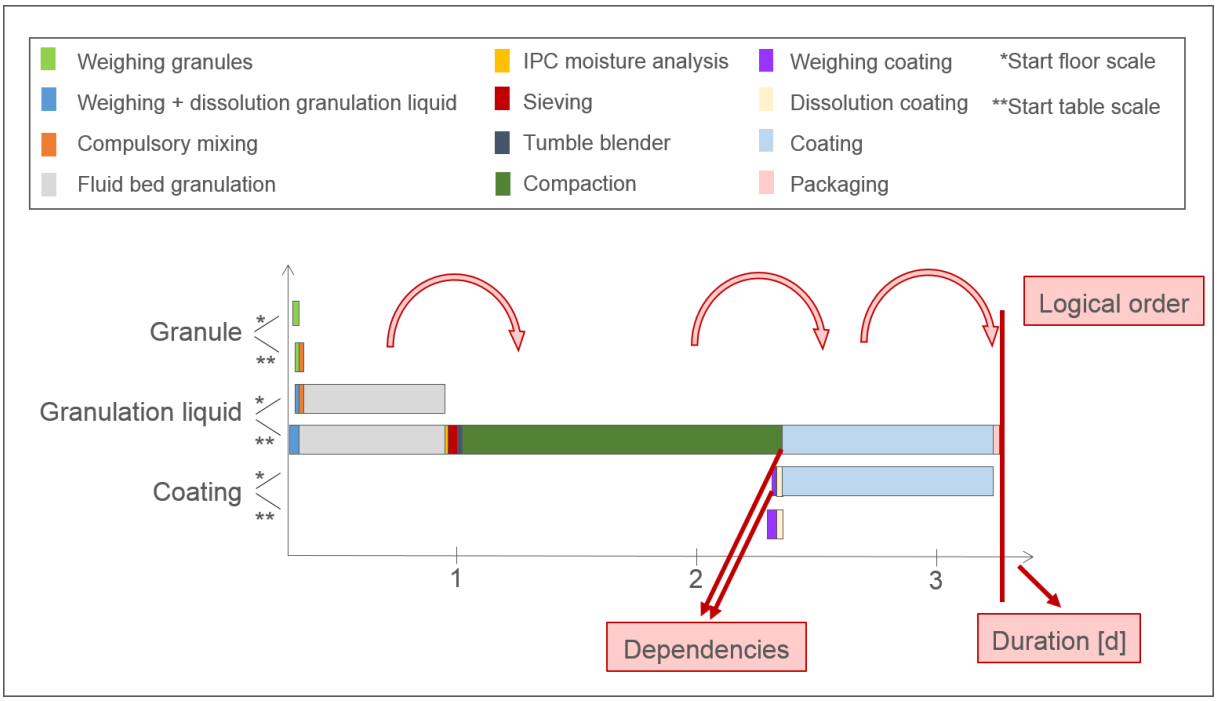

Figure 16: Schematic Item Trace Gantt chart for one batch and the resulting findings.With this chart type one can i) monitor the logical order of the process steps; ii) check the dependencies (e.g., the weighing of coating starts shortly before the compaction is finished); and iii) identify the campaign duration. Reproduced from (97).

The horizontal axis displays the duration of the production in days, while the vertical axis represents the flow items of one batch. One batch contains granule, granulation liquid, and coating. All of these consist of starting material, which is weighed in on a floor and on a table scale. Hence, six items, depicted as bars, represent one batch. The bars are split into multiple sections which are colored differently. Each section shows one process step. Looking at the first two bars, it can be seen that the first process steps are weighing granule (light green) and granulation liquid (blue). Afterwards the granule is mixed in a compulsory mixer together with some part of the granulation liquid (orange). The processor type of the compulsory mixer is a combiner, therefore, only one bar (the one of the upper granulation liquid) continues. Afterwards, the intermediate product is transferred into the fluid bed granulator (grey), also a combiner. Here, the remaining granulation liquid is added and one bar (the one of the lower

granulation liquid) displays further processing with IPC moisture analysis (strong yellow), sieving (red), and compaction (green). Shortly before the compaction process is finished, the weighing (purple) and dissolution (light yellow) of coating is started (last two bars). This was implemented by a trigger to prevent long holding times for liquid ingredients. The light blue parts indicate a joint, combining coating process, which leaves one bar for the final bulk packaging (rose). The end of bulk packaging can be considered as the end of the entire batch.

The order of the process steps is identical to the one of the flow chart. Also, the implemented processor types are correct, as well as the triggers assure the right dependencies between different steps. The model logic is thereby verified. The Item Trace Gantt charts of the case study contain four, respectively ten, batches and are therefore much more complex since multiple process steps of different batches occur simultaneously. They were examined replication-wise (P_{INA}: 25 replications; P_{EMB}: 45 replications) and successfully verified the overall model logic. On top, the total campaign duration is determined with these charts.

A schematic operators and processors chart can be found in Figure 17 (top: operator; bottom: processor). These remaining charts of the interactive report serve the same goal of verifying the **operating schedules**.

Their horizontal axis represents the duration in days. The operators and processors are displayed as vertically ordered bars. The bars are divided into colored sections as it was seen in the Item Trace Gantt charts. However, the sections represent different states, such as “break”, “idle”, “utilize” or “blocked”, instead of process steps.

The depicted operators states chart includes data about six operators, numbered 1 to 6. The first visualized information is the proof for compiling breaks (yellow), lunch times (red) and closing times (orange). All of these times start and stop for all operators at the same time. The second important information is their used capacity. While the first operator contains multiple green “utilize” sections and only few blue “idle” sections, the proportion is inverse for the last operator. This means that the capacity of operator 6 is not fully utilized. Therefore, either more work could be delegated to the operators or working with less operators could be more efficient.

The exemplary processors states chart shows only a cutout of the last six process steps (mixing in the tumble blender until packaging). The process steps are arranged in the chronological process order. Again, we see that the scheduled down times are

identical for all processors (orange). It becomes additionally evident, that all processors are more often “idle” (blue) than “utilized” (green). Purple sections display times, in

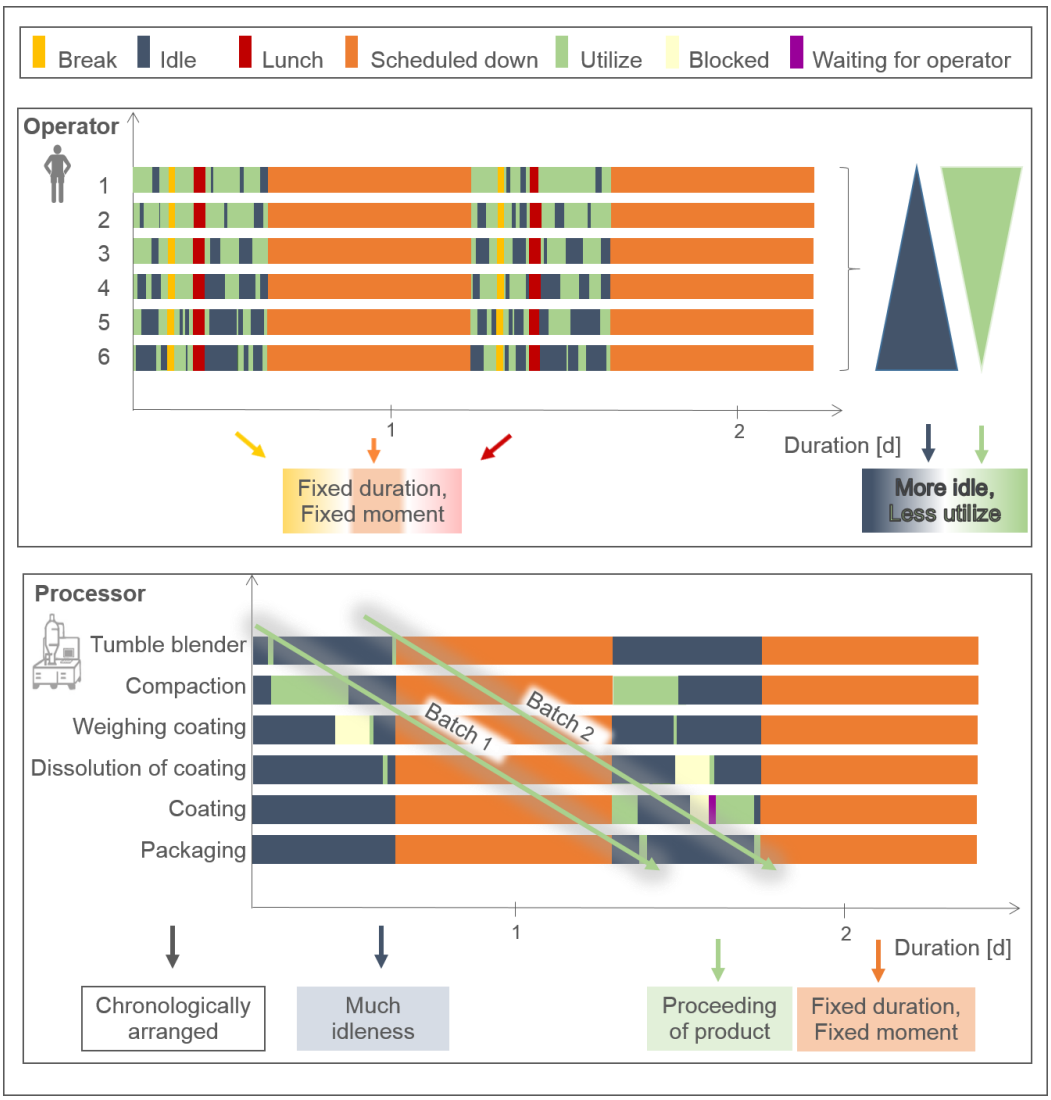

Figure 17: Cutout of schematic operators and processors states charts over two production days and the resulting findings.The major outcomes of both charts include the verification of break, lunch, and after-work hours, as well as of the capacity utilizations (idle/utilize). Thereby, the model can be tested (chronological order) and bottlenecks can be identified (capacity utilizations). Reproduced from (97).

which a processor is ready for processing and in which all necessary items are present. Processing, however, cannot start because no operator is available. The light-yellow parts indicate times, during which new items cannot enter a processor since it is still blocked by a previous, completely processed item that has not been transported to the next processor yet. By following the states “utilize” of the single processors, the overall production of the batch can be seen. Besides displaying the states in these graphs, a tabular presentation is possible. It is therefore easily possible to export these times and

to compare them to the specifications. This way, break times and process order were verified.

