THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Exploring Pharmaceutical Mass Customization

MARIA SIISKONEN

CHALMERS

Department of Industrial and Materials Science
CHALMERS UNIVERSITY OF TECHNOLOGY

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MARIA SIISKONEN

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Department of Industrial and Materials Science
Division of Product Development
CHALMERS UNIVERSITY OF TECHNOLOGY
SE–412 96 Gothenburg
Sweden
Telephone: +46 (0)31 – 772 1000

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Abstract

The core purpose of therapeutic pharmaceutical products is to induce responses to various diseases in patients and thereby bring societal value; however, unmet medical needs currently prevail. Conventional treatment of these products predominantly embraces a *one-size-fits-all* design and is manufactured in a mass-production context. A mass-production context is driven by economies of scale, however, a *one-size-fits-all* product design challenges the satisfaction of individual patient needs. Pharmaceutical product customization thus aims to satisfy individuals' treatment needs and thereby improve their therapeutic outcome; however, this implies a high product variety and low-volume production environment which challenges the cost-effective production with current mass-production platforms.

To address this challenge of achieving the cost-effective production of customized pharmaceutical products, this thesis explores a unified approach to cost-effective design, manufacturing and supply of customized pharmaceutical products. For this purpose, the mass customization principles of product modularization, process flexibility and postponement are adopted and adapted in a pharmaceutical production context.

This thesis proposes methodologies to design and model customized pharmaceutical products and production systems in a unified manner. Furthermore, customized product designs are proposed using product modularization as a design strategy and reconfigured pharmaceutical supply chain archetypes using postponement as a strategy for the cost-effective design, manufacturing and supply.

The findings suggest that an increased degree of modularization in the pharmaceutical product increases the patient benefit and thus improves therapeutic patient outcomes. In addition, current mass production platforms do not display the process flexibility required for the cost-effective production of customized pharmaceutical products. Moreover, with an increased degree of postponement, opportunities for reduced production costs in the supply chain emerge. Finally, the cost-effective customization of pharmaceutical products requires an integrated approach of product modularization and postponement. While modeling the production system, this thesis, however, considers a supply chain from the manufacturer to the pharmacy and patient assessing contemporary cost-effectiveness. Future research directions should investigate societal consequences from a wider, spatial and temporal, health care system perspective.

Keywords: pharmaceutical product customization, mass customization, product modularization, process flexibility, postponement

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Maria Siiskonen
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List of publications

This thesis is based on the following appended papers:

Paper A

Siiskonen, M., Malmqvist, J. and Folestad, S. (2021) Pharmaceutical Product Modularization as a Mass Customization Strategy to Increase Patient Benefit Cost-Efficiently. *MDPI Systems* 9(3):59

This is a reworked and significantly extended version of the paper: Siiskonen, M., Folestad, S. and Malmqvist, J. (2008) Applying Function-Means Tree Modelling to Personalized Medicines (2018) In *Proceedings of NordDesign 2018*. 14-17 August, Linköping, Sweden.

Distribution of work: Staffan Folestad first presented the idea of mass customization of pharmaceutical products. Johan Malmqvist supported with knowledge and tools of engineering design, such as product architecting. Maria Siiskonen developed the methodology, product designs, case study and conducted the experiments and analyzed the results. Maria Siiskonen wrote the manuscript. Johan Malmqvist and Staffan Folestad contributed with knowledge, discussions and critique with respect to the paper concept, results, content and disposition.

Paper B

Siiskonen, M., Malmqvist, J. and Folestad, S. (2020) Integrated product and manufacturing system platforms supporting the design of personalized medicines. *Journal of Manufacturing Systems* 56:281-296

Distribution of work: Maria Siiskonen conceptualized the paper, developed the methodology for the design of integrated product and production systems, conducted the experiments, analyzed the results and wrote the manuscript. Johan Malmqvist and Staffan Folestad contributed with kowledge, dicussions and critique to the papers concept, content and disposition.

Paper C
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Distribution of work: Maria Siiskonen conceptualized the paper, developed the supply chain designs, conducted the analysis and wrote the manuscript. Niels Henrik Mortensen provided knowledge regarding business models for customization and supported the early work of finding the direction and scope of the paper. Niels Henrik Mortensen, Johan Malmqvist and Staffan Folestad contributed with kowledge, dicussions and critique to the papers concept, content and disposition.

Paper D
Siiskonen, M., Govender, R., Malmqvist, J. and Folestad, S. (2022) Modeling the cost-benefit impact of integrated product modularization and postponement for pharmaceutical mass customization.
Submitted to: Journal of Manufacturing Systems

Distribution of work: Maria Siiskonen and Rydvikha Govender conceptualized the paper. Maria Siiskonen synthesized the framework and developed the product and production system design as well as methods for performance assessment. Rydvikha Govender developed the therapy archetype design and was responsible for the selection of therapy archetypes for the case study. Maria Siiskonen designed the case study, conducted the experiments and summarized the results. Maria Siiskonen and Rydvikha Govender analysed the results. Maria Siiskonen and Rydvikha Govender wrote the majority of the manuscript. Staffan Folestad supported with writing, knowledge and discussion throughout the whole work. Johan Malmqvist contributed with kowledge, dicussions and critique to the papers concept, content and disposition.

Acronyms

API – Active pharmaceutical ingredient

C – Constraint

CC – Configurable component

CCM – Configurable component modeler

CO – Component

CODA – concept design analysis

DRM – Design research methodology

DS – Deign solution

DSI – Descriptive study I

DSII – Descriptive study II

EF-M – Enhanced function-means

EVOKE – Early value oriented design exploration with knowledge maturity

FR – Functional requirement

MC – Mass customization

MP – Mass production

PS – Prescriptive study

QALY – Quality-adjusted life year

QFD – Quality function deployment

RC – Research clarification

RQ – Research question

SC – Supply chain

SSRI – Selective serotonin reuptake inhibitor

Contents

1

Introduction

This chapter introduces the topic of this thesis, which is the exploration of pharmaceutical product customization by the means of mass customization principles. The background is described followed by a problem analysis section, which leads to the clarification of the research focus of this thesis as well as the aim and hypothesis. Finally, research questions are presented and the research scope is clarified along with thesis delimitations.

1.1 Background

Healthcare systems and their provided treatments aim to improve the health and wellbeing of human beings (Akerman et al., 2018). Research within personalized medicines emerged with the main purpose to enhance the therapeutic outcome of the patient by providing them with safe and effective treatments (Crommelin et al., 2011; U.S. Food and Drug Administration, 2013; Deloitte Center for Health Solutions, 2017). In this thesis, *personalized medicines* are defined as treatments customized to the individual needs and preferences of the patient (Govender et al., 2020c), which refers to pharmaceutical products such as tablets and capsules. When addressing personalized medicines, this thesis focuses on the customization of pharmaceutical products according to design requirements; thus, the terms *customized pharmaceutical products* and *personalized medicines* are used interchangeably.

Innovations in healthcare have played a decisive role in societal development; for example, the findings of Lichtenberg (2014) show that out of the 1.74 years of global population life expectancy increase that

occurred between 2000 and 2009, 1.24 years were due to healthcare innovations. In addition, vaccination programs have prevented an estimated 103 million cases of childhood contagious diseases in the United States since 1924 (van Panhuis et al., 2013). Despite the increase in societal value achieved through healthcare innovations, an array of unmet medical needs of individuals prevail.

The U.S. Food and Drug Administration (2013) exemplified a few opportunities enabled by personalized medicines. Molecular diagnosis provides the physician with tools to select a treatment for patients with breast, colorectal, lung cancer and melanoma, which likely improves their chances of survival. HLA (human leukocyte antigen) genotyping has improved the outcomes of transplants as well as the ability to predict patient hypersensitivity to drugs used to treat HIV, hemophilia, epilepsy and bipolar disorder. Drug-metabolizing enzyme genotyping has provided means for proper dosing schedules for patients, which has helped thousands of patients avoid harmful side effects, drug interactions and ineffective treatments. Crommelin et al. (2011) describes Mammaprint™, by which a fingerprint of breast tumor tissue can be generated and used for further therapy guidance for the optimal outcome of the patient. These advancements represent outcomes of advancements in the field of personalized medicine, defined as diagnostic tools to describe the patient's health condition. These advancements have contributed to improved therapeutic outcomes for the patient, despite using the current product portfolio of pharmaceutical products as treatments, which are produced in a mass-production context. The current product portfolio has not been designed for a customization context, and Crommelin et al. (2011) discusses the ineffectiveness of pharmaceutical products today, exemplifying intravenous injection treatment technology which, in the context of targeting tumor or infection sites, at most 5%-10% of the product reaches the target site. This means that 90%-95% of the product ends up elsewhere in the body with the risk of inducing side effects. If the product portfolio were designed so that treatments could be customized according to individual patient needs by affordable means, further opportunities for enhanced therapeutic outcomes could be achieved.

Each patient embraces a set of treatment needs attributed to biological, environmental, behavioral and preference characteristics. Not only do these characteristics vary between individuals but also, within one individual over time (Thummel and Lin, 2014; Turner et al., 2015; Stegemann, 2016; Govender et al., 2020c). This diversity in patient characteristics

impacts the patients' responses to treatments, both from a performance perspective, when the treatment has been administered, as well as from a usability perspective. Govender et al. (2020c) provided a comprehensive framework for translating these patient characteristics into product design requirements according to which the treatment should be customized. These product design requirements include the API, dose strength, drug release functionality, composition, sensory attributes and dosage form appearance. Treatments, customized according to these product design requirements generate customized pharmaceutical products.

1.2 Problem analysis

The current pharmaceutical product portfolio does not extend the product variety to a level required to satisfy the vast array of treatment needs of individual patients. The current standard for pharmaceutical production is mass production, which entails a batch-based production of a low variety of product variants in large volumes, justified by economies of scales (Srai et al., 2015; O'Connor et al., 2016; Wilson, 2016; Govender et al., 2020c). The consequence of this low variety of pharmaceutical products is that drugs are rarely effective for everyone; for example, Spear et al. (2001) showed numbers regarding the efficacy and therapeutic response of many major drugs for several groups of therapeutic areas, and most drugs fell between 50%-75% of efficacy rate with reported numbers as low as 25%. Although commonly called a *one-size-fits-all* design, pharmaceutical products are typically produced in four-to-six dose strengths per product variant (Wilson, 2016). Four-to-six product variants leave the physician with a less optimal approach, however, when prescribing treatments to patients. The lack of a sufficient number of product variants combined with the lack of ability to predict individual patients' treatment success for diseases lead to a less-than-optimal, trial-and-error approach to treatment (U.S. Food and Drug Administration, 2013).

To provide patients with optimal treatments, pharmaceutical product customization requires a production context with a high variety of product variants produced in small production volumes; however, exceeding the number of four-to-six product variants has been argued to be cost-ineffective (Wilson, 2016). In a mass-production context, the pharmaceutical product portfolio arguably embraces a high complexity. When accounting for different dosage forms of a drug substance beyond tablets, such as liquids, the product variety is increased to 10-40 product variants. In addition, many companies operate globally, which adds complexity due

to regulations and rules requiring country-specific labeling (Savage et al., 2006). Such regulations are further expected to cause a 10-fold increase in product variety (Wilson, 2016; Govender et al., 2020c).

1.3 Research goal, challenge and focus

The goal of this research is to improve the therapeutic outcome of the patients through pharmaceutical product customization; however, this aim requires addressing a set of challenges. A customization context implies offering an increased external product variety to the patient, compared to the current pharmaceutical production paradigm. This external product variety should be achieved by cost-effective means. The high-variety, low-volume production challenge results from supplying an external product variety. If operated with their current design in a customization context, current production platforms for pharmaceutical products are simply expected to surpass their feasibility from an economic and technical perspective (Srai et al., 2015; O'Connor et al., 2016; Govender et al., 2020c). In a customization context, the economic and technical feasibility are challenged by the pharmaceutical product design, which was neither designed nor intended for a customization context. The most common dosage form is the tablet (Plumb, 2005; Nagashree, 2015; Wilson, 2016), which embraces an integral product design (as opposed to modular) and is rigid and difficult to adjust for increased product variety or for individual patient needs, which is a pre-requisite for product customization. Furthermore, the production processes regard the current mass-production context, where the incentive is to achieve economies of scale through lower product variety production (compared to a customization context), which is argued to be inefficient with low equipment utilization rates If the customized pharmaceutical products cannot be produced and supplied cost efficiently, the customized treatments will never reach the patients and the therapeutic outcome of the patient can never be enhanced.

Mass customization, a production paradigm that emerged in the 1980s, has been adopted by industries to increase business performance by providing a vast array of customers with customized products cost effectively (Pine II et al., 1993); thus, strategies to design, manufacture and supply a large variety of product variants were established. Hu (2013) formulated three principles of mass customization: product family architecture, reconfigurable manufacturing systems and delayed differentiation. Govender et al. (2020c) reformulated these three concepts as mass customization principles in a pharmaceutical context:

1. Product modularization
2. Process flexibility
3. Postponement

The research presented in this thesis focuses on exploring the three abovementioned mass customization principles to support the customization of pharmaceutical products.

1.3.1 Aim and hypothesis

The aim of this thesis is:

To explore a unified approach to the cost-effective design, manufacturing and supply of customized pharmaceutical products.

A unified approach intends to integrate the exploration of design, manufacturing and supply of customized pharmaceutical products in consolidation with cost effectiveness.

The overarching hypothesis is:

Mass customization principles adapted into a pharmaceutical context can support the cost-effective customization of pharmaceutical products.

Cost effectiveness concerns the design and production of customized pharmaceutical products that increase patient benefit more than the cost of doing so. The term *production* regards both the manufacturing or fabrication and supply of pharmaceutical products. Throughout this thesis, the concept of *value* describes trade-offs between the patient benefit and production cost of customized pharmaceutical products, which is used to determine cost-effectiveness. Value is adopted since it intends to capture the perceived satisfaction of stakeholder needs (Lindstedt and Burenius, 2003; Bertoni et al., 2018), which is pivotal to highlight in a pharmaceutical customization context.

1.3.2 Research questions

To explore the adaption of mass-customization principles in a pharmaceutical product customization context, four research questions are formulated based on the hypothesis. These research questions guide the research

presented in this thesis.

RQ1: *How can product modularization support the design of customized pharmaceutical products?*

RQ2: *What challenges the cost-effective production of customized pharmaceutical products?*

RQ3: *What reconfiguration strategies can support the cost-effective production of customized pharmaceutical products, and what challenges appear when trying to implement these strategies?*

RQ4: *How can a later point of variegation support a cost-effective production of customized pharmaceutical products?*

1.4 Research scope and delimitations

This thesis is concerned with therapeutic pharmaceutical products, and thus all references to pharmaceutical products regard therapeutic pharmaceutical products.

This thesis focuses on exploring the mass-customization principles of *product modularization*, *process flexibility* and *postponement* in a pharmaceutical product customization context. This thesis focuses on the conceptual and system-level design and modeling of pharmaceutical products, manufacturing systems and supply chains. Drug substance design and production on a molecule level, however, exceed the scope of this thesis.

This thesis concerns an approach to integrate key product design requirements into pharmaceutical products and the consequences of performing this integration. The product design requirements are treated from a product design and production perspective. The patient perspective is incorporated into the benefit assessment of the customized pharmaceutical products. Mapping patient needs by means of diagnostics or translating individual patient characteristics into design requirements is, however, outside the scope of this thesis. Furthermore, this thesis does not study the individual attributes of patients and the connected product design requirements.

The costs discussed in this thesis refer to production costs. Although interconnected to the production cost, the product price or any other costs

paid by the patient are not addressed.

Discussions concerning treatment approaches are presented from a consequential perspective of product and production system design. This thesis is not concerned with outlining treatment approaches of individual patients, such as whether the patient is responsible for treatment administration or if the treatment is provided by healthcare personnel at a hospital or nursing home. This thesis presents conceptual designs of healthcare systems on a general level. The focus is on commercial supply chains and requirements of healthcare system design; however, this thesis does not focus on any healthcare system of a specific country or region.

This thesis discusses pharmaceutical product and production system design implications on regulatory frameworks; however, research regarding how regulatory frameworks should be redesigned or adapted for a pharmaceutical product customization context is outside the scope of this thesis.

1.5 Outline of the thesis

The remaining of this thesis is structured as follows: Chapter 2 describes relevant literature and concepts underpinning the research performed in this thesis. Chapter 3 describes the applied research approach and methods used. Chapter 4 describes the research findings, and Chapter 5 discusses these findings by connecting them to research questions. Chapter 6 concludes the thesis and provides a brief outlook for future work. Finally, the four papers are appended.