The last step of model verification was the verification of the **processing times**, which were extracted out of the performance measure report. The single values were transferred into Minitab®. Initially, it was checked whether the data was normally distributed or not by probability plots. As most of the data was not normally distributed, Mann-Whitney tests (confidence interval 0.95) were performed to compare the historical batch data to the FlexSim-generated data. The results are summarized in Table 7. All *p*-values are bigger than 0.05, proving that the historical processing times of all process steps are never significantly different to the FlexSim-generated data.

Table 7: Statistical analysis during model verification comparing historical batch data to FlexSim-generated data with probability plots and Mann-Whitney tests. Reproduced from (97).

Process step	Normally distributed?		*p*-value	
	P_{INA}	P_{EMB}	P_{INA}	P_{EMB}
Dissolution of granulation liquid	✓	×	0.760	0.243
Compulsory mixer	✓	×	0.594	0.479
Fluid Bed Granulation	×	×	0.993	0.127
IPC Moisture Analysis	×	×	0.806	0.527
Sieving	×	✓	0.767	0.602
Tumble blender	×	×	0.319	0.110
Compaction	✓	×	0.331	0.107
Dissolution of coating	✓	×	0.399	0.561
Coating	✓	✓	0.679	0.246
Packaging	×	✓	0.886	0.086

Furthermore, comparative boxplots of both products were created for each process step for visual inspection. Compared parameters are sample size, mean, standard deviation, minimum and maximum value of the historical batch processing times and the FlexSim-generated data.

As an example, the boxplot of packaging for P_{EMB} is shown in Figure 18. The sample sizes for the historical batch processing times and the FlexSim-generated data are identical (n= 45) and neither the means (16 min vs. 15 min) nor the standard deviations (4.64 vs. 4.55 min) differ much. Also, the maximum is identical with 28 minutes, while the minimum values differ only slightly (6 minutes compared to 8 minutes). Hence,

both, the Mann-Whitney test and the boxplot, verified that the implemented statistical distribution for packaging of P_{EMB} fully represents the historical processing times.

The just shown proceeding was applied to all process steps of P_{INA} and P_{EMB}. All boxplots confirmed the results of the Mann-Whitney tests: the historical batch processing times never significantly differed to the FlexSim-generated data. In conclusion, all critical parts of the computer models (model logic, operating schedules, and processing times) have been verified successfully.

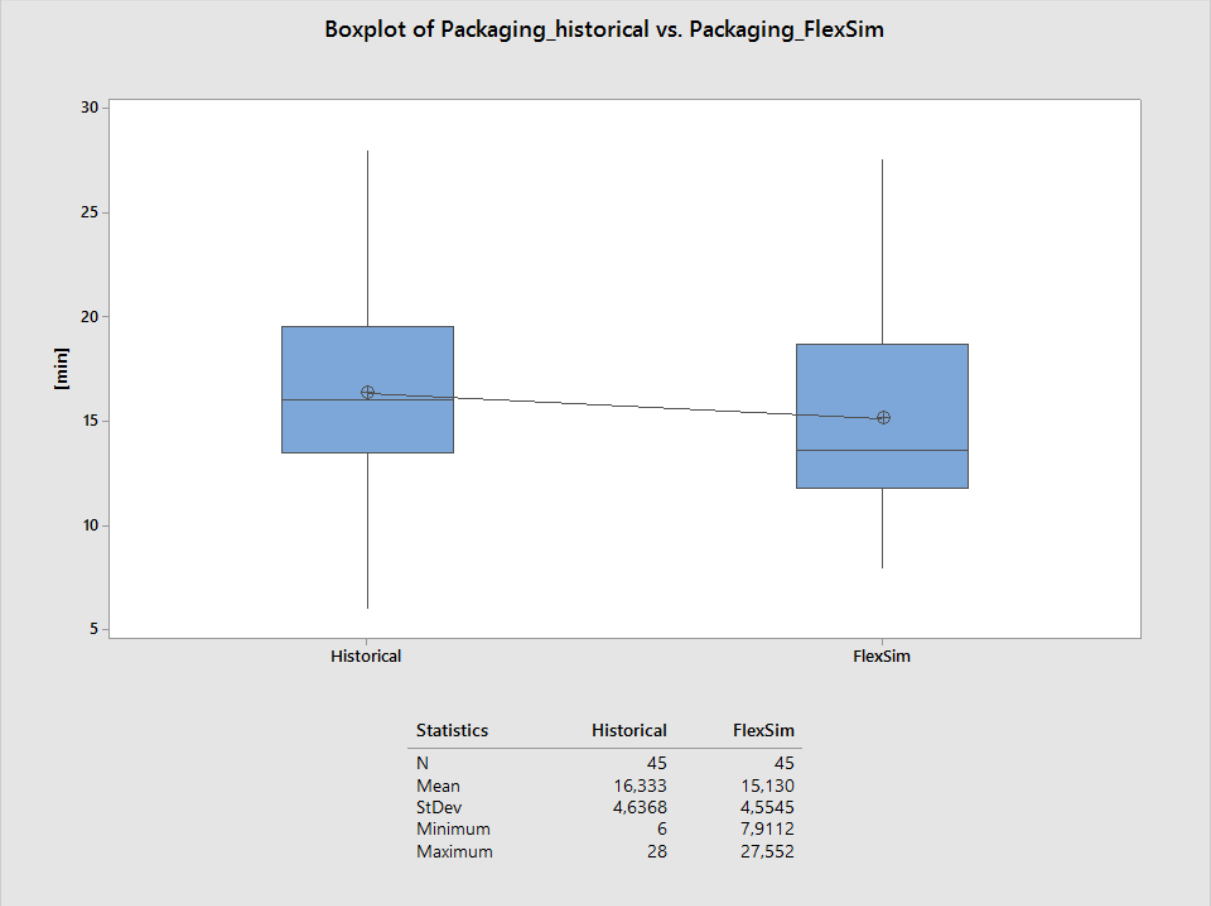

Figure 18: Comparing boxplot of historical and FlexSim-generated data for packaging of P_{EMB}.

3.3.4. Model validation

The purpose of the model validation was to prove and document the reproducibility of the computer models for the production processes of P_{EMB} and P_{INA} under the existing conditions.

The **definition** of “validation” combines two points of view in this case study. Firstly, it is about computer simulations so the IT interpretation must be considered. There, validation is understood to be a repetitious comparison of the model against the real production for model improvement until an acceptable model accuracy was achieved (84).

Secondly, the modeled process is a pharmaceutical production process. In the pharmaceutical environment, validation is an inherent part of GMP. This includes having documented proof of reproducibility and suitability. After exchanging opinions with the supplier of FlexSim, a mixture of both was chosen.

Realization. Initially, the as-is models and all relevant FlexSim-generated data were shown to the head of production. He examined whether the logic and the behavior of the models were reasonable. This way, he approved their face validity. For the following predictive validation, production campaigns of both products were picked in advance to compare their new data to the FlexSim-generated data. The one of P_{EMB} contained ten batches and the one of P_{INA} four batches. The productions took place in March/April and May 2019, respectively. Model parameters and their specifications were predefined and can be found in Table 8. The detailed listing for P_{EMB} can be found in the supplementary material (Supplementary table 2).

Table 8: Parameters and the according specifications for model validation.

Parameter	**Specification**
Process flow	• Process order identical to Cmap Tools flow chart • Process order identical to FlexSim model
Processing times (PT)	• $PT_{min\ Empirical} \geq PT_{min\ FlexSim} - 0.5$ SD; Standard deviation (SD) • $PT_{max\ Empirical} \leq PT_{max\ FlexSim} + 0.5$ SD
Campaign duration (CD)	• $CD_{min\ Empirical} \geq CD_{min\ FlexSim} - 0.5$ SD • $CD_{max\ Empirical} \leq CD_{max\ FlexSim} + 0.5$ SD

The campaigns were produced by the production staff under normal conditions. However, changes, deviations, and other non-standard conditions were monitored and documented. Afterwards, the processing times were transferred from batch documentation into Minitab® for the comparison to the FlexSim-generated data.

Analyzing the validation data was challenging for multiple reasons. There was a constant changing of head count during both production campaigns and only three instead of four fully qualified operators were available. A new operator supported the production, but cannot be counted as a separate one. Also, many non-standard conditions occurred. They can be clustered into:

- Machine breakdowns
- Personnel shortages

- Additional, non-campaign work cutting manpower
- Human errors.