2

Frame of Reference

To perform the research presented in this thesis, literature is reviewed to understand the current situation of the research challenge and to find relevant concepts to address the research challenge and thus change the current challenging situation into a desired one. Relevant literature and concepts are discussed in this chapter. This thesis integrates several scientific fields. This chapter addresses topics such as pharmaceutical product and production design, current practices for pharmaceutical customization, engineering design and engineering systems, mass customization, value-driven design and subtopics relevant to these beforementioned topics. At the end of this section, the results of the literature review are presented as research gaps concerning the discussed topics, which are addressed in this thesis.

2.1 Pharmaceutical production

The currently dominant pharmaceutical production can be described as mass production with a batch-based production approach and a *one-size-fits-all* product design.

2.1.1 Pharmaceutical product design

Pharmaceutical products refer to entities inducing therapeutic outcomes in the body as responses to various diseases. Pharmaceutical products can be administered, for instance, orally, topically, through inhalation or injection. Oral dosage forms are the most common, especially the tablet (Plumb, 2005; Nagashree, 2015; Wilson, 2016) which represents the product design studied throughout this thesis. A tablet can be characterized as a

rigid and integral product design (as opposed to modular) which can vary concerning contents, size and shape. Pharmaceutical products consist of active ingredients, called active pharmaceutical ingredient (API), and non-active ingredients called excipients. The API induces the pharmacological activity or the therapeutic effect in the body post-administration (U.S. Food and Drug Administration, 2017).The excipients' roles extend from pre-administration, such as improving the processability of the product formulation, to post-administration, such as determining the product functionality within the body (U.S. Food and Drug Administration, 2005; Dave, 2019).

2.1.2 Pharmaceutical manufacturing system design and operation

Pharmaceutical manufacturing, i.e., product fabrication, can be divided into primary and secondary production. The unit operations of the respective type of production are governed by batch production and are spread across separate firms and manufacturing sites and are commonly geographically distributed. This situation makes pharmaceutical manufacturing a highly disaggregated operation (Srai et al., 2015).

Primary production implies the manufacturing of a drug substance, meaning the API and excipients, usually in powder form (Savage et al., 2006). The primary production is not further detailed in this thesis and the produced drug substance in primary production is assumed to be unchanged.

Secondary production consists of several unit operations with the main purpose to transform API(s) and excipients, usually in powder form, into granules and then into compressed units such as tablets, which are then packaged. Unit operations thus include mixing, granulation, compression, coating and packaging (Shah, 2004; Savage et al., 2006; Srai et al., 2015). The batch-based production implies low manufacturing flexibility and has been described as a high-inventory, slow-response environment (Srai et al., 2015; Wilson, 2016). The nature of this type of manufacturing environment challenges manufacturing flexibility. The product design, regarding an integral product with a fixed formulation, causes low utilization rates due to frequent interruptions to the processing flow when another formulation is to be manufactured. Tedious change-over processes between formulations require two- to three-fold the processing time and further contribute to the low utilization rates. These change-over processes are tedious since

they need to comply with any quality assurance measure, and the quality assurance process of the product is commonly conducted batch wise via offline testing through analytical methods, which adds further challenges to the processing (Wilson, 2016).

2.1.3 Pharmaceutical supply chain design and operation

A simplified description of the pharmaceutical supply chain (SC) includes stakeholders beyond primary and secondary manufacturers such as the wholesaler, physician, pharmacy and patient (Shah, 2004; Savage et al., 2006; Aitken, 2016; Olson, n.d.). The wholesaler's main function is to procure pharmaceutical products from secondary manufacturers before bundling and reselling them to pharmacies (Shah, 2004; Derecque-Pois, 2010). The physician diagnoses the patients and prescribes treatments based on the diagnosis. The pharmacist's function is to provide patients with their prescriptions (Aitken, 2016; Olson, n.d.) and educate patients regarding side effects and treatment procedures and to correct any prescription errors (European Alliance for Access to Safe Medicines, n.d.). Finally, the patient acquires the prescription at the pharmacy, interferes with the product, if necessary, and then administers the treatment. Product interference activities include splitting tablets or combining treatments with food (Verrue et al., 2011; Govender et al., 2020c).

2.2 Pharmaceutical customization

Breakthroughs in pharmacological research have enabled understanding the interindividual drug responses of patients, which has provided conditions for the customization of pharmaceutical products according to the individual needs of the patient (Crommelin et al., 2011; Ahmed et al., 2016). Customized pharmaceutical products intend to customize treatments according to the individual needs of the patient (Wilson, 2016; Norman et al., 2017) to enhance the therapeutic outcome of the patient (Ahmed et al., 2016).

2.2.1 Patient-centric design

Treatments should be safe and effective for the patients (Crommelin et al., 2011; U.S. Food and Drug Administration, 2013). Beyond safety and effectiveness there is another pivotal determinant for the successful therapeutic outcome, which is the patient's willingness to take the treatment (Govender et al., 2020c). This willingness to adhere to the treatment has shown to

be a wide problem, for example, studies have shown that poor adherence is subject to an average of 50% of the population in developed countries (Brown and Bussell, 2016). Two principal challenges for poor adherence are the complexity of the treatment regimen, meaning the dosing frequency and time of dosing, as well as side effects (Brown and Bussell, 2016; Govender et al., 2020c).

Individual patient characteristics determine the safety and effectiveness of a treatment as well as the patient's willingness to adhere to their treatment. These characteristics can be divided into biological, environmental, behavioral as well as the preferences of the patient, that individually or collectively determine a patient's therapeutic outcome (Govender et al., 2020c). Govender et al. (2020c) provided a framework describing key product design requirements for customization to improve the safety and effectiveness of as well as the adherence to treatments. These key product design requirements are translated from the individual patient characteristics and include the API, dose strength, drug release functionality, composition, sensory attributes, and dosage form appearance.

Research concerning the connection between patient characteristics and product design requirements exist, to exemplify, the API determines treatment safety and effectiveness. This API should comply with drug-metabolizing enzymes and drug-drug interactions (Dailey et al., 2001; Personalized Medicine Coalition, 2014; Nolan et al., 2015). The dose strength should be customized according to the patient's biological characteristics for treatment safety and effectiveness. In addition, by customizing the dose strength, patient adherence to treatments can be improved; instead of administering several pills to achieve the desired dose the pill burden of the patient could be decreased by offering the patient a customized dose. Furthermore, by customized drug release properties the dosing frequency could be reduced (Govender et al., 2020c). For example, by customizing the drug release profile so that the drug is released in the right amount at the right time, the number of administrations the patient need to perform could be reduced; instead of the patient administering a treatment several times a day to obtain the needed dose. Biological characteristics, furthermore, determine how the drug is released in the body as well as the drug's uptake in the body (McConnell et al., 2008; Varum et al., 2010; Hens et al., 2017). Finally, customization concerning treatment appearance, such as the size and dosage form, could facilitate the handling and swallowability of the treatment; these factors have proven challenging in, for example, pediatric and geriatric populations (Klingmann et al., 2013; Messina et al.,

2015; Page et al., 2016; Ranmal et al., 2016).

This thesis is, however, not concerned with studying the patient characteristics and their translation into product design requirements. This thesis is rather concerned with designing flexibility into the pharmaceutical product concerning the key product design requirements to satisfy individual patient needs.

2.2.2 Customized pharmaceutical product designs

Some commercial pharmaceutical product designs have qualities displaying potential for customization; for example, scored tablets allow dose strength scalability since they can usually be split into two, up to four, units (Quinzler et al., 2006); however, Wening and Breitkreutz (2011) outlined challenges with tablet splitting such as inadequate dosing and tampered release properties. In addition, the sufficiency of the dose strength scalability achieved by tablet splitting, resulting in two or four units or dose strengths, remains debatable for a customization context. Multiple-unit dosage forms, such as pellet-based dosage forms or mini-tablets, have been discussed as having potential for customization. Multiple-unit dosage forms denote multiple units collected into an assembly to generate a treatment. These designs are currently used to increase the process flexibility; instead of producing tablets in several dose strengths one variant at a time, these multiple-unit dosage forms allow scaling the dose strength by varying the number used in treatment. Aleksovski et al. (2015) discussed multiple-unit dosage forms in a customization context from a scalable dose strength and flexible target release profile perspective. Multiple-unit dosage forms have also been discussed as supporting adherence or relieving swallowing difficulties (Klingmann et al., 2013; Aleksovski et al., 2015). Increased dose scalability and improved patient adherence contribute to improved therapeutic outcomes since they improve the safety and efficacy of the treatments Ahmed et al. (2016); however, multiple-unit product designs have not been designed with a customization intention and thus lack the intent of integrating different product design requirements into the treatment to comply with individual patient needs. Furthermore, multiple-unit dosage forms have solely been considered in a mass-production context and have thus far been used as a *one-size-fits-all* design.

2.2.3 Pharmaceutical production system design for customization

A few production technologies have been researched and shown to have potential for a pharmaceutical customization context. Additive manufacturing has been researched as a technology to individualize pharmaceutical products to the needs of the patient. To satisfy the need of individual patients, targeted product functionalities can be designed in a computer model which can then be printed by various technologies. Goyanes et al. (2015) illustrated, for example, the fabrication of tablets with variable release profiles by combining hot-melt extrusion and fused-deposition modeling. Eleftheriadis et al. (2021) used hot-melt extrusion as a printing approach for oral dosage forms, which were previously automatically designed by a computational algorithm to determine the optimal dose strength based on individual patient needs. Govender et al. (2020b) produced modular product designs where the API-containing core was produced through hot-melt extrusion and melt molding and the lids and cups for flexible target release profiles were produced by fused-deposition modeling. The challenges of additive manufacturing in a large-scale commercialization context remain, including material compatibility with the process, the precision of the process and economic challenges such as production cost, time and distribution (Govender et al., 2020c).

Research initiatives for continuous production, a technology currently featuring some coverage within pharmaceutical production, are found as a possible solution for pharmaceutical product customization. Continuous production has been discussed as a technology to increase process flexibility and thus as a solution to the high-variety, low-volume challenge arising due to pharmaceutical product customization (Lee et al., 2015; Srai et al., 2015; Harrington et al., 2017). These studies lack the consideration of product design customized to individual patient needs and thus consider a refined mass-production rather than customization context. Although these studies extend beyond a single stage of pharmaceutical production, an end-to-end perspective with cost-effective manufacturing and supply is not covered.

2.2.4 Compounding

Compounding is the practice of tailoring treatment to individual patients, which can be performed by licensed pharmacists or physicians and implies preparing customized medications that are not commercially available; in practice, this means to combine, mix and alter ingredients of drugs

(U.S. Food and Drug Administration, 2021b). Example patient populations for compounded medications include patients displaying allergies for some excipient in the commercial drug product or pediatric and geriatric patients requiring the alteration of the dosage form to one that is not commercially available, such as preparing a suspension to ease swallowing difficulties (Gudeman et al., 2013).

Compounding poses risks, however, and although FDA has proposed guidelines for compounding, the regulations governing this practice differ between organizations (U.S. Food and Drug Administration, 2012; Gudeman et al., 2013; Digori, 2021). In addition, breaking sterility or producing inadequate treatments regarding dose strength, product quality and purity display risks for the public health (U.S. Food and Drug Administration, 2012; Gudeman et al., 2013). Furthermore, these methods have not been clinically evaluated for safety and efficacy, and they lack standard labeling and instructions for safe use (Gudeman et al., 2013).

While compounding is a relevant example for pharmaceutical customization, the challenges of this practice remain. Compounding is performed on mass-produced products, which means that designing the products does not include individualizing the therapies, but rather alternations are performed on already produced and commercialized products. In addition, it is questionable whether a sufficient level of customization is achieved by altering commercialized products. The aim of pharmaceutical customization is to enhance therapeutic outcomes of the patient, which means to improve the safety and efficacy of the treatments (Crommelin et al., 2011; U.S. Food and Drug Administration, 2013; Deloitte Center for Health Solutions, 2017); however, according to the U.S. Food and Drug Administration (2012) and Gudeman et al. (2013) compounding represents challenges with respect to the treatment safety and efficacy. Compounding is an expensive practice (McPherson et al., 2016), and thus, sufficiency with respect to widescale availability of these products to patients is questionable.

2.3 Engineering design and engineering systems

The methods and tools of engineering design aim to design a functional product that provides a solution to an identified problem. These products cannot be designed in isolation from the context in which they function, however, since their behavior and performance depend on the indepen-

dent parts or subsystems of the products and more so on the interactions between these parts, subsystems and their functioning context. The design process of such engineering systems should thus consider their systemic context (de Weck et al., 2011; Isaksson et al., 2022).

2.3.1 The engineering design process

Numerous frameworks support the systematic design and development of products or systems, such as by Pahl and Beitz (1996) and Ulrich et al. (2020), where each aims to provide a general framework for the systematic development and management of complex products or systems applying science and engineering to create means satisfying the needs of a defined stakeholder (Pahl and Beitz, 1996). Figure 2.1 illustrates the product development process proposed by Ulrich et al. (2020), which extends from identifying the market need for a new product or system to preparing and ramping up the manufacturing of this product. This thesis is mainly concerned with the concept-development and system-level design phases, highlighted in Figure 2.1. A concept regards a description of a product or system, which can be further developed into something manufacturable and marketable. While the customer needs are assumed to be identified, the concept-development phase aims to develop sets of concepts satisfying these needs. Furthermore, refining and testing enable identifying concepts that best fulfil the identified needs, which can then be selected for further development.

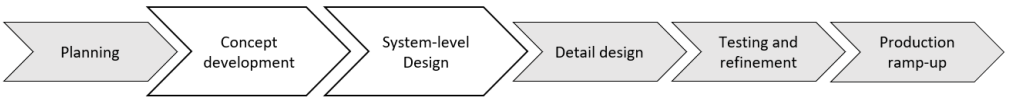

Figure 2.1: The generic process to engineering products and systems adapted from (Ulrich et al., 2020).

2.3.2 Integrated product development

Integrated product development is a strategy proposed by Andreasen and Hein (1987) to develop products by simultaneously exploring product development activities of different disciplines. This strategy contrasts with a sequential approach to product development, where usually one activity is finished before moving to the next. Disciplines regard the product design, production system design and marketing, between which a continuous information flow is established; thus, the market can be continuously

monitored while developing the product and production system designs. To concurrently consider several disciplines, enabling an information flow between the disciplines reduces the risks of mismatches between them. These types of mismatches in a sequential product development approach could require iterations back to previous stages and thus increase the risk of lead-time extensions (Andreasen and Hein, 1987).

2.4 Mass customization

With an increased market performance as a driver, product customization generally implies an increase in the external product variety offering of a company; however, increased production costs are induced due to an increased production complexity (Randall and Ulrich, 2001; ElMaraghy et al., 2013). As a production paradigm, mass customization emerged with the intent of increasing market value by providing customers with customized products with nearly mass-production efficiencies (Tseng and Jiao, 2001).

2.4.1 Product and production complexity as a consequence of customization

An increased product variety requires increasing the number of product designs, components to be produced for the products, manufacturing processes to manufacture the increased variety of components and the variety of products. Beyond manufacturing, consequential increases are inevitable in the effort required for managing the product designs, components, manufacturing processes and the supply chain as well as in the resources required to manage these beforementioned disciplines (Kvist, 2010). Yang and Burns (2003) remark that the consequences of this increased production complexity should be considered for both the internal operations of a stakeholder and the operations of SC partners. Stäblein et al. (2011) exemplify the effects of a growing product portfolio complexity on manufacturing costs and lead times, and Trattner et al. (2019) add that the risk of increased errors results from the quality and delivery reliability as well as increased risks in operation, product quality issues and manual handling. A trade-off exists between product variety and SC performance (Thonemann and Bradley, 2002; Barroso and Giarratana, 2013; Syam and Bhatnagar, 2015), and the key question is how much variety to offer. Answering this question requires addressing the trade-off between the increased costs and benefits (Lyons et al., 2020). When the

complexity of a product portfolio is discussed in thesis, a product portfolio with a high product variety is implied, and hence these terms are used interchangeably.