None of the batches were produced without any incidents. The head of production confirmed that no campaign has had that many incidents before. Further details for P_{EMB} can be found in the supplementary material (Supplementary table 3).

Nevertheless, one predefined parameter, the process order, met all specifications and the single processing times did in most cases (33 out of 36). However, the campaign durations could not be considered at all. During the campaign of P_{EMB}, the head count was reduced each day. Hence, it was impossible to perform the usual number of simultaneous process steps which prolonged the campaign duration.

Visualization of the validation times in boxplots indicated that they not only differed to the FlexSim-generated data, but also to the historical data. As an example, the boxplots of the process step fluid bed granulation are shown in Figure 19 (P_{INA}) and Figure 20 (P_{EMB}).

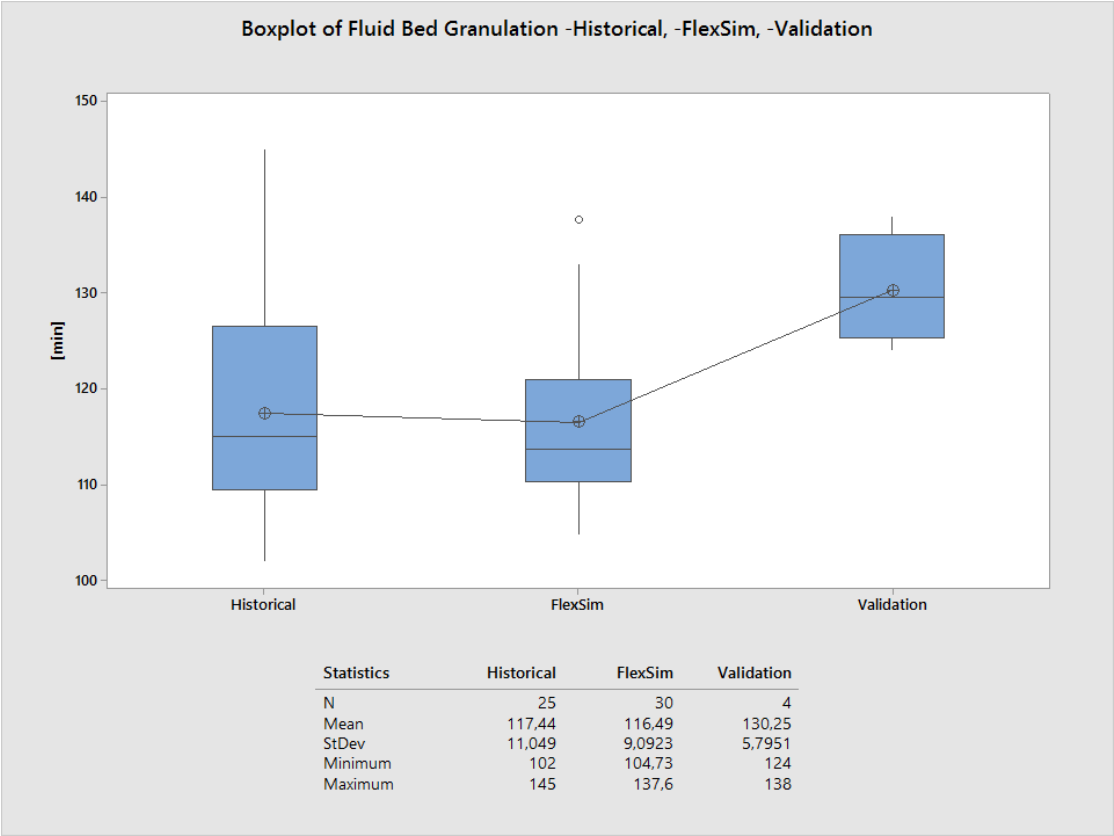

Figure 19: Comparing boxplot of the processing times for fluid bed granulation of P_{INA} including historical, FlexSim-generated, and validation data.

The minimum and maximum values of the P_{INA} validation data are still within the ones of the historical data. However, the mean of the validation is higher than the third quartile of historical one. Also, none of the validation data's single value is within the third quartile of the FlexSim-generated data. It is therefore expectable that the Mann-Whitney tests indicate a significant difference between the validation and FlexSim-generated data as well as between validation and historical data.

In contrast, the boxplot of P_{EMB} appears to be more balanced. All processing times of the validation data are within the minimum and maximum of the other data samples. It is nonetheless noticeable, that the mean is about 18 minutes shorter than the one of the historical data.

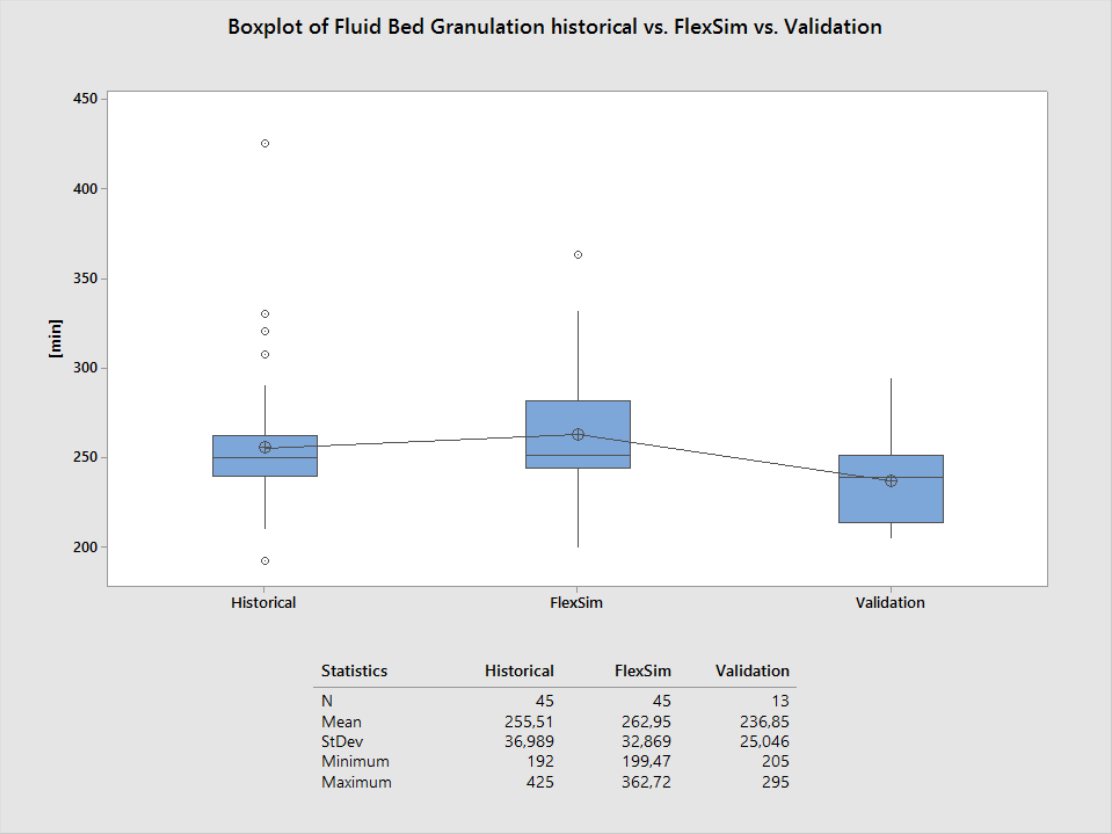

Figure 20: Comparing boxplot of the processing times for fluid bed granulation of P_{EMB} including historical, FlexSim-generated, and validation data.

Conducting the Mann-Whitney tests for comparing the validation data to the FlexSim-generated data for P_{INA} showed that the processing times of four out of nine process steps were significantly different (dissolution of granulation liquid, fluid bed granulation, compaction, coating; Table 9). For the IPC moisture analysis, the test was not applicable as all validation data points were identical. The same result can be seen looking at the P_{EMB} data (Table 10). The validation data for fluid bed granulation,

sieving, dissolution of coating, and coating differs to the ones of the FlexSim-generated data. The processing times for packaging also differ significantly. However, the bulk product was packed by three operators during validation and normally, packaging is done by two operators. When considering this and recalculating the processing time for two instead of three operators, there is no significant difference anymore. These findings proved that even if the processing times met the predefined specifications of the predictive model validation, the validation data was in some parts significantly different to the simulated data in FlexSim.

To investigate the cause of these differences, Mann-Whitney tests were performed to also compare the validation data to the historical data. The findings for P_{INA} completely mirror the previously found differences. The processing times of the same process steps (dissolution of granulation liquid, fluid bed granulation, compaction, and coating) differ significantly between historical and validation data.

For P_{EMB} it is almost analogous. Only the validation data for the dissolution of coating does not differ to the historical data, while IPC moisture analysis does differ in contrast to FlexSim-generated data.

These results of the Mann-Whitney tests stress, that only the processing times of the following process steps do not differ:

- Compulsory mixing
- Tumble blending
- Packaging.

The processing times of all other process steps (dissolution of granulation liquid, fluid bed granulation, IPC moisture analysis, sieving, compaction, dissolution of coating, coating) vary significantly and thereby have great economical potential.

Table 9: Comparing Mann-Whitney tests for P_{INA} testing validation data against FlexSim-generated data as well as against historical data (significantly different data is highlighted in red).