2.4.2 Mass customization principles

A mass customization paradigm can be defined as satisfying the wide array of customer needs with products that have been developed, produced, marketed and supplied by affordable means (Pine II et al., 1993; Hu, 2013; Mourtzis, 2016). The three prominent mass-customization principles outlined by Hu (2013), which regard product variety management strategies, are *product family architectures*, *reconfigurable manufacturing systems* and *delaying differentiation*. Each principle can facilitate complexity mitigation and/or complexity management, and different researchers use derivative but interconnected terms for these beforementioned principles. The derivative terms or differences between are not further discussed, but the selected terms for a pharmaceutical context and their intended meaning are subsequently presented.

2.4.3 Product family architectures

Hu (2013) describes product family architectures as a collection of shared functional modules from which by assembly, i.e., combining these modules, sets of derivative product variants, i.e., product families (Robertson and Ulrich, 1998) embracing modular product architectures can be generated. According to Meyer and Lehnerd (1997), these product family architectures can be termed *product platforms*, which is used in this thesis.

Modular product architectures are established through the act of *product modularization*. Product modularization is a proven strategy to generate external product variety at low cost (Meyer and Utterback, 1993; Robertson and Ulrich, 1998). Product modularization requires well-established product architectures as a foundation.

Product Architecture

Ulrich (1995) provides a prominent definition of product architecture, meaning the systematic allocation of product functions into physical components i.e., modules. Product architecture is required for configuring product variants dictating the collection of the modules. Each function within the modules then contributes to the overall product function (Ulrich and Eppinger, 2012). The *modular* approach to product variety implies

modules embedding one or a few functions of the product, which interact with one another to form the product. A modular product architecture brings flexibility by keeping the modules decoupled by their interfaces and then adding, removing and interchanging modules. Practicing these strategies for flexibility enables configuring sets of derivative product variants (Fujita, 2002; Du et al., 2014). Du et al. (2014) describe the scalar product architecture as another approach to product variety. A *scalar* approach is founded on a rigid product architecture with fixed interfaces between the physical components realizing product functions; however, the design parameters of these components are defined variables to enable changing values of the design parameters, and thus variety can be established (Simpson et al., 2001).

Function-means modeling, EF-M and CC

Function-means modeling, originally developed by Tjalve (1976) and Andreasen (1980), is an approach to establishing product architectures and has evolved over time. Through function-means modeling, the product's design rationale is expressed in terms of the product's functions and further subfunctions to these functions and their means, which intend to realize these subfunctions by serving as solutions. Function-means trees are an effective tool to visualize such function-means breakdowns of a product (Malmqvist, 1997). The starting point is to define an overall functional requirement (FR) for the product for which a means is defined to solve this FR; then, further decomposition is performed since lower-level FRs to the defined means emerge and, likewise, to these lower-level FRs means are searched for. This breakdown is performed until the desired level of detail of the product functions and their means are achieved; thus, the product's design rationale (DR) becomes represented as a tree structure based on Hubka's law (Malmqvist, 1997).

Schachinger and Johannesson (2000) enhanced function-means modeling and introduced constraints to the functional bandwidth of the FRs, thereby limiting the means of the respective FR. Hence, this version of the function-means modeling is, in this thesis, called enhanced function-means (EF-M) modeling. The configurable component (CC) method is a further evolvement of the EF-M method, where the product architecture is described through independently operating CC objects embedding one or a few functions of the product that contribute to the product's overall function (Claesson, 2006). In the CC method, each CC object is expressed in terms of its FRs and design solutions (DSs). The collection of these CC

objects establishes a modular product architecture. Within the CC objects, defining functional bandwidths to the FRs and defining the DSs to satisfy the functional bandwidth of the FRs establish the scalable property of each CC object, thereby achieving a scalar product architecture (Claesson, 2006). The CC thus represents an approach to integrated modular and scalar product architecture. Although the EF-M and CC methods are concerned with describing the product architecture in functional terms, they fail to capture the physical realization of the product. The physical realization is captured in the DSs to some extent but is deemed insufficient; thus, Levandowski et al. (2014) and Michaelis et al. (2015) proposed approaches to establish a connection between the product functions and means to product components (COs). Similar to the tree structure of the function domain, the COs describe the product using a component tree, which establishes concrete representations of otherwise abstract function models since the COs give a physical realization to the components and constitute the product by defining the components' design parameters, such as the geometrical dimensions or material characteristics.

Function-means modeling, EF-M and CC methods are generally concerned with product architecture descriptions of isolated disciplines; however, approaches to integrated architecture descriptions of disciplines have been proposed. Michaelis et al. (2013) connected the product design and manufacturing system design using the CC method. This approach emphasizes the interaction, identification and definition between the product and manufacturing system disciplines. Levandowski et al. (2014) elaborated the approach by Michaelis et al. (2013) and proposed identifying the manufacturing operations in which the product is transformed. The manufacturing system and product are then integrated in the manufacturing operations. Landahl et al. (2017) suggested an approach called the *producibility model*, which builds on the model developed by Madrid et al. (2016) to model the interaction between disciplines. Modeling this interaction implies identifying parameters that control the operational outcome, meaning they control the desired output of the product transformation within the capabilities of the manufacturing system performing this transformation.

Product modularization in a pharmaceutical context

Modularization has been discussed in a pharmaceutical context; for example, Körber Pharma Packaging (2018) and Savage et al. (2006) discuss the modularization of pharmaceutical packaging. Pharmadule Morimatsu

AB (2019) discusses modular fabrication and mentions oral solid dosage forms as their expertise; however, their expertise concerning customization to individual patient needs is unclear. In addition, as described in Section 2.2.2, modular pharmaceutical products have been discussed as holding customization potential; nevertheless, to the best of my knowledge, approaches utilizing product modularization as a design strategy for the pharmaceutical product in a mass-customization context are not represented.

2.4.4 Reconfigurable manufacturing systems

Hu (2013) describes reconfigurable manufacturing as a manufacturing system's ability to respond to high product variety and changing product mix and demand. Reconfigurable manufacturing systems aim to increase process flexibility to handle producing a complex mix of products; thus, the term *process flexibility* is used in this thesis. Reconfigurable manufacturing systems (RMS) were first proposed by Koren et al. (1999), which aim to enable a rapid, cost-effective response to changing market needs, uncertainties in product mix and demand. These machines should enable hardware- and software-level adjustments of the manufacturing system to change function and scale in response to sudden market changes (Koren et al., 1999; ElMaraghy, 2005).

Process flexibility in a pharmaceutical context

Govender et al. (2020c) describe *process flexibility* as a strategy for managing the emerging high-variety, low-volume challenge of pharmaceutical mass customization. Section 2.2.3 discussed a few approaches addressing this volume-variety challenge in pharma such as continuous production or additive manufacturing. While continuous production can, for example, increase production scalability compared to conventional batch production, there is a lack of studies concerning the production feasibility of treatments tailored to the individual needs of the patient. Additive manufacturing might provide opportunities to manufacture complex mixes of products; however, to the best of my knowledge, there is a lack of solutions to the economic challenge of wide-scale availability of such products.

2.4.5 Delaying differentiation

Hu (2013) describes delaying product differentiation, or *postponement*, which is the term used throughout this thesis, as delaying the point where the product variants acquire their unique characteristics. In this thesis,

this point marking where product parts become dedicated to a product variant is called the *point of variegation*. Delaying the *point of variegation* is a strategy to mitigate complexity and thereby improve responsiveness in production and reduce production costs (Lee and Tang, 1997). According to Kvist (2010), the *point of variegation* should be postponed to the latest possible point in the SC.

Postponement in a pharmaceutical context

Verhasselt and Friemann (2012) developed concepts for packaging and labeling postponement in a pharmaceutical SC and identified factors for the economic evaluation of pharmaceutical postponement. In the study by Ladsaongikar and Martinez (2016), to manage a complex product portfolio, the postponement of the packaging process of drug products was suggested as a strategy enabling a quick response to demand. Nolan and Ploszczuk (2021) performed a case study on therapeutics of rare genetic diseases, where they suggest a strategy to finalize the product and label it after the customer order has been received and then directly ship the product to the customers and thereby decrease lead times; however, these beforementioned studies focus on packaging and labeling postponement, and to the best of my knowledge, no studies concern the postponement of the pharmaceutical product for customization.

2.5 Value and value-driven design

The aim of developing products should be to increase the value that the product delivers to a customer or stakeholder. Product customization is an approach to increasing product value since it aims to serve the needs of individual customers. According to Hazelrigg (1998), value is the intuitive criterion used to make product design decisions. Product value is defined by Lindstedt and Burenius (2003) as the ratio between the benefit and cost, where benefit regards the perceived benefit of the customer and satisfaction of their needs, while cost concerns the use of resources of the customer and can be expressed in terms such as time, money or effort.

2.5.1 Value-driven design

Value-driven design is decision-based engineering design and usually a process by which system-level requirements are captured early and used as criteria to select the most suitable concept satisfying these system-level requirements (Collopy and Hollingsworth, 2011; Bertoni et al., 2018).

Value-driven design aims to describe the value provided by the product to the customer and stakeholders, and it uses this value as a decision criterion rather than narrowly focusing on technical requirements in which the customer needs are quickly lost, which is the traditional approach to perform design-decisions in systems engineering (Isaksson et al., 2013). Value-driven design is a technique to optimize the overall system, with respect to system requirements, rather than each component (Price et al., 2012).

There are numerous approaches to value-driven design. Concept screening (Ulrich et al., 2020), initially known as the method of controlled convergence by Pugh (1990), is a systematic method to describe customer and stakeholder needs with the purpose of qualitatively comparing early-stage concepts to a reference concept concerning selected criteria. This approach facilitates an engineering discussion of concepts with respect to the needs of customers and stakeholders (Frey et al., 2009). Rondini et al. (2020) discussed the controlled convergence method enabling concept screening and selection of still-immature, heterogeneous concepts. Moreover, they highlighted that less tangible value aspects, such as knowledge and experience-related dimensions, can be captured in the concept selection process, which might be more difficult to capture in a deterministic model.

The concept scoring matrix by Ulrich et al. (2020), which is closely related to value assessment by Pahl and Beitz (1996), is another systematic approach to assessing concept value. This quantitative approach is a weighted-average approach of normalized scores of selected performance criteria, where the relative importance of these criteria concerning the remaining criteria is established as weights. The concepts performing comparatively well on higher weighted performance criteria achieve a higher value.

An approach to concept selection called the concept design analysis (CODA) method was proposed by Eres et al. (2014), which poses similarities with the concept scoring matrix and enables value-based decision-making by assigning overall design merits to concepts. Customer and stakeholder needs are thereby captured and rank-weighted, conceptual engineering characteristics are described in measurable terms and the correlation is established between engineering characteristics and their impact on the satisfaction of customer needs. This correlation is assessed using strong, weak and minimal (0.9-0.3-0.1-0) coefficients, representing a quantifying approach of quality function deployment (QFD). This

correlation is not captured in the concept scoring matrix. Early Value Oriented design exploration with knowledgE maturity (EVOKE) by Bertoni et al. (2018) is another value-driven design approach based on the CODA method and has the purpose to maximize awareness of the value contribution from alternative subsystem selections on the overall system level. Finally, Bertoni (2019) showed how a multi-criteria decision-making process can be applied for concept selection from a value and sustainability perspective. This process utilizes the CODA method. These methods by Eres et al. (2014), Bertoni et al. (2018) and Bertoni (2019) enable simulating various business strategies by modifying the rank-weights of stakeholder needs.

2.5.2 Value in a pharmaceutical context

A discipline called health economics aims to facilitate decision-making at all levels of healthcare by providing frameworks for relating healthcare innovation benefits to the resources incurred during production (Kernick, 2003). Cost-effectiveness analysis is the most commonly used approach and is usually presented as ratios such as cost per gained life years (Kernick, 2003).

The quality-adjusted life year (QALY) is another measure that incorporates both quality and quantity of life, where the effectiveness of a new medicine is compared to the current one to assess the quality of life acquired by using the medicine rather than solely the extra life years; however, using such an approach requires data regarding health outcomes (Salomon, 2017; Terkola et al., 2017). Hatz et al. (2014) performed a systematic literature review to elicit the cost-effectiveness of individualized medicine, and they argued cost-utility analyses (such as QALY) to be the most common approach to assess cost-effectiveness. Terkola et al. (2017) discussed the challenges of describing the value of personalized medicine: firstly, there is no accepted definition of value; and secondly, using QALY to evaluate personalized medicine is challenging due to the absence of real-world data.

Hörn et al. (2014) proposed an approach to describe the benefit of new drug products by assessing the treatment outcomes achieved in clinical trials. Srai et al. (2015) discuss pharmaceutical product customization and cost; however, this study has a narrow cost focus and fails to address the patient benefit delivered by pharmaceutical product customization. To the best of my knowledge, no approach describes the system-level value of

customized pharmaceutical products regarding a patient benefit while the product has been offered to the patient and its costs of manufacture and supply.

2.6 Results of literature review

Reviewing the literature identified the following research gaps concerning challenges in pharmaceutical product customization:

- The conventional pharmaceutical product, when embracing an integral tablet design, results in challenges regarding the adaptability, concerning key product design requirements, required in a customization context. Current commercial product designs, such as tablets enabling splitting and multiple-unit dosage forms have not been designed for a customization context, and their sufficiency in a customization context is debatable. There is thus a lack of pharmaceutical product designs suitable for cost-effective customization.

- The pharmaceutical production platforms in a mass-production context are characterized as being resource tedious with low flexibility and low utilization rates. Process flexibility is a prerequisite for a customization context to enable producing and managing a high-variety, low-volume product portfolio. Few studies investigate whether the required process flexibility can be achieved by current mass production platforms.

- There is a lack of approaches to assess the system-level cost- effectiveness of customized pharmaceutical products and production system designs. The costs of pharmaceutical product customization have been discussed but were isolated from discussions on increased patient benefit. Approaches to assessing the cost-effectiveness of pharmaceutical products are generally present in literature, such as QALY; however, they require data regarding health outcomes and have not been shown as a tool to estimate the patient benefit and production cost in the context of customized pharmaceutical products.

The research presented in this thesis aims to address these abovementioned gaps. To achieve this goal, concepts from the fields of engineering design, mass customization and value-driven design have been adopted and adapted into the pharmaceutical context.

3

Research approach

This chapter describes the research approach applied in this thesis by defining the engineering design research and describing how this research fits the definition. Furthermore, common design research methodologies are discussed and used as a basis to discuss the applied research approach along with research methods and outcome evaluation.

3.1 Design and engineering design research

Design regards a complex term since it can assume different, interrelated meanings. A design can be a tangible or intangible product and can regard the activity to create a product or to generate knowledge about the product. Simon (1996) defines design as the act of changing an existing situation to a desired one.

Engineering design research is defined by Horváth (2001) as "generating knowledge about design and for design." According to Blessing and Chakrabarti (2009), design research has two aims which are ideally considered jointly: the first aim is to generate an understanding of design by formulating and validating theories and models of the phenomenon design; the second aim is to enhance the engineering design as a practice by developing and validating tools, methods or methodologies based on the models and theories of the phenomenon design that support conducting the design.

The design phenomenon for which understanding is created by the

research performed in this thesis regards *mass-customization principles enabling the cost-effective customization of pharmaceutical products*. While formulating theories and models of this phenomenon, conceptual models (referring to design methodologies and models) and knowledge have been generated to study the phenomenon and support its practical activity of design. The research presented in this thesis thus fits within the second aim of design research, which is to enhance the design as a practice, specifically in the context of design for pharmaceutical customization. The nature of this research is theoretical and adapts engineering design theories, methods and tools developed for other, non-pharmaceutical contexts into the pharmaceutical context. This adaption and knowledge thereby generated, which is used to support the design practice in a pharmaceutical context, are the major research outcomes of this thesis.

3.2 Frameworks for design research

The scientificity of design research remains a debated topic. In contrast to natural sciences such as physics, chemistry or biology, which study natural phenomena, design research studies the artificial. To counter this critique regarding scientificity, research methodologies are suggested to guide and support the research performed in the engineering design research field to increase the confidence in producing scientifically valid research results. Blessing and Chakrabarti (2009) argue that the chances of producing successful research outcomes might increase while supporting the research process with a framework for design research. Successful research outcomes are described as valid and useful results.

A few frameworks exist for engineering design research. The design research methodology (DRM) by Blessing and Chakrabarti (2009) and the spiral of applied research by Eckert et al. (2003) are frameworks that to different extents have been applied in the research presented in this thesis. While these frameworks progressively ensures the scientificity of the performed research, there is another facet to engineering design research which rather aims to ensure research scientificity in retrospect, commonly called *validation*, e.g., Pedersen et al. (2000); Isaksson et al. (2020). The validation square Seepersad et al. (2006) is one such framework for research validation. These frameworks will be described below.