Confidence Interval 95%	FlexSim-generated data vs. Validation data		Historical data vs. Validation data	
	***p*-value**	**Evaluation**	***p*-value**	**Evaluation**
Dissolution of granulation liquid	0.008	significantly different	0.021	significantly different
Compulsory mixing	0.190	not significantly different	0.137	not significantly different
Fluid Bed Granulation	0.015	significantly different	0.077	significantly different
IPC Moisture Analysis	not possible, all validation data points are identical			
Sieving	0.407	not significantly different	0.448	not significantly different
Tumble blending	0.378	not significantly different	0.776	not significantly different
Compaction	0.015	significantly different	0.016	significantly different
Dissolution of coating	0.323	not significantly different	0.577	not significantly different
Coating	0.004	significantly different	0.010	significantly different
Packaging	0.209	not significantly different	0.267	not significantly different

Table 10: Comparing Mann-Whitney tests for P_{EMB} testing validation data against FlexSim-generated data as well as against historical data. Validation data being different to both other data sets are colored red and validation data being different to only one other data set are colored orange.

Confidence Interval 95%	FlexSim-generated data vs. Validation data		Historical data vs. Validation data	
	***p*-value**	**Evaluation**	***p*-value**	**Evaluation**
Dissolution of granulation liquid	0.563	not significantly different	0.756	not significantly different
Compulsory mixing	0.361	not significantly different	0.560	not significantly different
Fluid Bed Granulation	0.005	significantly different	0.046	significantly different
IPC Moisture Analysis	0.062	not significantly different	0.041	significantly different
Sieving	0.000	significantly different	0.001	significantly different
Tumble blending	0.765	not significantly different	0.524	not significantly different
Compaction	0.371	not significantly different	0.655	not significantly different
Dissolution of coating	0.026	significantly different	0.168	not significantly different
Coating	0.000	significantly different	0.002	significantly different
Packaging	0.000	significantly different	0.000	significantly different
Packaging by 2 operators	0.146	not significantly different	0.773	not significantly different

To investigate these findings, I-MR charts and interval plots were created with Minitab®. The graphs of fluid bed granulation for both products are shown exemplarily in Figure 21, Figure 22 (both P_{INA}), Figure 23, and Figure 24 (both P_{EMB}).

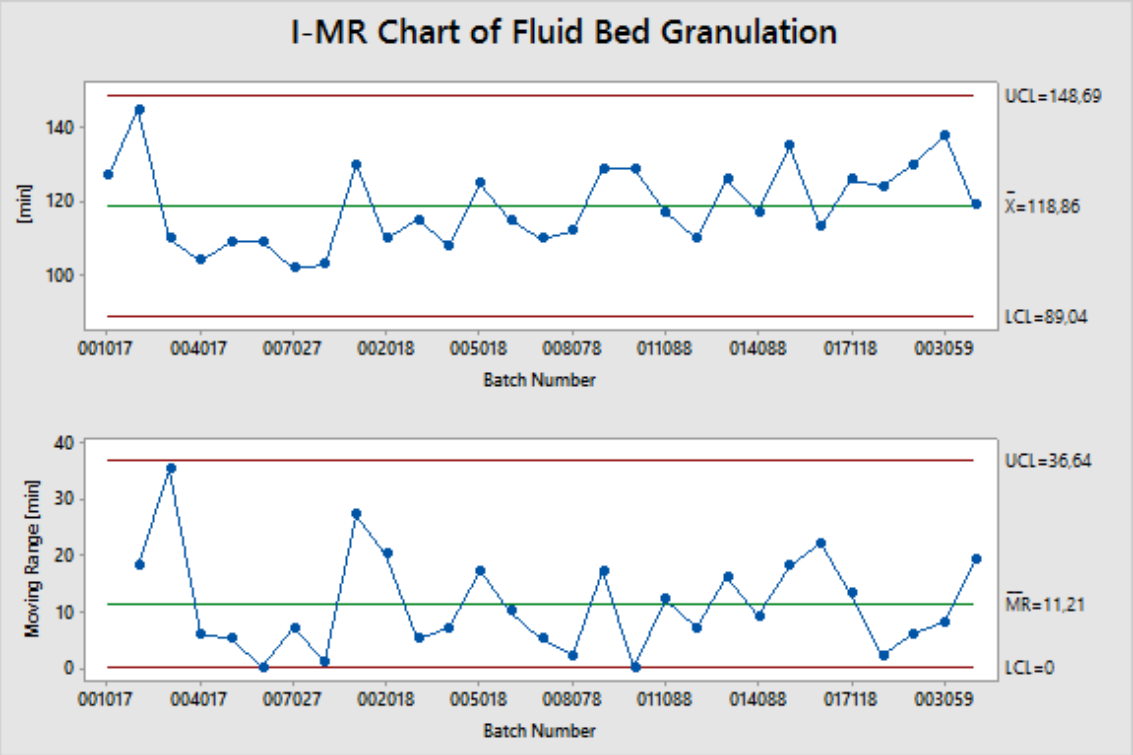

Figure 21: I-MR chart of fluid bed granulation processing times for P_{INA} including historical and validation data in chronological order.The individual chart is on top, showing all individual processing times of each batch. The moving range on bottom indicates the differences between the different batches.

The I-MR chart includes two separate charts, the individual one on top and the moving range chart on bottom. For both graphs, all batches are aligned chronologically on the x-axis. The y-axis represents the processing time of each batch for the process step of fluid bed granulation for the individual chart, and the moving range in minutes for the moving range chart. The green line illustrates the mean and the red lines are the upper and the lower control limits. They are set as 3σ above and underneath the mean.

The last four data points are validation data. All of them are at least equal or higher as the mean processing time. And even if no data point is out of the control limits, the individual chart seems to visualize a process following a slight trend towards longer processing times. The moving range in between the validation data is very little, meaning that the validation times do not differ too much.

The applied interval plots enable the comparison of the confidence intervals of the processing times of historical, FlexSim-generated, and validation data. A confidence interval of 95% for each group is shown.

For P_{INA}, the confidence interval of the validation data does not meet any confidence interval of another group. It must be taken into consideration that validation data includes only four batches. Therefore, the confidence level is high and not precise.

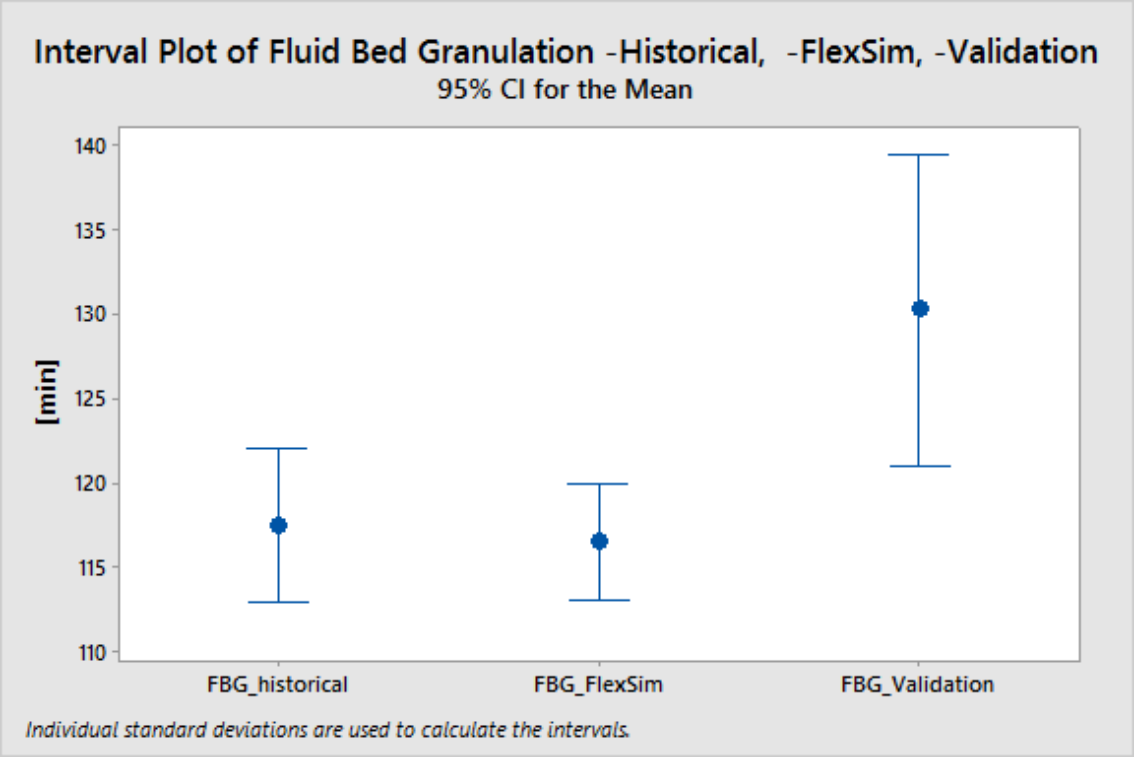

Figure 22: Interval plot of fluid bed granulation processing times for P_{INA} comparing historical, FlexSim-generated, and validation data.

The plots however emphasize again that the validation data is not comparable to the previously collected historical data. Hence, the computer model was built correctly and a successful validation of the P_{INA} model was impossible having significantly different processing times.

The product P_{EMB} is produced more regularly in bigger campaign sizes. Therefore, more data points (batches) can be found in the respective I-MR chart (Figure 23). Three gaps can be seen in both charts and are caused by a lack of data. Reasons for this can include faulty processing times in batch documentation or deviations during production. Also, outliners were excluded during data preparation.