3.2.1 Design Research Methodology

The DRM by Blessing and Chakrabarti (2009) is divided into four research stages: *research clarification*, *descriptive study I*, *prescriptive study* and *descriptive study II*, which are described below.

Research clarification

The aim of the *research clarification* (RC) stage is to establish the research focus, where the area of a planned research contribution is identified and relevant disciplines for the performed research are reviewed. In this stage, the current state is described along with the desired situation into which the current state is to be changed by the performed research. The research goals expected to be realized through the performed research are identified, and thus hypotheses and research questions are formulated. Furthermore, the preliminary set of success criteria is defined. Measurable success criteria are also defined since the success criteria of the research are seldom measurable within the scope of the research performed. These criteria determine the success of the research and align with the defined research goals. The literature review is the main method of this stage.

Descriptive study I

The second stage of the DRM is the *descriptive study I* (DSI) stage, where a better picture of the current state is comprehended and refined through an initial description of the current state by reviewing empirical research within the researched topic, performing empirical research and by reasoning. More clarity regarding the research goals and measurable success criteria is hence acquired. Furthermore, key factors are identified that will be addressed by the performed research to change the existing situation to the desired one.

Prescriptive study

Based on the understanding acquired in the DSI stage, support is developed in the *prescriptive study* (PS) stage, which can include software, knowledge, methodology, checklist and so forth. The aim is to use the support to change the existing situation to the desired one. Such support intends to facilitate the design in practice and increase the understanding of the design phenomenon studied. The main asset of development is

the creativity of the researcher. Initial evaluation of the support should be conducted, such as checking the consistency and completeness of the support.

Descriptive study II

This stage aims to use empirical studies to evaluate the usability and usefulness of the support developed during the PS stage. This evaluation includes assessing whether the support can change the existing situation to the desired one. The measurable success criteria outlined in the DSI stage evaluate how well the situation has been changed to the desired one, such as by conducting empirical studies to test the support. Furthermore, necessary improvements to the support are identified as a result of evaluating the usability and usefulness of the support. Finally, the assumptions underpinning the current and desired situation should be evaluated.

3.2.2 The spiral of applied research

The spiral of applied research by Eckert et al. (2003) complies with the DRM to some extent. The spiral of applied research addresses the integrated nature of design research to produce outcomes with scientific and industrial relevance, and it aims to address the multidisciplinary nature of design research and the consequential challenge of predicting the consequences of implementing research findings in an industrial context. Eckert et al. (2003) thus suggest introducing an evaluation exercise accompanying each research activity as a primary research theme to validate the research findings. This approach consists of four stages of research activities: *empirical studies of design behavior*; *development of theory*; *development of tools and procedures*; and *introduction of tools and procedures* as well as evaluation exercises accompanying each activity; *evaluation of empirical studies*; *evaluation of theory*; *evaluation of tools*; and *evaluation of dissemination*. All research activities generate outputs such as information and insights, which can be further used to formulate requirements of the research efforts at another stage, thereby forming a logical spiral for conducting engineering design research. This approach diverts from the DRM which mainly discusses evaluation in connection with the developed support, its usability and usefulness in the DSII stage; nevertheless, both the DRM and spiral of applied research seek to provide structure for conducting and evaluating research.

3.2.3 Validation and verification of design research

Within the validation of design research, the common themes to address are validation and verification (Isaksson et al., 2020). These themes are associated with two fundamental questions: *Did we do the right things?* refers to the validity of the research findings, and *did we do the things right?* refers to the reliability of the research process. *Validity* intends to increase confidence in the ability of the research outcomes to describe the measured phenomena and by *verification* the trustworthiness of the research outcomes can be increased (Creswell, 2014; Le Dain et al., 2013).

Buur (1990) suggests that the quality of research can be confirmed by *verification by acceptance*, which aims to validate theories, methods or methodologies through their acceptance by other designers. Almefelt (2005) suggests using *transferability* to claim validity by the degree of generalization beyond the research setting. According to Almefelt (2005), a careful description of the conducted research regarding its context, hypothesis, sample and so forth can increase the degree of transferability.

For research verification, research consistency should be ensured; for example, Buur (1990) suggests using *logical verification* to assure that no internal conflicts exist between the theoretical elements synthesized into new theories or methodologies. The consistency of these theories and methodologies synthesized from the theoretical elements must remain consistent with the theory after synthesis. Furthermore, all phenomena studied in the literature or empirically should be explained by the theory, meaning the theory must be complete (Buur, 1990). Yin (2018) suggests the criterion *internal validity*, which is the confidence in the research findings being affected by the studied variable rather than by external effects.

The validation square

A major aim of engineering design research is to improve the practice of design. Thus, design research outcomes often regard design methods, methodologies and approaches to facilitate the practice of design. Complying with this aim, Seepersad et al. (2006) describe research validation as "a process of building confidence in its usefulness with respect to a purpose," where "its" refers to the proposed design method. Seepersad et al. (2006) presented a prescriptive and systematic approach to validate and verify a *design method*, or *support* which is the term used by Blessing and Chakrabarti (2009), called the validation square, presented in Fig-

ure 3.1. The validation square, which is based on the works by Pedersen et al. (2000), incorporates the elements of evaluation suggested by Blessing and Chakrabarti (2009) and can be viewed as a complement to the DRM framework.

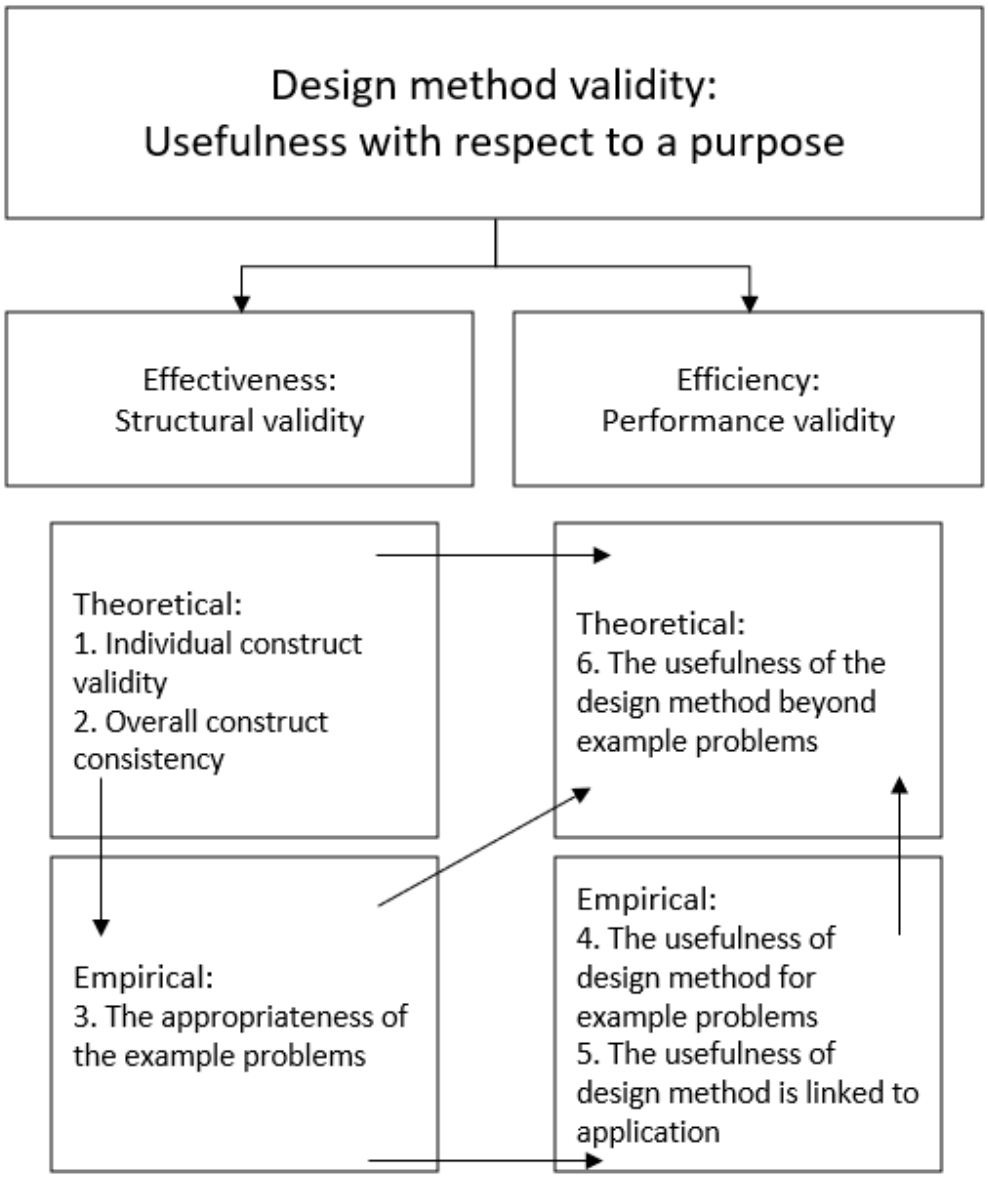

Figure 3.1: The validation square redrawn from Seepersad et al. (2006)

The validation square suggests starting by defining the design method requirements against which the evaluation of the design method's usefulness shall be performed. These requirements align with the measurable

success criteria suggested by Blessing and Chakrabarti (2009); however, the measurable success criteria are defined at the beginning of a research project before performing the research activities. Two categories of requirements are suggested: The first category relates to the design method process, such as the efficiency of the method, and the second relates to the design method outcomes, such as the quality of the products produced by the design method.

When the requirements of the design methods have been determined, the validation square consists of four stages of evaluation. Two stages aim to assess whether the design method correctly provides a solution: *theoretical structural validity* and *empirical structural validity*.

Theoretical structural validity is a domain-independent verification for which two steps are suggested:

1. To accept individual construct validity;
2. To accept the internal consistency of the design method assembled from the individual constructs.

To fulfill step (1), confidence should be built in the design method so that it generates adequate information and is based on valid assumptions. Seepersad et al. (2006) thus suggest conducting literature reviews to show the wide acceptance of the individual constructs of design method, which closely relates to the *verification by acceptance* criterion suggested by Buur (1990). To fulfill step (2), the suggested approach is to describe the information flow throughout the individual constructs of the design method. Inputs into constructs that likely cause the construct outputs should be documented, and this output should be verified an adequate input into the next construct. This approach aligns with the concept of *logical verification* by Buur (1990). To demonstrate internal consistency, Seepersad et al. (2006) suggest, for example, using flow charts to describe information flow, logical verification by logical arguments, formal or informal mathematical proofs or empirical techniques to test the capability of the method.

Empirical structural validity is domain dependent and consists of the following step:

3. To accept the appropriateness of the case example.

In this step, confidence is built by establishing the appropriateness of the selected case examples used to verify the performance of the design

method. This can be done by showing the similarity between the selected case examples and problems generally addressed by the constructs, by illustrating the adequateness of the case examples as representatives of the problems for which the design method is intended and finally, by showing the adequateness of the data collected to support conclusions drawn regarding design method performance.

To assess whether the design method provides the correct solutions two stages are suggested: *empirical performance validity* and *theoretical performance validity*.

Empirical performance validity is a domain-dependent validation for which two steps are suggested:

4. To accept the usefulness of the design method, concerning its initial purpose, for some case examples;
5. To accept that this usefulness is linked to the application of the design method.

This stage is specific to the selected case examples. The usefulness of the design method should be evaluated regarding the requirements defined at the start. To verify that the usefulness is linked to the design method application, the suggested approach is to compare the achieved solutions with or without using the constructs/design method.

Theoretical performance validity is a domain-independent validation for which the following step is suggested:

6. To accept the design method usefulness beyond the case examples.

This step builds confidence in the generalizability of the design method beyond the case examples investigated using inductive reasoning and based on the successful validation of the preceding stages of the validation square. This stage closely relates to the concept of *transferability* by Almefelt (2005).

3.3 The applied research approach

The targeted outcome of the research performed in this thesis is the appended publications. The research activities which resulted in the appended publications were more or less conducted in parallel; however,

the DRM framework (Blessing and Chakrabarti, 2009) is used to communicate the conducted research. The DRM is also utilized as a checklist of the types of activities that should be performed to increase the success of the research project. This section describes the research performed in each publication using the DRM stages illustrated in Figure 3.2, where the utilized research method is described for each stage. Although the DRM discusses the activity of research evaluation to some extent, mainly in the DSII stage, research evaluation is performed in terms of the *validation square* by Seepersad et al. (2006). In Figure 3.2, the final research stage is thus termed evaluation rather than DSII. Each stage of the DRM is covered in each paper to different extents.

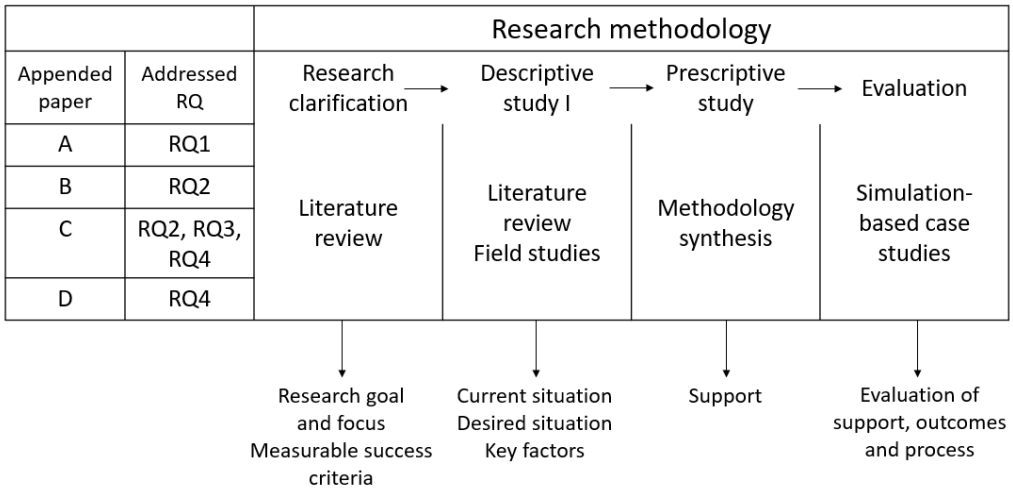

Figure 3.2: Illustrating the applied research approach, the main methods utilized as well as the addressed RQs of each publication.

3.3.1 Research clarification

The starting point of research is to analyze the research problem, which regards the industrial challenge of non-optimal therapeutic outcomes for patients. Literature reviews are conducted as a main method, which allows elaborating on the current challenging situation. The conclusion is that a major research gap for the non-optimal therapeutic outcome of the patients concerns the lack of cost-effective approaches to design, manufacture and supply pharmaceutical products customized to individual patients' needs.

Reflecting on the research goal and desired situation entails a cost-effective provision of customized pharmaceutical products that enhances

the therapeutic outcome of patients. The hypothesis is formulated based on the research problem and the current and desired situations explored. The hypothesis is divided into research questions to enable testing the hypothesis in parts (see Section 1.3). These research questions correspond to the scoping of respective appended papers and to the mass-customization principles *product modularization*, *process flexibility* and *postponement*, which are explored as solutions to achieving a cost-effective pharmaceutical customization context. The research focus of paper A is to explore *product modularization* as a design strategy to establish customized pharmaceutical products and aims to answer RQ1. Paper B focuses on exploring the *process flexibility* of the current manufacturing system of pharmaceutical products when operated in a customization context and aims to capture the challenges of cost-effective manufacturing; thus, paper B aims to partly answer RQ2. Paper C aims to answer RQ2, RQ3 and RQ4 by exploring the mass customization principle of *postponement*. RQ2 is addressed by eliciting challenges of the cost-effective operation of the current pharmaceutical SC in a customization context, and then RQ3 is addressed to propose strategies to enable a cost-effective operation of the pharmaceutical SC chain and to capture the challenges of these strategies. Answering RQ2 and RQ3 also captures the effects of postponing the *point of variegation* in the SC, thereby addressing RQ4. Finally, paper D explores an integrated approach of the principles *product modularization* and *postponement* for the design, manufacturing and supply of customized pharmaceutical products, and it generates an answer to RQ4.

After outlining the desired situation, the success criteria of the research project can be identified and includes the cost-effective product design, manufacturing and supply of customized pharmaceutical products. Cost-effectiveness describes patient benefit and production cost and is achieved when the patient benefit, increased through pharmaceutical product customization, exceeds the production cost of providing it; however, the trade-off between patient benefit and production cost cannot be measured within the scope of this thesis. Measurable success criteria proxies for cost-effectiveness have been formulated using various terms for patient benefit and production cost formulated throughout the thesis. Finally, the concept of *value* has been used to consolidate the patient benefit and production cost terms into a single measure. Value has been used to indicate the cost-effectiveness of any customized pharmaceutical product and its production system design.

3.3.2 Descriptive study I

Further clarification of the research gap through literature reviews facilitates identifying key factors to be addressed throughout the research project in order to change the current situation to the desired one. These key factors are *pharmaceutical product design*, *manufacturing system design* and *supply chain design*.

In paper A addressing RQ1, further understanding of the challenge of current pharmaceutical product design and its limitations in a customization context was acquired by a review-based approach; thus, the key factor *product design* was mainly addressed. Furthermore, approaches to pharmaceutical product customization and their limitations from a cost-effective perspective were studied. In addition, the lack of full exploration was verified regarding commercially existing multiple-unit dosage forms for a customization context. The prescriptive nature of RQ1 requires exploring possible solutions; for this purpose, topics were studied such as mass customization and theories and methods from the engineering design field such as product modularization, product architecture, product platforms and value-driven design. From these topics, theoretical elements were collected to serve as constructs which were then synthesized into the support developed in the PS stage.

At this stage in paper B addressing RQ2, literature reviews were conducted to better understand pharmaceutical manufacturing challenges, where the focus was on the current manufacturing system's insufficient flexibility for the cost-effective manufacturing of customized pharmaceutical products. Furthermore, the lack of integrated approaches to product and manufacturing system design in a pharmaceutical context was addressed; thus, the key factors addressed in paper B were *product design* and *manufacturing system design* in an integrated manner. To investigate the challenges of manufacturing customized pharmaceutical products, a support was developed in the PS stage, and in preparation, engineering design topics such as integrated product development and function-means modeling were reviewed to collect theoretical elements.

Paper C further addressed RQ2; however, rather than focusing on the technical details of manufacturing (the scope of paper B), paper C addresses challenges of operating the pharmaceutical SC in a customization context from an end-to-end perspective. The research gap was addressed regarding the absence of system-level analysis of pharmaceutical SCs operating in a customization context. Moreover, the research gap was

addressed regarding SC designs for the cost-effective manufacturing and supply of customized pharmaceutical products. Literature reviews focused on understanding the currently operating pharmaceutical SC; thus, paper C mainly addresses the key factor *supply chain design*. The descriptive nature of RQ2 aims to generate an understanding of the operation of pharmaceutical SC in a customization context; however, due to the absence of pharmaceutical SCs operating in a customization context, a support must be developed to describe this phenomenon. Literature reviews thus consisted of reviewing performance evaluation methods and performance criteria by describing patient benefit and production cost to align with the measurable success criterion. The literature was reviewed to identify performance criteria concerned with pharmaceutical production and to identify literature beyond the pharmaceutical context, such as literature concerning product portfolio complexity and operational performance. Paper C also addresses RQ3. Due to the prescriptive nature of RQ3, solutions to the previously elicited challenges were explored. For this exploration, business models beyond the pharmaceutical context that pose different degrees of postponement, manage a large product variety or operate in a mass customization context were studied and selected for adaption into a pharmaceutical context during the PS stage. Knowledge with respect to different degrees of postponement is thereby acquired and generates an answer to RQ4.

Paper D mainly addresses RQ4 and builds on Papers A and C and thus further concerns the research gaps of cost-effective product, manufacturing system and SC designs for a pharmaceutical customization context. In addition, Paper D concerns the lack of system-level models for integrated product and production systems enabling the assessment of cost-effectiveness in a pharmaceutical customization context. Paper D mainly addresses the key factors of *product design* and *supply chain design*. A support was developed during the PS stage to describe the phenomenon of product modularization and postponement in a pharmaceutical customization context facilitating a cost-effective environment for product design, manufacturing and supply, thus, the literature was reviewed to collect theoretical elements for this purpose. The topics for literature reviews mainly concerned product variety management and value-driven design.

3.3.3 Prescriptive study

In this stage, supports were developed to address the key factors defined in the DSI stage aiming for a change toward the desired situation. The main method of this stage is methodology synthesis, and the resulting supports are design methodologies and models. Paper A established a design methodology enabling the systematic redesign of the pharmaceutical product for customization. The methodology included developing a computational model of a product platform on which simulations can be performed, and simulations enable evaluating the effect of product design alternatives on value.

Paper B established a design methodology for the integrated design of pharmaceutical products and manufacturing systems. Based on the methodology, a computational model or a product and production system platform can be developed which enables simulating the consequences of product redesigns on the manufacturing system design and vice versa. The consequence assessment approach suggested is describing the value of integrated product and manufacturing system designs.

Paper C suggests models for reconfigured SC archetypes for a pharmaceutical customization context. These SC archetypes address the challenges of the cost-effective manufacturing and supply of customized pharmaceutical products. Furthermore, an approach to assess the value of these reconfigured SC archetypes is suggested.

Paper D proposes a design methodology for the integrated design and modeling of product and production system concepts in a pharmaceutical customization context. Using this methodology, computational models can be developed to perform simulations. These simulations aim to generate knowledge regarding integrated pharmaceutical product and production system concepts from a cost-effective customization perspective; thus, an approach to value assessment is suggested.

3.3.4 Evaluation

In this stage, the supports established in the PS stage are evaluated using the validation square by Seepersad et al. (2006). Requirements for the design method or support should be defined before the evaluation. The evaluation requirements of the research outcomes of this thesis originate from the measurable success criteria defined in the RC stage, meaning "the

cost-effective product design, manufacturing and supply of customized pharmaceutical products," where for measurability, cost-effectiveness is described in terms of *value*. These criteria are further refined here:

(A) From a *process* perspective, the supports developed in the PS stage should:

  i enable the design of customized pharmaceutical products by enabling the integration of product design requirements complying to patient needs;

  ii enable the design of pharmaceutical products with adaptable product design requirements according to individual patient needs;

  iii enable the integrated design of products, manufacturing systems and SCs;

  iv enable the assessment of the patient benefit, production cost and value of the established product, manufacturing system and supply chain designs.

(B) From an *outcomes* perspective, by applying the supports developed in the PS stage, cost-effective designs for pharmaceutical product and production systems in a customization context should be achieved.

Case studies were selected to demonstrate the application and usefulness of the supports developed in the PS stage. In Papers A, B and D, design methodologies were proposed to establish computational models and were evaluated from a process perspective to determine whether they are applicable for the task for which they were intended. To evaluate the supports from an outcomes perspective, simulation-based case studies were performed to assess the consequences of various product, manufacturing system and SC designs on cost-effectiveness in a customization context. For these simulation-based case studies, real-life therapy archetypes were selected as model therapies serving as input data. Paper C proposes conceptual models of reconfigured SC archetypes for cost-effective customization. The case study of paper C considered the analytical assessment of these SCs when operated in a customization context.

The case study in Paper A was designed to investigate the effects of various degrees of modularity of a tablet on cost-effective customization. These modular product designs thus embraced scalable dose strengths,

flexible target release profiles and scalable treatment sizes to various degrees. A selective serotonin reuptake inhibitor (SSRI) treatment was selected as a model therapy.

The case study in Paper B investigated the process flexibility of the current pharmaceutical manufacturing system from a cost-effective pharmaceutical customization perspective. In this case study, the product design for customization embraced a modular product design for dose strength scalability. The tablet punching machine was selected as a manufacturing system since, when modularizing the product for dose-strength scalability, the manufacturing system would require adjustment to the tablet punching machine to be able to fabricate modules. A commercial treatment for diabetes was selected as a model therapy.

The case study in Paper D investigated the effect on cost-effectiveness when integrating modular product designs with postponing the *point of variegation* in the SC. The SSRI treatment (from the case study in Paper A) and an antiepileptic drug were selected as model therapies. The selected SC archetypes for this case study are based on the SC archetypes proposed in paper C.

The results of the evaluation in terms of the validation square are discussed in Section 5.5.

3.3.5 Research methods

The research methods used for conducting the research are described herein and include field studies, literature reviews, methodology synthesis and simulation-based case studies.

Field studies

Field studies concern data-collection activities conducted outside a laboratory environment, such as observations and interviews (Creswell, 2014).

Prior to starting this thesis, I worked in the industry as a process engineer within pharmaceutical production, which enabled acquiring insights into pharmaceutical production processes and all surrounding activities making pharmaceutical production possible. Furthermore, this thesis project is conducted in close collaboration with a case company within pharmaceutical production, which has included visits to the company's production site. The knowledge and experience acquired from

working with and observing pharmaceutical production underpin the research performed in this thesis. Beyond the pharmaceutical production context, industries were visited in Sweden and in Japan, which included a two-week stay with the intent of visiting more than 10 manufacturing sites. The visited industries ranged from automotive to tooling and sensor production. The observations made during these visits gave insights into discrete part production and further inspired solutions to the research problem formulated in this thesis.

Literature review

Literature reviews represent the primary data collection activity of this research. According to Blessing and Chakrabarti (2009), literature reviews should continuously be performed during the research project to keep up with the latest findings within the research field. A literature review validates the research aim and research problems to be addressed and helps guide the research direction Blessing and Chakrabarti (2009).

In this thesis, literature reviews were used to establish a comprehensive understanding of the current situation regarding the pharmaceutical product, manufacturing system and SC designs as well as their challenges if operated in a customization context. Literature reviews were used to verify the gaps in cost-effective approaches to pharmaceutical product customization and to seek solutions to the established research gaps by studying literature from fields beyond the pharmaceutical context. Topics were reviewed such as mass customization, product variety management, SC management and integrated product development. From these topics, theoretical elements were collected and used during methodology synthesis to develop methodologies and models to solve the research problem addressed. The results of the literature review are presented in Chapter 2. In addition, the literature review results are presented in each, to this thesis appended, paper.

Methodology synthesis

The theoretical elements collected from literature reviews were synthesized into methodologies and conceptual models, which represent the supports developed in the PS stage. Two major facets of engineering design were selected to serve as a theory basis, from which constructs were selected to synthesize methodologies and models; function-means modeling for establishing product and manufacturing system architectures; value-driven design approaches for describing system value; and enabling

the cost-effectiveness assessment of various product and production system concepts.

In Papers A, B and D, function-means modeling provides the means for product and manufacturing system design. In paper A, the configurable component (CC) method (Claesson, 2006), is the main method for establishing customized pharmaceutical product designs, while the enhanced function-means modeling (EF-M) method (Schachinger and Johannesson, 2000) (of which the CC method is a further development) was used in paper B for product and manufacturing system design. Due to their function-modeling nature, the CC and EF-M methods enable integrating product/manufacturing system design requirements. In addition, these methods allow creating system modules by encapsulating functions into independently operating objects, constraining the bandwidths of functional requirements, defining non-functional requirements such as flexibility and exploring alternative solutions. In Paper B, the approach to integrated product and manufacturing system design adds the producibility model by Madrid et al. (2016) and Landahl et al. (2017) to EF-M tree modeling, which enables integrating the product design domain with the manufacturing system domain in the manufacturing processes and allows creating an environment for requirement change propagation throughout the integrated system model.

In each appended paper, value-driven design has been used for evaluating the cost-effectiveness, described as value, of the established product, manufacturing system and SC designs. Value-driven design approaches were chosen due to their benefits of promoting a value-based view in the decision-making process between different concepts rather than focusing on monetary terms. Value-driven design approaches also encapsulate several views of a product's lifecycle in contrast to purely focusing on cost, for example (Eres et al., 2014; Bertoni et al., 2018; Bertoni, 2019). Value-driven design enables capturing the ultimate aim of the pharmaceutical product, which is to bring societal benefits, in the decision-making process from a wide perspective. In addition, patient benefit is thus far a difficult concept to monetize. The concept scoring matrix of Ulrich et al. (2020) was adapted to enable a value assessment of the product and production system designs developed in papers A and D. The concept scoring approach enables the study of different weighting factors on the criteria used for assessment and thus enables simulating different business strategies, such as promoting patient benefits before production costs. Value was assessed as a trade-off between production costs and benefits for the patient. The

aim is to maximize value expressed as a weighted sum of patient benefit and production cost. In paper C, the concept screening matrix by Ulrich et al. (2020) is proposed to assess the value of the reconfigured SC designs, which enables a qualitative comparison of concepts based on selected criteria. The qualitative concept screening does not require detailed data and thus represents a convenient approach to visualize the needs of the customer in the early-phase concept-selection process.

Simulation-based case studies

Case studies can be performed to investigate contemporary phenomena within their real-life context in contrast to historical events. Case studies are well suited for exploratory research (Yin, 2018). In case studies, the phenomenon cannot be separated from its context since the boundaries between the phenomenon and the context are not evident, which contrasts with experiments where the variables to be studied should be isolated from their context. The phenomenon studied in this thesis is pharmaceutical mass customization; thus, separation from the context is not suitable and case studies fit the study purpose better than experiments. Mass-customization principles in a pharmaceutical context regard a nonexistent phenomenon, however, and this phenomenon is thus modeled as mathematical models. These models are also selected to describe and understand the generally complex phenomenon of pharmaceutical product and production system networks. Simulation studies have the advantage of resource-efficiently describing complex systems (Papakonstantinou et al., 2012); thus, the case studies conducted in this thesis do not fit within the definition by Yin (2018) but rather assume the nature of simulation-based case studies. The software configurable component modeler (CCM) (Claesson, 2006) is a platform modeling tool and is used for product and production system modelling and simulation. CCM represents a research tool that poses limitations; thus, support has been provided by MATLAB and MS Excel. Model execution is used to generate product and production system concepts, whose performance is assessed with respect to production cost, patient benefit and value. The simulations are thus used to determine the relationship between the key factors of product design, manufacturing system design and SC design and the measurable success criteria of production cost, patient benefit and value.

4

Research findings

This chapter presents the main findings from the conducted research. The key findings of the four, to this thesis appended, publications are described. This chapter discusses the findings connected to the mass customization principles. Furthermore, case studies were designed to investigate the implication of the mass customization principle(s) on cost-effectiveness. The case studies' aim and design are described and the results are presented.

4.1 Summary of the addressed mass customization principles in each appended paper

Table 4.1 summarizes the mass customization (MC) principle(s) addressed in each publication and described in subsequent sections. The MC principle(s) constituting the main theme of the paper is marked with a "✓✓," and the respective MC principles which attend to but do not constitute the main theme are marked with a "✓" in Table 4.1.

4.2 Paper A - Product modularization

The overall aim of paper A was to study *product modularization* for the cost-effective customization of pharmaceutical products. The research challenge addressed in paper A was the design of the current, *conventional*,

Table 4.1: Paper contributions to each mass customization principle: product modularization, process flexibility and postponement

MC principle	Paper A	Paper B	Paper C	Paper D
Product modularization	✓✓	✓		✓✓
Process flexibility		✓✓	✓	
Postponement			✓✓	✓✓

pharmaceutical product, which is dominated by a rigid, integral tablet design with low flexibility concerning adaptation to individual treatment needs of patients. This conventional tablet design thus challenges the compliance to patient needs and cost-effectiveness of the consequential increase in product variety due to customization. The findings of paper A aim to answer **RQ1**:

How can product modularization support the design of customized pharmaceutical products?

An approach to designing customized pharmaceutical products is proposed by applying the MC principle of product modularization. The configurable component (CC) method (Claesson, 2006) was adapted for this approach. A CC model is presented for pharmaceutical products that integrates three product design requirements as product functions that originate from individual patient needs and are adaptable for customization: a scalable dose strength, a flexible target release profile and a scalable treatment size. Furthermore, an approach to describe the value of these customized pharmaceutical products is proposed to support design decision-making between concepts concerning stakeholder needs. To describe concept value, the concept scoring approach of Ulrich et al. (2020) was adapted.