The last 13 data points are validation data, as spontaneously, three more batches were added to the validation campaign. It was decided to integrate this extension in the validation, since bigger sample sizes are advantageous for statistical analysis. In contrast to the P_{INA} graphs, this I-MR chart does not indicate a trend towards longer processing times at all. This shows that the trend during fluid bed granulation is product dependent, not equipment dependent. Processing times of three batches are out of the set control limits (batches: 002018, 021078, and 006049). Additionally, we see a short trend of increasing processing times for 006018 over 008018 (red highlighted) until 010018. No obvious reasons could be found in batch documentation for any of these findings.

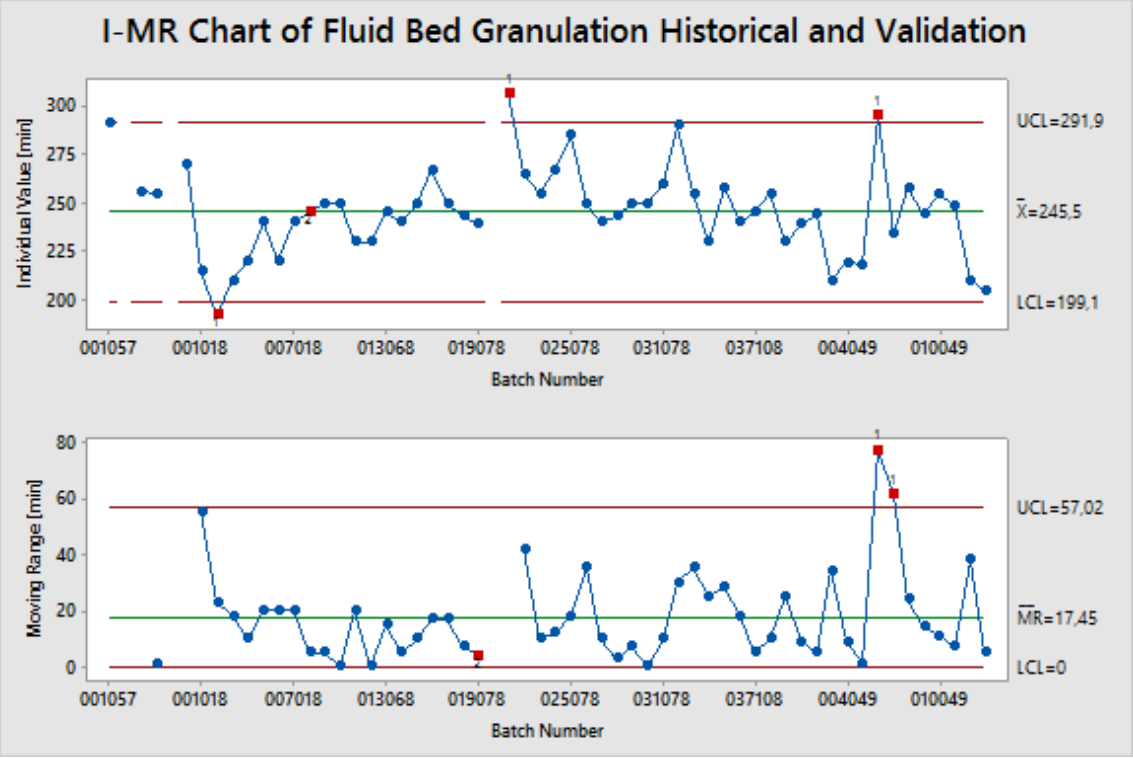

Figure 23: I-MR chart of fluid bed granulation processing times for P_{EMB} including historical and validation data in chronological order.The individual chart is on top, showing all individual processing times of each batch. The moving range on bottom indicates the differences between the different batches.

The interval plot of P_{EMB} comparing the confidence intervals of all groups shows an intersection between validation and historical data.

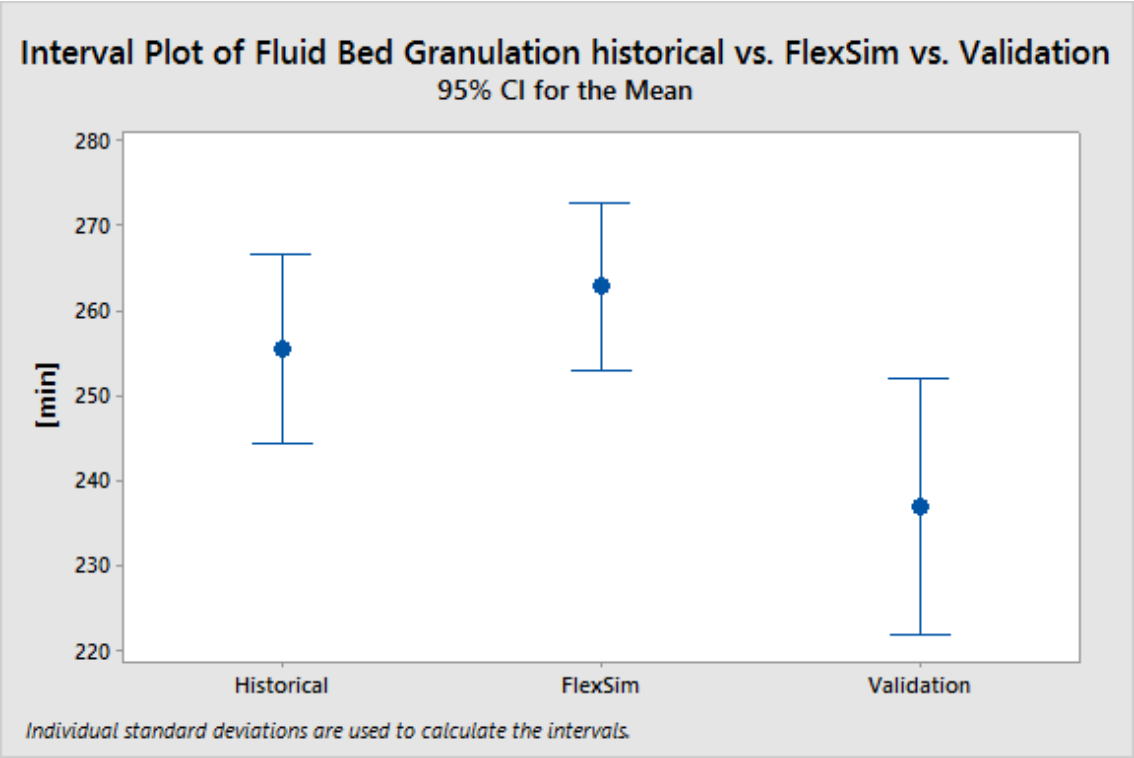

Figure 24: Interval plot of fluid bed granulation processing times comparing historical, FlexSim-generated, and validation data of P_{EMB}.

Unfortunately, the confidence interval of FlexSim-generated data is slightly higher than the one of the historical data. Therefore, validation data and FlexSim-generated data do not match. All things considered; the processing times of fluid bed granulation are more stable for P_{EMB} than they are for P_{INA}. Nevertheless, the processing times still vary.

Due to the length of processing times, the process steps of fluid bed granulation, compaction, and coating are the most influencing ones in the model. At least one significant difference between validation data and historical data is found for each process step. This caused the process owner to perform internal root cause analysis. The according findings are out of the scope of this dissertation and include company internal matters.

However, some explanations beyond company internals are to be mentioned here. A fluid bed granulation is strongly weather dependent as three drying steps are included. The inlet air can only be heated up but not cooled down and humidity cannot be reduced. Therefore, longer drying times occur during the summer due to higher moisture content in the air. Technical changes, such as the implementation of a new cooling coil could probably stabilize the processing times. For the process step of compaction, different rotational speeds of the tablet press are validated. As mentioned earlier, only three fully qualified operators were available during the validation campaigns. A more

experienced operator can run the tablet press faster. Training the new operator in the process of compaction may have slowed down the process during validation. The longer processing times for coating may have the same reason as the ones for fluid bed granulation: the inlet air regulation does not allow any other air modification than heating. Whenever the incoming air is already hot and humid, the two cooling down phases during coating, slow down the overall process.

A further finding for the process owner concerned the batch documentation. Some processing times were not captured and also, the understanding and interpretation of some start and stop times differed between the operators. The latter was solved by training and the missing process times are not of GMP but of optimization relevance. An important lesson learned for the modeler was that one formulation includes a hydrochloride which damages the processors by oxidations. Therefore, some processes, for example the compaction, cannot be stopped overnight but must always be finished and the product must be removed. This resulted in optimizing the according computer model and integrating different schedules for some processors (compaction, sieving). Additionally, a rule was implemented to stop processing new items in these processors, whenever the mean processing time was longer than the remaining time before closing.

In summary, the predictive validation was not entirely successful due to multiple reasons. However, face validity was proven, important information was gathered and process weaknesses were identified. It must be emphasized that all data is real process data having disturbances and real-life conditions. Simple repetitions and rearrangements are not possible. The produced bulk was an authorized product for tuberculosis patients, met all GMP and quality control specifications and was released to the market. The computer models have been verified and represent the historical data for all process steps of both products. It was proven that the model logic is applicable, and almost all processing times met the predefined specifications. The validation processing times of multiple steps were significantly different to the historical ones. Since the models were intentionally built to represent only standard production scenarios without any non-standard conditions, the occurrence of such conditions during model validation led to the expected, significant differences. Therefore, the further use of the models was possible, regardless of the partly failed model validation.

3.3.5. Model application

The as-is models of P_{INA} and P_{EMB} have been successfully verified and also partly validated. Changes to the existing, approved processes could be tested afterwards in-silico by changing parameters in the computer models. As the applied FlexSim version did not contain any optimization module, the changes had to be implemented manually. Throughout model building, verification, and validation, limitations of the processes have become evident. After consultation with the head of production, easily implementable organizational changes were set as primary areas of interest. Especially during model verification, the long idle times of processors have come to light (Figure 17). It was found that processors stop working at closing time, some even at least one processing time before. Also, daily routines, such as setting up of systems, cleaning, and documentation work should be reduced whenever less work days are necessary. It was therefore investigated if changing the existing one-shift (OS) system to a one-and-a-half-shift (OHS) system or a two-shift (TS) system increases profitability. In this study, profitability includes a short campaign duration and low labor costs.

The operating schedules for the different shift systems were defined and are listed in Table 11. Until an in-company agreement was valid, the weekly hours of some operators differed. The historical data, and therefore the verified OS has two different closing times. As the optimization scenarios represent the current status with the new equalized hours, the OHS and the TS systems do not differ anymore.

Table 11: Operating schedules of the different shift systems.The one-shift system includes the meanwhile obsolete difference of the weekly hours for some operators (*).

	One-shift *	**One-and-a-half-shift**	**Two-shift**
Operating schedule	07:00 a.m.–03:15/03:45 p.m.	06:00 a.m.– 02:15 p.m. 09:15 a.m.– 05:30 p.m.	06:00 a.m.–02:15 p.m. 02:00 p.m.–10:15 p.m.

Models were built with two varying parameters: the operating schedule (OS, OHS, TS) and the product kind (P_{INA}, P_{EMB}). The models for P_{INA} cover four batches and the ones for P_{EMB} ten batches. However, it was not possible for all scenarios to create a running model. Apparently, the number of operators was too low and was therefore added as one extra parameter (four vs. six operators).

The first result stood out even before analyzing the results. During adjusting the as-is model into the optimization scenarios, the hours of one work day were extended. Thus, the times for weighing in (WT) granule and granulation liquid could be brought forward.

A constant supervising of the Item Trance Gantt chart of the interactive report enabled finding the best WT after campaign start. These WTs did not depend on the number of operators, except for the OS system of P_{INA}. Hence, two different variants are displayed in Figure 25.

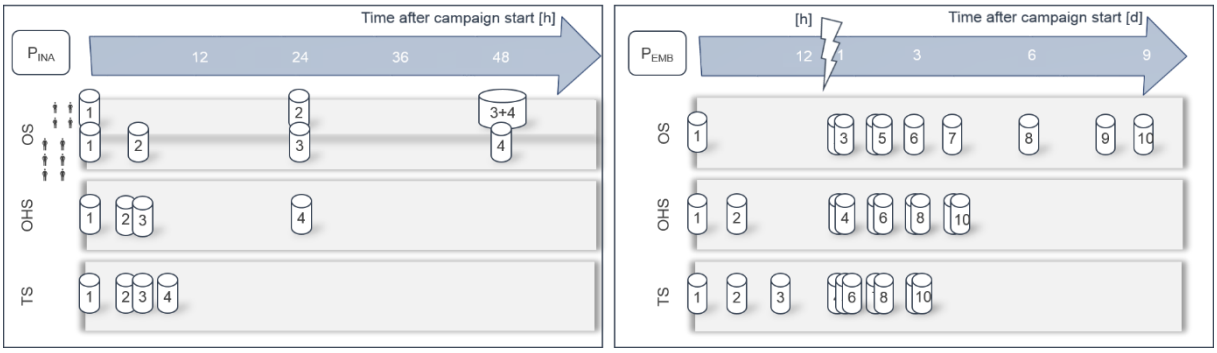

Figure 25: Comparison of the starting times for weighing in granule and granulation liquid after campaign start for P_{INA} and P_{EMB} in dependency of the applied shift system (OS, OHS, TS) and the head count (four vs. six).Reproduced from (97).

The figure is divided into P_{INA} (left) and P_{EMB} (right). For both parts, the campaign duration after campaign start is spanned from left to right in hours. As more batches need to be weighted in for P_{EMB}, the timeline contains a cut after twelve hours and continues counting in days. The weighing of one batch is represented by a numbered barrel. The WT of the last, fourth barrel of P_{INA} could be brought forward from 48 h (OS system) to 8 hours (TS system) after campaign start. This was the first hint that changing the shift system will have a great impact on the overall campaign duration.

Further evaluations of the newly created models consider three aspects: the number of replications, the utilization of the operators, and the campaign duration. Only stable models finish all runs. If there are modeling issues or if a scenario is simply impossible to realize, the runs will not finish but freeze. It was already explained in 3.3.3 how the utilization of the operators is evaluated (Figure 17) and how the overall campaign duration is identified (Figure 16).

Six different cases were modeled for each product distinguishing between the shift system (OS, OHS, TS) and the number of operators (four, six). The number of operators represents the entire head count. Except for the OS system, the operators work at staggered intervals, each two or each three in one shift. The predefined number of replications for P_{INA} was 30 and for P_{EMB} 40. The results are summarized in Table 12.

Table 12: Results of the optimization scenarios for P_{INA} and P_{EMB} regarding the number of replications, the utilization degree, the campaign duration, and the labor costs. The operators utilization degree is symbolized by arrors (↓ = some idleness, ↓↓= much idleness, ↓↓↓= operator is barely working, ↑↑↑= work overload, and ✓=appropriate work load). Reproduced from (97).

		One-shift (OS)		One-and-a-half-shift (OHS)		Two-shift (TS)	
	P_{INA}	4	6	4	6	4	6
Operators $_{total}$		4	6	4	6	4	6
Replications		30/30	30/30	30/30	30/30	28/30	30/30
Operator Utilization		✓	Op5 + Op6 ↓↓	✓	Op6 ↓↓	↑↑↑	✓
Duration $_{mean}$ [d]		3.2 ± 0.00	3.2 ± 0.00	2.4 ± 0.02	2.3 ± 0.00	2.3 ± 0.02	1.6 ± 0.02
Labor costs [€]		7488	8928	7128	7866	8798	6840
	P_{EMB}						
Operators $_{total}$		4	6	4	6	4	6
Replications		41/45	41/45	45/45	44/45	--/45	42/45
Operator Utilization		✓	Op4 - Op6 ↓↓	✓	Op1 - Op6 ↓	↑↑↑	✓
Duration $_{mean}$ [d]		9.4 ± 0.01	9.4 ± 0.01	7.2 ± 0.01	6.1 ± 0.02	--	4.4 ± 0.01
Labor costs [€]		21,996	26,226	21,384	20,862	--	18,810

All models of P_{INA} could finish their replications; except the TS system model with only four operators. Nevertheless, only two replications froze out of 30. This reveals that producing four batches of P_{INA} is possible for all scenarios. However, the TS system might be hard to realize. This finding is supported when examining the operator utilization: all operators seem to work at the load limit. Producing with six operators in the OS or the OHS systems on the contrary, creates many idle times. One operator (OHS), respectively two operators (OS) are barely working. For the OS and the OHS systems, the head count has no influence on the campaign durations. However, it does influence the ones for the TS system. Also, the campaign duration could be cut from 3.2 days (OS) to 1.6 days changing to a TS system with six operators. Besides having the shortest campaign duration, the labor costs for the TS system with six operators is also the lowest. This makes it the best production scenario for P_{INA}. The second-best option is to produce in an OHS system with four operators; the labor costs are only 4% higher and the campaign duration is in the middle range.

The models for P_{EMB} are more complex, simply by covering ten instead of four batches. This is more challenging for the replications as more process steps and dependencies overlap. It is therefore not surprising that not all replications finished for multiple scenarios. In particular, the TS model with four operators was strongly affected. No noteworthy number of replications ran successfully and the utilization was too high. It also becomes evident, that the combination of six operators in an OS system does not create enough work for all operators in a P_{EMB} campaign. While the six operators in the OHS model also have some capacities left, the workload is equally distributed. Having some free capacities must not be evaluated too disadvantageously, since some additional work or breakdowns can always happen on a production site as it was seen during model validation. The campaign durations last from 9.4 days (OS) to 4.4 days (TS); hence, a bisection is possible. The duration in the OHS models differ depending on the head count. With four operators, the production of ten batches takes 7.2 work days, with six operators it takes 6.1 days. The saving of one workday lowers the labor costs from 21,384 € to 20,862 €, even if two more operators receive their salary.

The most important findings of the optimizations are summarized in the following:

- Impossible: Working in a TS system with 4 operators
  - ⇨ freezing of replications, work load > operator capacities
- Best option: six operators working in a TS system

- ⇨ campaign duration: −50% (P_{INA}) and −53% (P_{EMB}) compared to as-is models
- ⇨ labor costs: −9% (P_{INA}) and −14% (P_{EMB}) compared to as-is models

- Best option with four operators: OHS system
  - ⇨ campaign duration: −25% (P_{INA}) and −23% (P_{EMB}) compared to as-is models
  - ⇨ labor costs: −5% (P_{INA}) and −3% (P_{EMB}) compared to as-is models
- Worst option: six operators working in an OS system
  - ⇨ campaign duration: no changes compared to as-is models
  - ⇨ labor costs: +19% for both products compared to as-is models

The best option with four operators is listed as only four fully qualified operators were employed during this case study. It must be taken into consideration that even if six operators were employed, sick days and holidays decrease the number of work days with all operators. The results were presented to the head of the production. His experiences confirmed that the OHS system is superior to the OS system with four operators regarding the campaign duration. Also, experiments had shown that it is not possible to work with only four operators in a TS system.