4.2.1 The integration of product design requirements into the pharmaceutical product

Figure 4.1 illustrates the resulting CC model of a pharmaceutical product which integrates the product design requirements *scalable dose strength*, *flex-*

ible target release profile and *scalable treatment size*. Each design requirement was realized through the respective CC object. The design requirement *dose strength* is incorporated in the CC object *API core* in which the FR *define dose* and the corresponding DS *API dose* were defined. The design requirement *target release profile* is incorporated in the CC object *release control system*, where the functional requirement (FR) *control drug release through top surface area* is solved by the design solution (DS) *lid* and the FRs *prevent bottom and side release* and *provide structural stability* are solved through the DS *cup*. Based on the DSs *lid* and *cup* defined in the CC *release control system*, a further breakdown into two separate CCs is performed, namely *lid* and *cup*, because these CCs will be physically realized as separate components and manufactured separately. Finally, the design requirement *scalable treatment size* is incorporated in the CC object *filling module*.

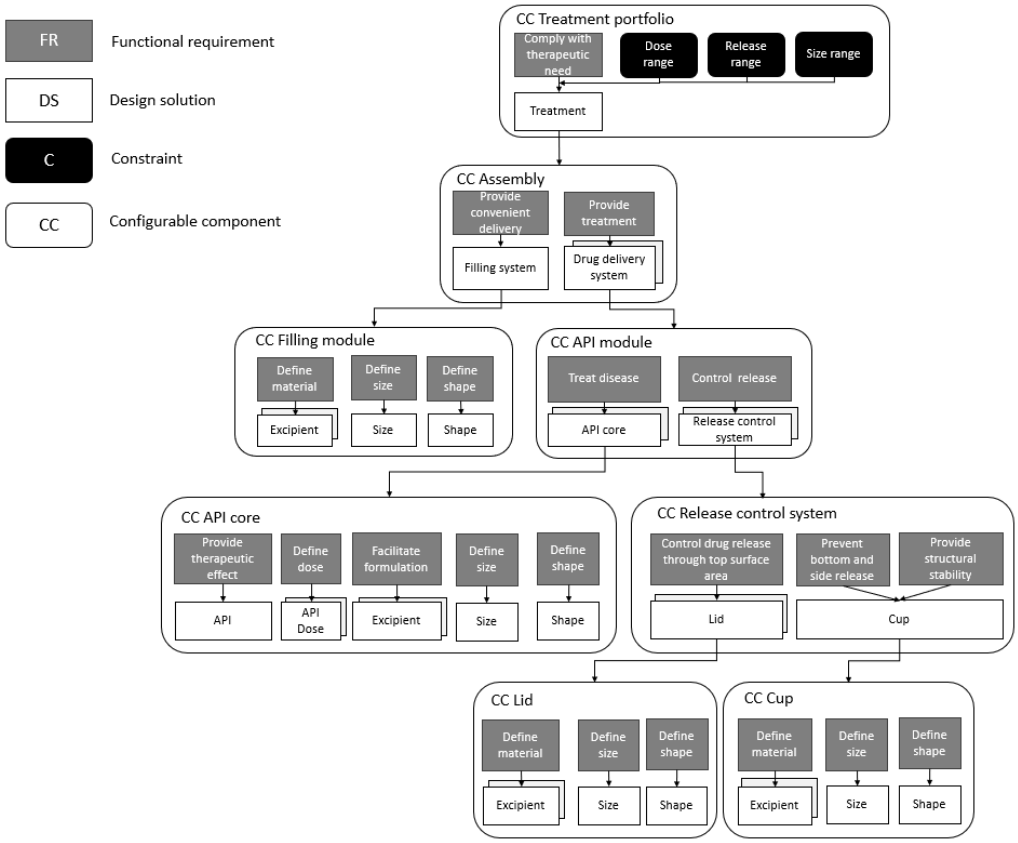

Figure 4.1: CC model of a pharmaceutical product integrating three product design requirements: *dose strength*, *target release profile* and *treatment size*

To enable the adaptability of the product design parameters for cus-

tomization according to patient needs, the flexibility of the design requirements is defined in the CC model constraints (Cs) regarding *dose range*, *release range* and *size range*. These constraints define the bandwidths of the design requirements; for example, dose strength flexibility is defined in the C *dose range* which describes the interval of dose strengths for which pharmaceutical products are configured. CC model execution generates instances of product variants (treatment variants) where the design parameters of product variants are assigned various parameter values within the described interval of the constraints. This approach represents a *scalable approach* to product variety; thus, treatment variants with different parameter values are configured from the same CC model. These treatment variants constitute a treatment portfolio consisting of a vast array of treatments aiming to satisfy the needs of a patient population.

Product variety is also achieved through the inclusion or not of the independently operating CC objects, representing a *modular approach* to product variety. By including excluding a CC object in the CC model, any product design requirement can be incorporated or excluded in the overall product. Treatment variants within a treatment portfolio include the same CC objects in their CC model; thus, another treatment portfolio is established by adding or excluding a CC object to the model. This type of modular variety is further illustrated in Section 4.2.2 by, for example, a treatment portfolio using lids and cups for controlled release and another treatment portfolio relying on the inherent release properties of the API core, thus not incorporating the lids and cups and thereby displaying two portfolios embracing different modular variety.

4.2.2 Modular product realization and assembly

While the CC model is an abstract representation of the product architecture, the CC model is connected to a component tree for realizability. In the component tree, the lower-level DSs of the FRs within the CC objects are described in design parameters creating components (COs) that allow the executability of the CC model (see Figure 4.2). The term *component* is connected to the CC method and the usage of component trees; however, the nature of these components can vary since they can assume the nature of parts, modules and assemblies.

Figure 4.2 shows the realizable components that comprise the physical product. The CC *API core* is connected to the CO *API core* where design parameters of DSs within the CC *API core* are defined, and thus the physical

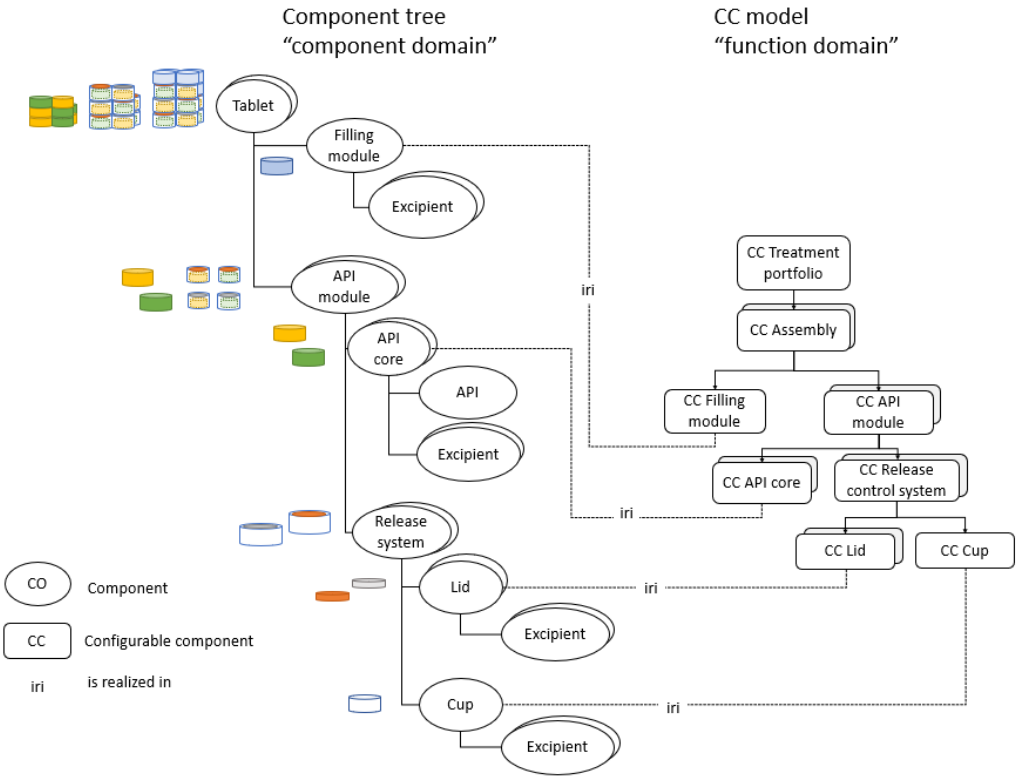

Figure 4.2: The CC model of a pharmaceutical product connected to its component tree

form of the CO *API core* is established. The lower-level COs of the CO *API core* visualize the realizable COs of the API core needed for realization of the API core, which are the API and excipients (these are on a material level). Similar to the CO *API core*, the remaining COs for the CC objects *lid*, *cup* and *filling module* are realized.

The COs *lid* and *cup* together generate the *release system* visualized in Figure 4.2. Assembling the *API core* and *release system* generates *API modules*. When the design parameters for the *lid* and *cup* of the *release system* are defined as zero (i.e., excluding the CC *release control system*), the *API module* is identical to the *API core*.

The CO *tablet* is defined on the highest hierarchical level of the component tree. Tablet is an assembly that constitutes a number of the CO *API module* and a number of the CO *filling module* in ratios defined within the Cs in the function domain (as these define the execution bandwidth). The tablet is the treatment customized to the individual need of the patient. A few examples of treatments are displayed in Figure 4.2 and do not

represent an exhaustive set of possible treatment variants.

Two types of assembly processes to assemble COs are defined: a pre-assembly and final assembly process, which are described in Figure 4.3 along with the components that are transformed during the respective assembly process. The pre-assembly process is set to transform parts of the treatment into modules; thus, parts are defined as the components which undergo the preassembly process to form assemblies, including API cores, lids and cups. The final assembly process is set to transform modules into assemblies, including API cores (when design parameter values for lids and cups are zero), API modules and filling modules. Modules are thus defined as components that undergo the final assembly process to establish assemblies. Assemblies are defined as final administrable treatments configured from various ratios of modules.

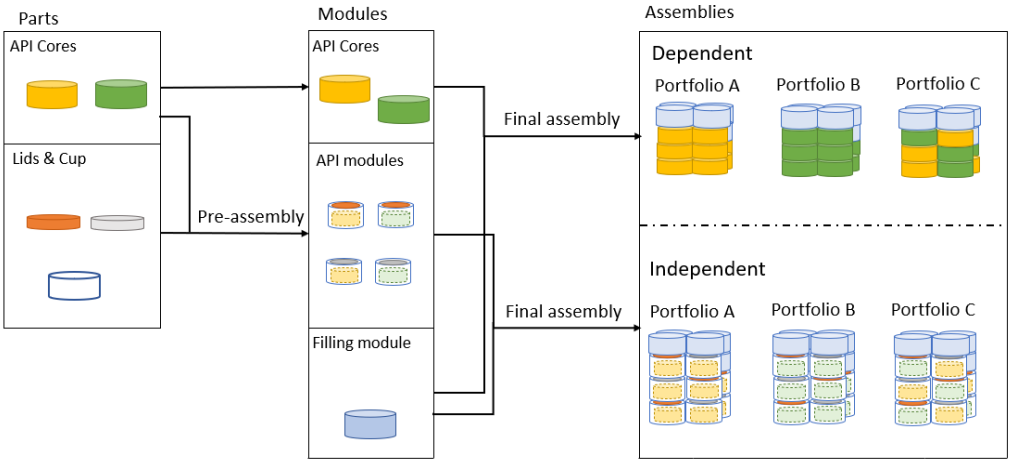

Figure 4.3: The transformation process of parts into modules and of modules into assemblies is displayed along with the respective assembly process

4.2.3 Value modeling of pharmaceutical product designs for customization

The concept of value is adopted for use as a proxy for the cost-effectiveness of customized pharmaceutical products. The value model consists of two terms but is then consolidated to consist of performance metrics for patient benefit and production cost.

Patient benefit

Patient benefit describes the therapeutic outcome of the patient by assessing the compliance to the individual patient needs, which is achieved by the customized pharmaceutical products. Patient benefit metrics comply to the product design requirements of *scalable dose strength*, *flexible target release profile* and *scalable treatment size*.

B_{dose} regards the concept of *quality decay* by Blackenfelt (2001) and is adapted to assess the benefit from a scalable dose strength perspective. B_{dose} describes how well the dose strength acquired by means of the customized pharmaceutical product matches the dose strength need of the patient, where a difference in these dose strengths represents a decrease in treatment quality. B_{dose} is obtained through Equation 4.1, which describes how well a treatment portfolio can satisfy the needs of a defined patient population. In Equation 4.1, $Dose_{rec,m}$ is thus the received dose of a patient m, meaning the dose that a treatment portfolio can offer the patient, $Dose_{optimal,m}$ is the optimal dose strength of a patient m and $population$ is the size of the population.

$$B_{dose} = \frac{1}{Population} \sum_{m=1}^{n} \frac{|Dose_{rec,m} - Dose_{optimal,m}|}{Dose_{optimal,m}} \tag{4.1}$$

Based on the flexible target release profile and scalable treatment size perspectives, the patient benefit is assessed using the number of product variants from which a patient can select, which is obtained through Equation 4.2. The number of target release profiles that the patient can select is assessed using the dose strength acquired by the patient. This means that, given the dose strength acquired by the patient, the number of release profiles available for that dose strength that the patient can select from is used as a measure for patient benefit from a target release profile perspective. Similarly, the number of treatment sizes the patient can select is assessed using a selected target release profile of the patient.

$$B_{release/size} = \sum_{k=1}^{l} x_k \times Release/Size\ Variants_k \tag{4.2}$$

In Equation 4.2, $Release\ Variants_k$ describes the number of release or treatment size variants that a treatment portfolio can generate for a given dose strength, and x_k describes the fraction of the patient population belonging to the patient segment k receiving the given dose. $Size\ Variants_k$ regards an average of all size variants configurable by a treatment with a fixed dose strength and target release profile. A segmentation of the

patient population was thus performed according to dose strength and is described in paper A. For a treatment portfolio, an average number of target release profiles and treatment sizes is used to make treatment portfolios comparable to each other.

Production cost

The cost of assembling product parts into treatments is used to assess production cost. Two metrics are used: the pre- $Ca_{pre,PDx}$ and final assembly cost $Ca_{fin,PDx}$ obtained through Equations 4.3 and 4.4 respectively, which correspond to the respective assembly process described in Figure 4.3. PDx refers to the respective treatment portfolio. The models of these assembly costs are adapted from the Pugh complexity factor (Pugh, 1990).

$$Ca_{pre,PDx} \sim \sqrt[3]{Np_{parts} Ni_{parts} Nt_{parts}} \tag{4.3}$$

$$Ca_{fin,PDx} \sim \sum_{k=1}^{l} x_k * \frac{1}{Variants_k} \sum_{p=1}^{r} \sqrt[3]{Np_{mod,k,p} Ni_{mod,k,p} Nt_{mod,k,p}} \tag{4.4}$$

In Equation 4.3, Np_{parts} is the number of parts assembled into an API module, Ni_{parts} is the interfaces between the parts and Nt_{parts} is the number of types of parts in the pre-assembly process. In Equation 4.4, $Np_{mod,k,p}$ is the number of modules assembled into a final treatment (assembly) for treatment variant p in patient segment k, and $Ni_{mod,k,p}$is the number of interfaces between the modules. The approach to calculating the interfaces in an assembly is described in paper A. $Nt_{mod,k,p}$ is the number of types of modules in the final assembly. Since each treatment portfolio can generate several assembly variants for each patient segment $Variants_k$, an average is calculated. Finally, to establish a single representative value for each treatment portfolio, the patient segment fraction x_k is used to generate a weighted average.

Value

The value model assesses the cost-effectiveness of a treatment portfolio. Displayed in Equation 4.5, this model calculates a weighted average of normalized scores for patient benefit and production cost. The normalized scores of each benefit metric i, $P_{B,i}$ and each production cost metric j, $P_{C,j}$, for respective treatment portfolios are assigned according to linear scales created based on the performance of each treatment portfolio on

the patient benefit and production cost metrics calculated through Equations 4.1-4.4. Paper A describes the creation of the linear scales and the translation of the treatment portfolio performances on patient benefit and production cost metrics into normalized scores. $Nr_{B,i}$ and $Nr_{C,j}$ describe the number of patient benefit and production cost metrics respectively. Finally, the weight factors w_B and w_C allow emphasizing the performance of a treatment portfolio from a patient-benefit or production-cost perspective.

$$V = w_B \frac{\sum_{i=1}^{n} P_{B,i}}{Nr_B} + w_C \frac{\sum_{j=1}^{m} P_{C,j}}{Nr_C} \tag{4.5}$$

4.2.4 Case study A

The case study in paper A investigated the impact of the degree of modularization of the product design on the capabilities of modular product designs with respect to the number of product variants configured. In addition, the impact of the degree of modularization of the product design was investigated from a cost-effectiveness perspective, which meant describing the products' value, so that the perceived satisfaction of stakeholder needs is visible in terms of the therapeutic outcome of the patient and production cost.