3.4. Discussion

This practical part of the thesis pursued two different purposes. Firstly, it was an actual implementation of a theoretically classified LCM strategy. Therefore, it reproduced and optimized two approved production processes of film-coated tablets. And secondly, an intuitive approach on model building, verification, validation, and application was established using Cmap Tools, Minitab®, and FlexSim.

For the second aim, a **new approach** was conceived. The obligatory efforts and the feasibility will be furtherly evaluated. Data collection was tedious but not demanding work. Newer equipment could ease and accelerate this process. The subsequent data preparation followed common scientific, analytical thinking. The critical analysis of the production processes went beyond the understanding during daily business. All process steps with the according dependencies and the workflow were scrutinized which did not only create a detailed process knowledge but also a keen sense of weaknesses and instabilities. For model building, it was of fundamental importance to know the special requirements of the pharmaceutical environment (galenic, GMP, and quality management). Only having this background knowledge enabled the modeler to merge or separate, to include or exclude aspects in the discrete-event simulations, which was

challenging, as computer-science is not part of the common pharmaceutical education. Also, there is no one correct way to build the production processes in FlexSim; there are many ways to establish the model logic. Hence, the models are always unique and depend on the modeler's creativity and knowledge. The unavoidable programming for the later model verification was most difficult, as neither the necessary elements nor programming knowledge was available. The added information of the software provider closed the gap and set the basis for the knowledge transfer. Hence as demonstrated, it was manageable and effective (bisection of work days, about 10% reduction of labor costs). Whenever the newly gained programming skills were applied once, the transfer to other tasks and models was much easier. During model verification, the logical background was already set and analytical thinking along with data handling regained importance. The selection of the aspects to verify was based on severity and the detection probability. The floor plan, the position as well as the number of processors and operators become directly evident by looking at the model, even without starting a simulation. Only if the priorities were set correctly, the simulations make sense. Otherwise, processors, operators or queues would be blocked at some point. Also, the model scope was easily revealed after one simulation run. The remaining steps of implementing model logic, operating schedules and processing times remained critical and needed to be checked precisely. In the end, model verification was a satisfying process and approved the previous working steps as well as the obtained models. Model validation is known to be crucial for the debottlenecking of production processes with computer simulations. Production steps, being unsteady or irregular, are described to hinder successful validations (104). This makes it even more important to apply the best fitting validation strategy. The initial face validity was time intensive for the process owner but easy to apply. The later predictive validation was split into the fulfillment of basic specifications (Table 8) and more detailed statistical tests (Table 9, Table 10). After all, the validation was not entirely successful since the basic specifications were met but Mann-Whitney tests proved a significant difference between some validation, FlexSim-generated, and historical data. It must be remembered here, that non-standard data was excluded during model building. Nevertheless, this could be the initial point for further investigations of model validation in FlexSim, looking for mandatory aspects and possible flexibilities. Even though the validation of both models

was not successful for all aspects, process steps with economical relevance were determined and the process owner could start root analyses to find causes and solve problems.

The applied software was feasible, albeit having different advantages and disadvantages. Cmap Tools, the freely available software, sometimes had cumbersome handling but was perfectly suitable for building the basic flowcharts. Different hierarchies can be created by using several colors, sizes, shapes, or styles. Minitab® is, on the contrary, a licensed software which was very supportive and user friendly. Creating graphs was done by only a few clicks and the individual adjustments were easy to select. Handling big data pools was immensely simplified and the program could help finding the adequate statistical tests if needed. So, this case study greatly profited from the application of Minitab®; in particular, the combination with FlexSim was very fruitful. FlexSim, the most important software, is appropriate for simulating process flows. It covers parameters like processing times, head count, ground floor, batch numbers, and process logic. It is however limited and solely represents the processes in a superficial way. Masses and the resulting film-coated tablet quantities were not included. Also, the processes inside the processors and their performance were only reflected by the processing times. Changes, like a different speed of a tablet press cannot be considered. Simulations of single process steps must be regarded individually with different software based on other simulations, such as CFD. FlexSim, in contrast, aims to provide a general conspectus and can therefore depict the process flow of an entire production site. It furthermore increases the process understanding and the effects of changes and errors. Therefore, this software can be used to convince decision makers having a management background of new pharmaceutical ideas or to teach process changes to production staff.

The results of the **process optimization** clearly indicated that producing bulk products with six operators in a TS system is superior to any other scenario. It must be taken into consideration that the bulk production is followed by primary and secondary packaging and that more departments contribute to a releasable product. Warehousing and the supply chain management guarantee the availability of material and the storage. QC tests starting materials, intermediate and bulk products, while QA monitors the GMP compliance amongst others. Technicians provide the production with qualified equipment and repair it in cases of breakdowns. It is therefore not enough to simply

increase the headcount in bulk production for the implementation of a running TS system. Some of the other departments, such as the QC, would probably also need to change their shift system. The change from OS to an OHS system in bulk production is definitely possible even if the other departments remain on their previous working schedules. This was already tested in real life. Another aspect is that hiring two more bulk operators includes qualifying them for the production of over 20 different products. It takes a lot of time (> one year) and resources until they can work completely on their own. All these obstacles and downsides must be traded off against the benefit of producing more batches. When we transfer the result of saving about 50% of the campaign duration to all other 20 products of the production site, around 300 batches could be produced instead of 150. This is an enormous potential, yet, the implementation of the optimization would need a high input in the first place. Also, the market demand must be high enough to sell twice as much.

One limitation during model building was the time registration and resolution of the processing times. An operator manually starts a processor whenever he is available and documents the date and time for the start. Some processors operate for a predefined time, while others need to be stopped by hand. Again, the time and date are written down for the process end. Hence, the resolution is always minute-wise and strongly depends on the availability of an operator. The processing times of long process steps, such as compaction (mean duration P_{INA} 269 minutes), are not strongly biased if five extra minutes are written down. For compulsory mixing however (P_{INA}: 1-10 minutes for setting up + standard 10 minutes mixing), five minutes waiting time for an operator has a great impact as the relative standard deviation increases. Furthermore, the resolution in minutes works better for longer process steps than for short ones (P_{INA}: start-up scales 8 minutes vs. compaction 269 minutes). This affects further data handling. Some processing times do not seem to be normally distributed even though they may be. Other statistical tests are chosen as well as different distributions for the historical data in FlexSim. However, it is more important that the longer process steps are represented correctly since they have more impact on the entire campaign duration.

Machine breakdowns, personnel shortages, and other human failures were excluded intentionally from the very beginning to obtain standard processes. An integration of such incidences would have needed a substantiated analysis of past quality issues and was beyond the scope of this work. To minimize this limitation, assumptions can

be made. The examined bulk productions of P_{INA} and P_{EMB} are of linear structure. This means, that a breakdown of one processor stops the production of the entire batch and cannot be replaced or bypassed. Also, subsequent batches are affected and the exceedance of shelf lives must be considered. Breakdowns therefore strongly influence the overall campaign duration but not the processing times of other process steps. Personnel shortages have the same effect as seen during model validation. The missing manpower limits the number of simultaneously running process steps. Therefore, the presented results are still conclusive as only few workarounds are available.

3.5. Conclusion

The presented work proved the practicability of computer simulations for optimizing pharmaceutical production processes and thereby strongly recommends it. Even with a small headcount, this case study was mainly conducted by one person, it was achieved to reduce the campaign duration by 50% for both production processes. It is therefore expected that more resources (working hours, cross-functional team) would greatly increase ideas and benefits and would shorten the project time. In particular, process verification was quite challenging leaving the user with the desire for easier and better standardized software modules. The software developers will probably need an economic stimulus and a higher market demand to pursue this objective. Hence, an extensive application of discrete-event simulations for pharmaceutical productions could even exponentiate the current benefits.

4. Thesis Conclusion and Outlook

The introduction of this dissertation raised the question why the pharmaceutical industry should not also succeed in transforming its productions into stable and sustainable processes. The presented LC analysis revealed the challenges hindering easy improvements; especially the strict regulations for medicinal products distinguish the pharmaceutical industry from other sectors. However, valid strategies were presented and successful examples listed proving that LCM can be well established in the pharmaceutical industry. Throughout all LC phases, the industry has found attempts to tackle specific issues. Also, technological advances, such as HTS or computer simulations, provide new means and thereby ease innovation, planning, and management. Even if a holistic approach addressing the overall LC is still missing, the currently available tools enable profitable pharmaceutical productions within western countries.

The consequent computer simulations of film-coated tablet productions impressively demonstrated their power and possibilities for classical, standard production processes. They created a deeper process understanding, identified weaknesses and confirmed the superiority of specified scenarios through figures. Relatively simple means sufficed without interrupting or risking the ongoing operation. Optimizing organizational procedures significantly reduced the campaign duration and respectively the production costs. An improved capacity utilization of operators and processors along with building up the head count can enable the doubling of the annual batch production. FlexSim was proven to be a beneficial software for conducting material flows simulations, however, pharmaceutical and chemical processes cannot be captured. Hence, its use is recommendable for gaining information about supply and production flows but not for technological demands.

Outlook

The shown case study was limited to the bulk production of two products. The implementation of the indicated best scenarios would require changes in other contributing departments, such as packaging, QC, and warehousing, as well. Therefore, it would be interesting to extend the models to all involved departments and all productions.