The CC model and value-modeling approach were developed into an executable platform model which generates treatment portfolios with different degrees of modularization by embracing sets of customized pharmaceutical products for which the value can be assessed. A case study was designed to generate and assess these treatment portfolios.

Platforms were developed for modular product designs and the conventional product design (to use as a reference). Six treatment portfolios of customized treatments were generated with varying degrees of modularization along with a treatment portfolio for the conventional product design. As a model therapy, a commercial selective serotonin reuptake inhibitor (SSRI) treatment embracing a tablet design was selected. This therapy is offered in two dose strengths: 50 and 100 mg, which the conventional product design is based on. For modular product designs, two API cores were used for treatment configuration with dose strengths of 10 and 5 mg respectively, two types of lids A and B, a single cup and a single filling module. Two scenarios were evaluated: a dose-dependent release scenario, in which the target release profile relies on the inherent release properties of the API cores, and a dose-independent release scenario, in

which the target release profile is controlled through a release system represented by the lids and cups. The treatment portfolios for modular product designs are visualized in Figure 4.3, which displays the parts and modules used for the treatment configuration of each portfolio.

Based on the model therapy, a patient population was generated to describe the dose strength need of each patient. The model therapy defines the execution bandwidth of the dose strength as 25 to 100 mg, and the patient population generated is a normal distribution where 99.7% of the population falls within the dose strength interval. The value for the treatment portfolios was calculated for three scenarios assuming different weights on w_B and w_C in Equation 4.5. In scenario *Value 50-50*, w_B and w_C were assigned equal weights 0.5 and 0.5. In scenario *Value 67-33*, the patient benefit was prioritized before production cost, and the w_B and w_C were assigned weights 0.67 and 0.33 respectively. In scenario *Value 33-67*, cost was prioritized before benefit, and thus w_B and w_C were assigned the weights 0.33 and 0.67 respectively. The value scores of the concepts were then used to compare the concepts with each other. The cost-effectiveness of a treatment portfolio was assumed when the value score of a treatment portfolio exceeds the value score of the reference design, meaning the conventional product design.

Case study results

Table 4.2 displays the number of components (i.e., the number of parts for the modular product designs and the number of tablet variants for the reference design) produced for each treatment portfolio and the number of product variants generated from the components. In addition, the increase in the number of produced components and product variants is displayed in percentage when comparing the treatment portfolios of the modular product designs to the reference design. Although the results in Table 4.2 are not presented in the context of patient benefit, they show that by modularizing the product, the same number of components or a few more can be produced and simultaneously obtain a substantial increase in the number of product variants. By producing two components for treatment configuration (portfolio A and B, dependent scenario), for example, instead of two tablet variants (reference), the number of product variants can be increased by 2,800% (portfolio A) and 3,300% (portfolio B).

Table 4.2: The number of product variants for both reference and modular product designs are displayed

		Dependent			Independent		
	Ref.	A	B	C	A	B	C
Produced components	2	2	2	3	5	5	6
Increase in %	ref	0	0	50	150	150	200
Product variants	4	116	136	1,540	828	1,496	27,472
Increase in %	ref	2,800	3,300	38,400	20,600	37,300	686,700

The value score of each concept is presented in Table 4.3, where the increase in the number of product variants is assessed in the context of patient benefit and production cost. Rankings are determined based on the concepts' value score to give an overview how the concepts relate to each other. The results in Table 4.3 show that assuming equal importance for patient benefit and production cost (scenario *Value 50-50*), the reference design obtains the highest value score. This is also the case when the cost is prioritized before the benefit (*Value 33-67*), which means that cost-effectiveness cannot be achieved through product modularization in these scenarios, as cost-effectiveness was determined as the value score of modular product designs exceeding that of the reference design. If prioritizing patient benefit before production cost (*Value 67-33*), however, an increase in value is obtained by increasing the degree of modularization, which means that portfolio C obtains the highest value score for the independent-release scenario and also embraces the highest degree of modularization.

4.3 Paper B - Process flexibility

Paper B aims to assess the *process flexibility* of the current manufacturing system of pharmaceutical products when operated in a customization context. Pharmaceutical product customization requires producing a large variety of product variants in small volumes, and the current manufacturing system is dominated by mass production and is hypothesized to lack

Table 4.3: The value score is displayed for each treatment portfolio for three scenarios of weightings, i.e., *Value 50-50*, *Value 67-33* and *Value 33-67* as well as the ranking of the concepts based on their value score

		Dependent			Independent		
	Reference	A	B	C	A	B	C
Value 50-50	3	2.98	2.60	2.95	2.87	2.80	2.84
Ranking	1	2	7	3	4	6	5
Value 67-33	2.32	3.10	2.75	3.31	3.26	3.34	3.47
Ranking	7	5	6	3	4	2	1
Value 33-67	3.68	2.86	2.45	2.60	2.48	2.27	2.22
Ranking	1	2	5	3	4	6	7

the process flexibility required to cost-effectively produce a large variety of customized pharmaceutical products. The findings of paper B aim to answer **RQ2**:

What challenges the cost-effective production of customized pharmaceutical products?

An approach to integrated product and manufacturing system platform design is proposed for the design and manufacturing systems of customized pharmaceutical products. Function-means modeling, specifically the enhanced function-means modeling (EF-M) method (Schachinger and Johannesson, 2000), was used to establish these integrated designs and the producibility model (Landahl et al., 2017) was used to integrate the product and manufacturing system domains in the process domain. Furthermore, an approach is proposed to integrated product and manufacturing system redesign using requirement change propagation. This approach adjusts the manufacturing system design as a response to changing product design requirements and thereby assures the producibility of the redesigned product. An approach to the cost-effectiveness assessment of these integrated platform designs was suggested to include terms for patient benefit, production cost and value.

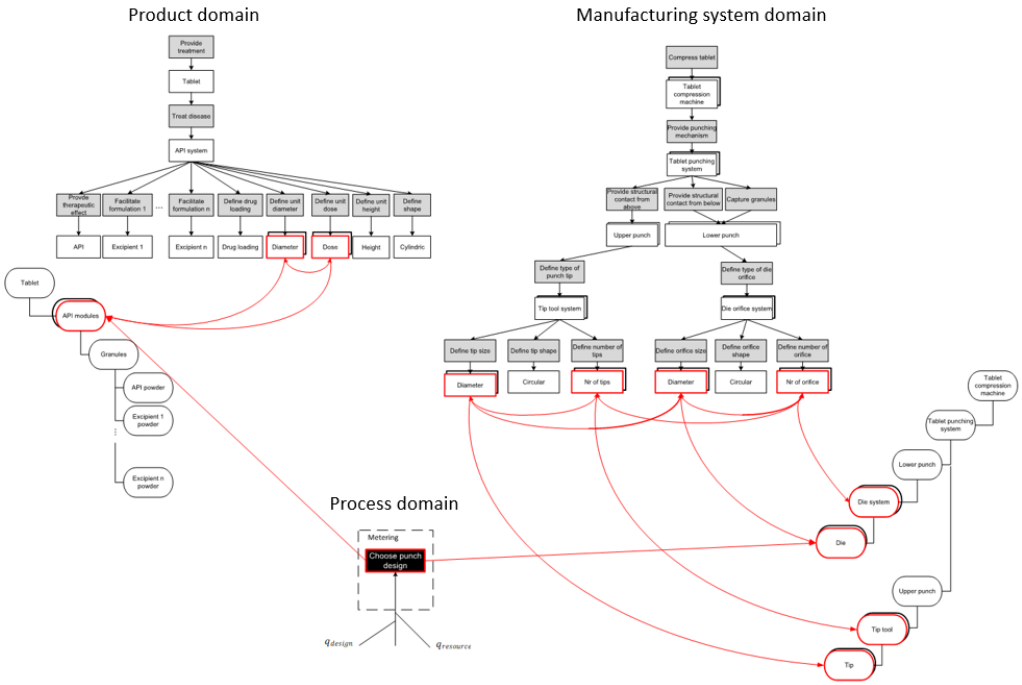

Figure 4.4: An integrated model of a product and manufacturing system design

4.3.1 Manufacturing system reconfiguration as a consequence of pharmaceutical product modularization

Figure 4.4 displays an EF-M model for an integrated product and manufacturing system. In this model, the product design domain and manufacturing system domain are joined in the production process, which the manufacturing system performs to manufacture the desired product.

A consequence of product modularization is the need for manufacturing system reconfiguration. Modularizing the pharmaceutical product entails new requirements and adjustments to the manufacturing system to ensure the producibility of the modular pharmaceutical products. The process of adjusting the manufacturing system is illustrated by the process of requirement change propagation using red arrows in Figure 4.4. The requirement change propagation displays how the requirements of the product design propagate first to the production process of the product and then to the manufacturing system, which performs the production process.

4.3.2 Value modeling of integrated product and manufacturing system designs for customization

To describe the value of integrated product and manufacturing system concepts for customization, the change in value is used. The redesigned integrated product and manufacturing system, for customization, is compared to the conventional integrated product and manufacturing system (i.e., the reference design before requirement change propagation).

The change in value ΔU is obtained in Equation 4.6, which is based on the production time of the modular product design t_m and the "allowed" production time of the modular product design $t_{new,m}$. The "allowed" time is obtained through Equation 4.7 and is based on the production time of the reference design t_{m-1} and adds a quantity ΔQ to the production time based on the increased benefit generated by the redesigned product or modular product design. ΔQ is obtained in Equation 4.8 and assesses the patient benefit from a dose strength perspective using the concept of quality decay (Blackenfelt, 2001), where q_m describes the quality decay for the modular product design and q_{m-1} describes the quality decay for the reference design. The approach to quality decay is the same concept described in Section 4.2.3; however, the level of decay here is measured rather than how close the dose of the offered treatment is to the optimal dose of the patient.

$$\Delta U = \frac{t_{new,m}}{t_m} - 1 \tag{4.6}$$

$$t_{new,m} = t_{m-1} + t_{m-1}\frac{-\Delta Q}{100} \tag{4.7}$$

$$\Delta Q = \frac{q_m - q_{m-1}}{q_{m-1}} \tag{4.8}$$

4.3.3 Case study B

The case study in paper B investigated the process flexibility of the current, mass-production, manufacturing system in a customization context by reconfiguring the manufacturing system. The cost-effectiveness of producing modular pharmaceutical product designs was assessed using an adjusted manufacturing system design.

Based on the EF-M model, platforms were developed for integrated product and manufacturing systems. Executing these platforms generated

treatment portfolios and manufacturing system designs which produce these portfolios. Furthermore, the platforms enable assessing these integrated product and manufacturing system designs in terms of patient benefit, production time and value. A case study was designed to generate and assess these integrated product and manufacturing systems.

As a case example, the tablet manufacturing process was selected since producing modular product designs instead of integral tablets requires adjusting the tablet-punching system. Two integrated platform variants were developed, where for the first variant regarding the reference design, the product embraces the conventional, integral tablet design and a tablet punch consisting of a single tip. For the second variant, the product embraces a modular product design and a multi-tip punch consisting of eight tips. Commercial diabetes treatment was selected as a model therapy offered in three dose strengths, 500, 850 and 1000 mg, which formed the basis for the reference design. The modular product design used an API core containing 50 mg to configure product variants. Cost-effectiveness was assumed when the time of tablet punching for the modular product design became inferior to the ”allowed” time of tablet punching, meaning when $\Delta U > 1$.

Case study results

The result of ΔU is presented in Table 4.4, which also displays the change in tablet-punching time ΔT when comparing the modular product design to the reference design, which increases by 95% when producing modular product designs. The quality decay ΔQ decreases by 80%, which displays an improved performance of the modular products compared to the reference design from a patient-benefit perspective. The results show that pharmaceutical product modularization results in an overall decrease in value by 7%, however, which indicates that cost-effectiveness cannot be achieved by pharmaceutical product modularization, even though product quality can be substantially increased from a patient-benefit perspective by adjusting the manufacturing system so that the manufacturing system design, in its current mass production context, can manufacture modular product designs. The current manufacturing system thus does not provide the process flexibility required to produce customized pharmaceutical products.

Table 4.4: The change in tablet punching time, quality decay and overall value is displayed when comparing an integrated platform for modular product design to an integrated platform for a conventional tablet design

Performance indicator	ΔT	ΔQ	ΔU
Change in platform performance	+95%	-80%	-7%

4.4 Paper C - Postponement

The overall aim of paper C was to address the challenges of the cost-effective manufacturing and supply of customized pharmaceutical products in the current pharmaceutical SC. The currently dominant mass-production platforms are not designed or intended for the manufacturing and supply of customized pharmaceutical products, and such customization results in the increasing complexity of the manufacturing and supply of a product portfolio when compared to a mass-production context. This product portfolio complexity challenges the cost-effective manufacturing and supply of customized pharmaceutical products, where a reason is hypothesized to be the lack of process flexibility in the pharmaceutical SC. The findings of paper C aim to answer **RQ2**:

What challenges the cost-effective production of customized pharmaceutical products?

Solutions to the product and production system design challenges of pharmaceutical products manufactured and supplied in a customization context have previously focused on optimizing one or a few stages of the SC. Beyond these solutions, system-level analysis of a pharmaceutical SC operating in a customization context was performed to propose solutions to the high product variety challenge of a pharmaceutical customization context. The findings of paper C thus also aim to answer **RQ3**:

What reconfiguration strategies can support the cost-effective production of customized pharmaceutical products, and what challenges appear when trying to implement these strategies?

Finally, the MC principle of *postponement* is investigated as a potential solution for the cost-effective production of customized pharmaceutical

products; thus, the findings of paper C also aim to answer **RQ4**:

How can a later point of variegation support a cost-effective production of customized pharmaceutical products?

Four conceptual models of reconfigured pharmaceutical SC archetypes are proposed and assessed from a value perspective.

4.4.1 Pharmaceutical supply chain reconfiguration for mass customization

Figure 4.5 displays four pharmaceutical SC archetypes with various degrees of postponement, which are reconfigured to manage an increasing product portfolio complexity. The red arrow in Figure 4.5 indicates the position of the *point of variegation*, meaning where the final treatment is assembled. The position of the *prescription statement*, which regards the point where information regarding the patient needs are elicited, aligns with the *point of variegation* in each archetype.

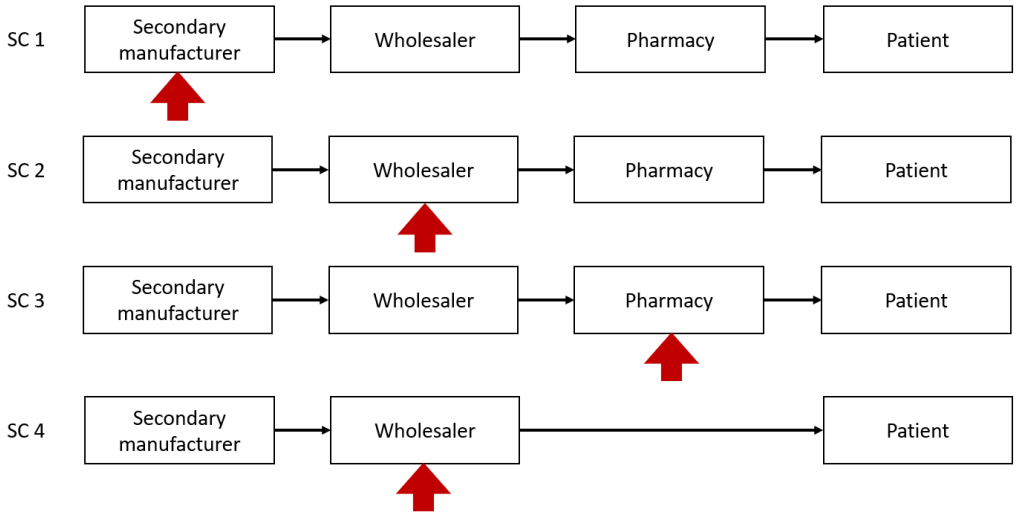

Figure 4.5: Four supply chain archetypes with various degrees of postponement. The red arrow designates the position of the *point of variegation*.

Postponement in pharmaceutical supply chain

In each SC archetype, the stakeholders manage components before the *point of variegation* (depending on the product design, these components

can assume the nature of parts, modules or tablets). Post-*point of variegation*, a portfolio of customized pharmaceutical products is managed, which regards assembled treatments according to individual patient prescriptions.