Another restriction of this work was the limitation to organizational changes avoiding post-approval changes. Considering the benefits achieved with these low-budget changes, more extensive ones would probably hold even greater benefits. A possible starting point is the exchange or update of equipment for inefficient process steps. As

discussed, the implementation of cooling coils for the fluid bed granulator and the coater could be promising. Alternatively, a rethinking of the “batch” definition could immensely reduce the workload and costs. Some production steps could be merged, retooling and setting up times reduced as well as the amount of batch-wise analytics minimized. This would involve the purchase of new equipment, the modification of working steps and therefore lead to post-approval changes. Before making far-reaching, risky decisions, conducting such computer simulations to predict risks and changes in advance, could reassure the decision-makers before making the final decision.

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Supplementary Material

Supplementary table 1: Provided distributions in ExpertFit

Available discrete distributions		
Bernoulli	Hypergeometric	Poisson
Binomial	Logarithmic series	Uniform (discrete)
Geometric	Negative binomial	
Continuous (non-negative) distributions		
Chi-square (E)	Inverted Weibull	Pearson type VI
Erlang	Log-Laplace	Random Walk
Exponential	Log-Logistic (E)	Rayleigh
F	Lognormal (E)	Wald (E)
Gamma (E)	Pareto	Weibull
Inverse Gaussian (E)	Pearson type V	
Continuous unbounded distributions		
Cauchy	Extreme value type B	Normal
Error	Johnson SU	Student’s t
Exponential power	Laplace	
Extreme value type A	Logistic	
Continuous bounded distributions		
Beta	Triangular	Uniform
Johnson SB	Power function	

Supplementary table 2: Summary of process parameters for model validation of P_{EMB}

Process step	**Object of interest**	**Acceptance criteria**	**Collection**	**Respon-sibility**

Weighing granule	Table scale	• Previous step: -
		• Subsequent step: Weighing granulation liquid
		• Processing time
		  ○ Min: 2.52 min
		  ○ Max: 34.48 min
			Batch record	Production staff

Weighing granule	Floor scale	• Previous step: -
		• Subsequent step: Weighing granulation liquid
		• Processing time
		  ○ Min: 1.77 min
		  ○ Max: 30.23 min
			Batch record	Production staff

Weighing granulation liquid	Table scale	• Previous step: Weighing granule
		• Subsequent step: Dissolution of granulation liquid
		• Processing time
		  ○ Min: 0.6 min
		  ○ Max: 35.40 min
			Batch record	Production staff

Weighing granulation liquid	Floor scale	• Previous step: Weighing granule
		• Subsequent step: Dissolution of granulation liquid
		• Processing time
		  ○ Min: 1.00 min
		  ○ Max: 18.00 min
			Batch record	Production staff

Dissolution of granula-tion liquid	Employee	• Previous step: Weighing granulation liquid
		• Subsequent step: Mixing and 1st granulation
		• Processing time
		  ○ Min: 1.98 min
		  ○ Max: 30.01 min
			Extra docu-ment	PhD Student

Mixing and 1st granula-tion	Compul-sory mixer	• Previous step: Dissolution of granulation liquid
		• Subsequent step: 1st Drying to 3rd Drying
		• Processing time
		  ○ Min: 2.66 min
		  ○ Max: 55.34 min
			Batch record	Production staff

Process step	Object of interest	Acceptance criteria	Collection	Respon-sibility

1st Drying to 3rd Drying	Fluid bed granulator	• Previous step: Mixing and 1st granulation
		• Subsequent step: IPC: Moisture analysis
		• Processing time
		  ○ Min: 173.51 min
		  ○ Max: 443.49 min
			Batch record	Production staff

IPC: Mois-ture analy-sis	Moisture analyzer	• Previous step: 1st Drying to 3rd Drying
		• Subsequent step: Sieving
		• Processing time
		  ○ Min: 4.13 min
		  ○ Max: 36.87 min
			Batch record	Production staff

Sieving	Rotation sieve	• Previous step: IPC: Moisture analysis
		• Subsequent step: IPC: Yield
		• Processing time
		  ○ Min: 11.41 min
		  ○ Max: 43.59 min
			Batch record	Production staff

IPC: Yield	Floor Scale 2	• Previous step: Sieving
		• Subsequent step: Mixing
		• Processing time
		  ○ Min: 0 min
		  ○ Max: 53.11 min
			Extra docu-ment	PhD Student

Mixing	Tumble blender	• Previous step: IPC: Yield
		• Subsequent step: Compac-tion
		• Processing time
		  ○ Min: 7.11 min
		  ○ Max: 15.89 min
			Batch record	Production staff

Compaction	Tablet press	• Previous step: Mixing
		• Subsequent step: Weighing coating
		• Processing time
		  ○ Min: 182.19 min
		  ○ Max: 272.81 min
			Batch record	Production staff

Weighing coating	Table scale	• Previous step: variable, compaction at the latest
		• Subsequent step: Dissolution of coating
		• Processing time
		  ○ Min: 1.13 min
		  ○ Max: 18.87 min
			Batch record	Production staff

Process step	Object of interest	Acceptance criteria	Collection	Responsibility

Weighing coating	Floor scale	• Previous step: variable, compaction at the latest
		• Subsequent step: Dissolution of coating
		• Processing time
		  ○ Min: 0.21 min
		  ○ Max: 15.79 min
			Batch record	Production staff

Dissolution of coating	Disperser	• Previous step: Weighing coating
		• Subsequent step: Coating
		• Processing time
		  ○ Min: 1.29 min
		  ○ Max: 27.71 min
			Extra document	PhD Student

Coating	Coater	• Previous step: Dissolution of coating
		• Subsequent step: IPC: Yield
		• Processing time
		  ○ Min: 137.80 min
		  ○ Max: 272.81 min
			Batch record	Production staff

IPC: Yield	Floor Scale 2	• Previous step: Coating
		• Subsequent step: Packaging
		• Processing time
		  ○ Min: Insufficient data available, empirical value
		  ○ Max: Insufficient data available, empirical value
			Extra document	PhD Student

Packaging	Employee	• Previous step: IPC: Yield
		• Subsequent step: end of batch production
		• Processing time
		  ○ Min: 3.68 min
		  ○ Max: 30.32 min
			Extra document	PhD Student

Supplementary table 3: Incidents during model validation of P_{EMB}.

Day	Head count	Incident	Effects	Batch
1	3	Audit preparation	Additional work, Start + 20 min Weighing start: 2:25 p.m.	All 1
2	3	Audit preparation	Additional work, compaction delay until day 3	All 1
2	3	API not supplied	Weighing delay	2
3	2	Additional work	Start + 25 min	-
3	2	Breakdown tablet press Audit	Delay of compaction and all other process steps	1
3	2	Breakdown FBG	+ 30 min	2
4	3	Breakdown tablet press Audit	Delay of compaction and all other process steps	1
5	3	Additional work	Start + 25 min	-
5	3	Breakdown tablet press	Delay of compaction and all other process steps	1
8	Until 9:00 a.m. 2, afterwards 3	Boiler issues	Limited number of process steps possible	1 - 4
8	3	IPC compaction set-ting up issues	+ 60 min	1
9	Until 9:00 a.m. 3, afterwards 2	Personnel shortages	Limited number of process steps possible	All
10	2	Personnel shortages	Limited number of process steps possible	All
11	2	Personnel shortages	Limited number of process steps possible	All
12	2	Personnel shortages	Limited number of process steps possible	All
15	Until 12:00 a.m. 3, afterwards 2	Breakdown tablet press	Delay of compaction and all other process steps	7
15	Until 12:00 a.m. 3, afterwards 2	Coating not solved	Coating + 25 min	6

Day	Head count	Incident	Effects	Batch
16	Until 12:00 a.m. 4, afterwards 3	Breakdown tablet press	External Technician; change of component	7
17	Until 10:30 a.m. 3, afterwards 2	Personnel shortages	Limited number of process steps possible	8 + 9
18	Until 9:15 a.m. 3, afterwards 2	Breakdown tablet press	+ 2 h, change of component	9
19	2	Personnel shortages	Limited number of process steps possible	9 + 10
21	3 + new OP until 11:00 a.m., afterwards 2 + new OP	-	-	11 + 12
22	3 + new OP	Breakdown fluid bed granulator	External Electrician	12 + 13
23	3 + new OP	-	-	12 + 13
24	3 + new OP	-	-	13

Scientific Output

Research paper

Hering S., Schäuble N., Buck T. M., Loretz B., Rillmann T., Stieneker F., Lehr C.-M. Analysis and Optimization of Two Film-Coated Tablet Production Processes by Computer Simulation: A Case Study. Processes. 2021;9(1):67.

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Review article

Hering S., Loretz B., Friedli T., Lehr C.-M., Stieneker F. Can lifecycle management safeguard innovation in the pharmaceutical industry? Drug Discovery Today. 2018;23(12):1962-73;

Requested as secondary publication: Hering S., Loretz B., Friedli T., Lehr C.-M., Stieneker F. Can lifecycle management safeguard innovation in the pharmaceutical industry? Pharm. Ind. 2019;81(5),618-631

Poster presentation

Hering, S. et. al. Analysis and optimization of a pharmaceutical production process by computer simulation, Poster session should have been presented at: PBP World Meeting; 2020 Mar 22-26; Vienna; accepted but event was cancelled due to COVID-19 pandemic

Hering, S. et. al. A safeguard of Innovation: Life Cycle Management and its background for Computer Modeling, Poster session presented at: DPhG Jahrestagung; 2017 Sept 26-29; Saarbrücken

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