In SC 1, the *point of variegation* is placed at the secondary manufacturer. The point of variegation is thus placed where the most knowledge of pharmaceutical production exists. In SC 2, the *point of variegation* is placed by the wholesaler. In this archetype, the secondary manufacturer produces components which are then supplied to the wholesaler, who then performs the final assembly according to patient prescriptions. In SC 3, the *point of variegation* is placed by the pharmacy. Various degrees of postponement are exhibited by SCs 1 to 3, which incrementally move the *point of variegation* closer to the patient but keep the traditional path of product supply through each stakeholder. In SC 4, the individual patient prescriptions are directly delivered from the wholesaler to the patient. SC 4 represents an environment postponing the final assembly to the wholesaler and where the patient effort of acquiring their prescriptions at the pharmacy is eliminated.

Production process reconfiguration

Due to structural reconfigurations to the SC, stakeholder production processes require reconfigurations. A description of the "as-is" operation of the SC is provided in Section 2.1.3 and in paper C. The reconfigurations to the SC are described in Table 4.5 for the SC to be operated in a customization environment. Table 4.5 lists each adjusted (**A**), reallocated (**R**) or new (**N**) processes added into stakeholders' operations. In this section, DP refers to drug products and assumes the nature of tablets or product components (depending on the nature of product design) that are transformed into an FDP, which refers to the final drug product assembled from DPs and are labeled according to the individual patient before being supplied to the patient.

For each reconfigured SC archetype, the process *finalize DP assembly*, located at the patient, is eliminated since the patient receives readymade customized treatments according to their individual needs. In a mass-production context, a patient can currently interfere with their product before administration, but this activity is eliminated in the reconfigured

Table 4.5: Reconfigurations to the production processes of the supply chain stakeholders when operating reconfigured supply chain archetypes

Supply chain archetype	Secondary manufacturer	Wholesaler	Pharmacy	Patient
SC 1	Manufacture DP **(A)** Produce packaging **(A)** Assemble FDPs **(A)**	Manage FDPs **(A)**	Manage FDPs **(A)** Dispense FDPs **(A)**	Finalize DP assembly **(E)**
SC 2	Manufacture DP **(A)** Produce packaging **(A)** Assemble DPs in IM-packaging **(A)**	Procure DPs in IM-packaging **(A)** Finalize FDP assembly **(N)** Produce packaging **(R)** Manage FDPs **(A)**	Manage FDPs **(A)** Dispense FDPs **(A)**	Finalize DP assembly **(E)**
SC 3	Manufacture DP **(A)** Produce packaging **(A)** Assemble DPs in IM-packaging **(A)**	Procure DPs in IM-packaging **(A)** Manage DPs **(A)**	Procure DPs in IM-packaging **(A)** Finalize FDP assembly **(N)** Produce packaging **(R)** Manage FDPs **(A)** Dispense FDPs **(A)**	Finalize DP assembly **(E)**
SC 4	Manufacture DP **(A)** Produce packaging **(A)** Assemble DPs in IM-packaging **(A)**	Procure DPs in IM-packaging **(A)** Finalize FDP assembly **(N)** Produce packaging **(R)** Manage FDPs **(A)** Product delivery **(R)**	Ensure patient safety **(R)**	Acquire FDPs **(E)** Finalize DP assembly **(E)**

SCs.

Compared to the "as-is" design, the major change of SC 1 is the number of product variants produced and packaged by the secondary manufacturer. Market-ready prescriptions customized according to individual patient needs are finalized by the secondary manufacturer instead of packaging DPs separately in their standardized packages, which means that the FDPs are assembled according to each individual (*assemble FDPs*). The product portfolio consisting of FDPs is then supplied downstream of the SC to the patient. The main operational changes of the stakeholders are the manufacturing (*manufacture DP*) and product variety management of individual patient prescriptions (*manage FDPs*). The pharmacist role, collected in the function *dispense FDPs*, is reduced to a prescription-dispensation activity.

In SC 2, the assembly of FDPs is finalized at the wholesaler. The secondary manufacturer's operation is reduced to producing standardized bulks of DPs in intermediate (IM) packaging. The production of final packaging needs to be reallocated (*produce packaging*) since the final assembly and packaging are performed at the wholesaler (*finalize FDP assembly*). *Procure DPs in IM packaging* is the activity of wholesalers acquiring DPs from various manufacturers and also represents an opportunity to treat identical DPs acquired from various manufacturers as a single type of DP, thereby decreasing the number of product variants in the product portfolio.

In SC 3, the advantages of SC 2 can be exploited. In addition, a less complex product portfolio can be managed throughout the SC up to the point of the pharmacy, representing bulks of DPs in IM packaging. The pharmacy performs the final assembly of FDPs (*finalize FDP assembly*). Strategically positioned pharmacies close to the market eliminate complexity induced by country-specific requirements on the packaging. Similar to the SC 2 archetype, the *produce packaging* activity needs to be reallocated.

In SC 4, treatments directly delivered to the patient from the wholesaler eliminate the activity of patients acquiring their prescriptions at the pharmacy (*acquire FDPs*); however, this approach requires delivery systems to provide for the direct delivery, thereby reallocating the process *product delivery*. Another consequence of direct delivery is the elimination of the pharmacy's physical contact with treatments; thus, the process *ensure patient safety* performed by the pharmacy is reallocated as other means

provide for this process.

4.4.2 Value modeling of SC archetypes in a pharmaceutical production context

The approach to value modeling of the SC archetypes adopts the concept screening matrix (Ulrich et al., 2020). For a selected set of performance criteria, SC archetypes are assessed by comparing their performance concerning the performance criteria to a reference concept. If the performance of an SC archetype exceeds that of the reference, a "+" is assigned to the concept; if the performance is worse, a "-" is assigned, and if the performance is equal or nonconclusive, a "0" is assigned. The net value of the number of "+":s and "-":s is calculated. Five categories of performance criteria are selected: **cost of operation**, **time to patient**, **quality assurance**, **process change** and **value for the patient**, and the criteria within each category are defined in Table 1 in paper C.

4.4.3 Case study C

Case study C had a twofold aim: the first was to investigate whether the current "as-is" design of the SC displays the process flexibility required for operation in a customization context. From there, the aim was to identify the challenges of operating the "as-is" design in a cost-effective customization context by comparing the performance of the "as-is" design in a customization context to its performance in a mass-production context, which is selected as the reference concept. This assessment is performed using concept screening.

The second aim was to assess the performance of the reconfigured SC archetypes, presented in Figure 4.5 and Table 4.5, as remedies to the challenges of the "as-is" design operated in a customization context. The performance was assessed by comparing the reconfigured SC archetypes to the "as-is" design operated in a customization context, which was thus selected as a reference concept, and the assessment was performed using concept screening. The cost-effectiveness of a reconfigured SC archetype is assumed if the overall net value from concept screening is positive.

Case study results

Table 4.6 presents the results of comparing the "as-is" design operated in a customization context to when operated in a mass production (MP)

context. The premise in the assessment is that the SC design is retained as is; however, in a customization context, the prescriptions received by the patient at the pharmacy have an increased degree of customization.

Table 4.6: A qualitative performance assessment of operating the ”as-is” design of the SC in a customization context using the ”as-is” design operating in a MP context as a point of comparison

Category	Performance criteria	”As-is” MP	”As-is” custom.
Cost of operation	Capacity utilization	0	-
	Capital investments	0	0
	Inventory	0	-
	Material consumption	0	-
	Economy of scale	0	-
Time to patient	Operational lead time	0	-
	Delivery complexity	0	-
Quality assurance	Effort in quality control	0	-
	Risk of errors	0	-
Process change	New working procedures of stakeholder	0	-
	New working procedures across stakeholders	0	0
Value for the patient	Therapeutic outcome	0	+
	Patient effort	0	+
$\sum$ +		0	2
$\sum$ -		0	9
$\sum$ 0		13	2
Value score		0	-7

The results in Table 4.6 show that when manufacturing and supplying customized pharmaceutical products in the “as-is” design of the SC, the criteria within the **value for the patient** category increase in performance. This occurs because offering the patients readymade customized treatments enhances the therapeutic outcome of the patient, and the effort of the patient required to interfere with the product in various ways is

eliminated.

Most cost-inducing criteria within the categories **cost of operation**, **time to patient**, **quality assurance** and **process change** decrease in performance, however, due to the substantial increase in product portfolio complexity to be manufactured and supplied throughout the SC, which is a consequence of a customization context. The criteria *capital investments* and *new working procedures across stakeholders* are unchanged since the SC is assumed to be operated in its current "as-is" design, and thus no structural changes to stakeholder operations are performed. The final value score results in an overall decrease in performance (i.e., -7), and thus cost-effectiveness is not assumed. The current "as-is" design operated in a customization context hence does not display the process flexibility required for the cost-effective production of customized pharmaceutical products.

Table 4.7 displays the results of the performance of the reconfigured SC archetypes compared to the "as-is" design operating in a customization context. The results suggest that with an increasing degree of postponement, the cost-effectiveness of manufacturing and supplying customized pharmaceutical products increases. Cost-effectiveness is achieved in SC 3, resulting in a value score +5, where the *point of variegation* is placed at the pharmacy. In SC 3, standardized components can be further produced and supplied in bulk in IM packaging in the SC compared to the remaining SC archetypes, thereby improving production cost-related performance metrics. This approach, however, requires structural changes to the SC, thus resulting in a decrease in performance for the category **process change**.

4.5 Paper D - Integrated product modularization and postponement

Paper D aimed to study an integrated approach to *product modularization* and *postponement* for the cost-effective design, manufacturing and supply of customized pharmaceutical products. Building on the studies presented in papers A and C, paper D further addresses the challenge of the lack of cost-effective approaches to pharmaceutical customization from product, manufacturing system and SC design perspectives. Since paper D expands the model of paper A with mathematical models based on findings of

Table 4.7: A qualitative performance assessment of operating the reconfigured supply chain archetypes in a customization context using the ″as-is″ design operating in a customization context as a point of comparison

Category	Performance criteria	″As-is″ custom.	SC 1	SC 2	SC 3	SC4
Cost of operation	Capacity utilization	0	-	0	+	0
	Capital investments	0	-	-	-	-
	Inventory	0	+	+	+	+
	Material consumption	0	+	+	+	+
	Economy of scale	0	-	+	+	+
Time to patient	Operational lead time	0	-	0	+	0
	Delivery complexity	0	-	0	+	-
Quality assurance	Effort in quality control	0	-	0	+	-
	Risk of errors	0	-	0	+	-
Process change	New procedures of stakeholder	0	-	-	-	-
	New procedures across stakeholders	0	-	-	-	-
Value for the patient	Therapeutic outcome	0	0	0	0	0
	Patient effort	0	0	0	0	+
$\sum$ +		0	2	3	8	4
$\sum$ -		0	7	3	3	5
$\sum$ 0		13	4	7	2	4
Value score		0	-5	0	+5	-1

paper C, paper D mainly answers **RQ4**:

How can a later point of variegation support a cost-effective production of customized pharmaceutical products?

A methodology is proposed for the design and modeling of integrated product and production system concepts for a pharmaceutical customization context. This methodology integrates the therapy domain, product and SC design domains as well as evaluative domain. Cost models are proposed to assess the production cost of manufacturing and supplying pharmaceutical products throughout the SC. A computational model is established using the proposed methodology. The cost-effectiveness of

the integrated product and production system concepts developed by applying the methodology is assessed using simulations, which assess the impact of the degree of modularization and the degree of postponement of the integrated concepts on their value. To describe value, the concept scoring approach (Ulrich et al., 2020) was adapted.

4.5.1 The design of integrated pharmaceutical product and production system concepts

The framework for the design methodology of integrated product and production system concepts is displayed in Figure 4.6. This framework consists of three categories of input domains: **therapy domain**, **design domain** and **evaluative domain**.

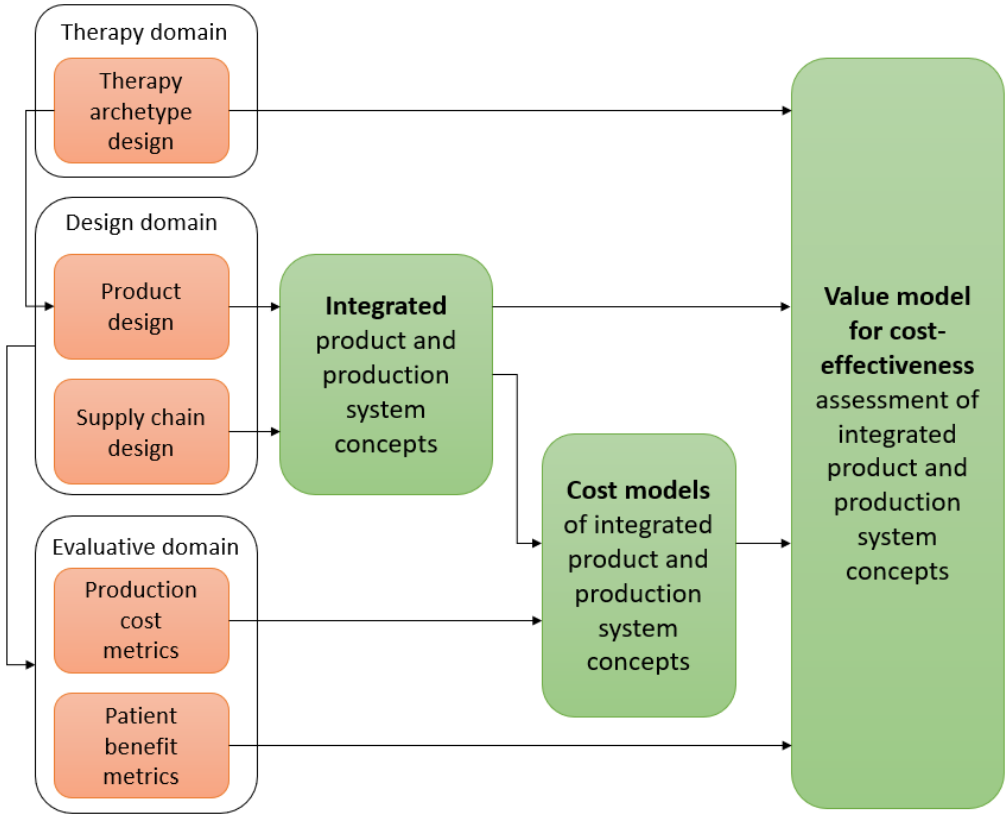

Figure 4.6: The methodology for the design and modeling of integrated product and production system concepts

The **therapy domain** describes the treatment regimen, meaning the dose strength window of a therapy archetype, and the patient needs from

a dose-strength perspective. The treatment regimen is informed by the therapy archetype for which integrated product and production system concepts are to be designed.

The **design domain** consists of the product design which adopts product modularization as a design strategy for modular product design, as described throughout Sections 4.2.1 and 4.2.2. The product designs are set to comply with the design requirements, scalable dose strength and flexible target release profile; hence, dose-independent treatment portfolios are selected (see Figure 4.3). The design domain also includes the SC design and adopts the reconfigured SC archetypes SC 1, SC 2 and SC 3 presented in Figure 4.5 and Section 4.4.1.

The final input domain is the **evaluative domain** consisting of metrics to assess the production cost and patient benefit. Production cost is assessed using the product variety management cost and assembly cost. Patient benefit metrics comply to the product design requirements scalable dose strength and flexible target release profile; thus, B_{dose} and $B_{release}$ are adopted (Equations 4.1 and 4.2).

These three input domains contribute to three output domains: **integrated product and production system concepts** (which also serve as an input domain); **cost models of integrated product and production system concepts** (which also serve as an input domain); and **value model for cost-effectiveness assessment of integrated product and production system concepts** (see Figure 4.6).

Integrated product and production system concepts

Figure 4.7 displays integrated product and SC concepts. Three degrees of product modularization are applied for the integrated product and production system concepts: the conventional product design or reference (R) and two treatment portfolios embracing modular product designs, where the lower-Np design (L) poses a lower degree of modularization and the higher-Np design (H) poses a higher degree of modularization. Lower/higher degree of modularization refers to the degree of modularization of the final assembly. Furthermore, three degrees of postponement in the SC are applied: where the final assembly is placed by the secondary manufacturer (R-SC1, L-SC1 and H-SC1), the wholesaler (R-SC2, L-SC2 and HSC2) and the pharmacy (R-SC3, L-SC3 and H-SC3). Nine concepts of integrated product and production systems are thus established.

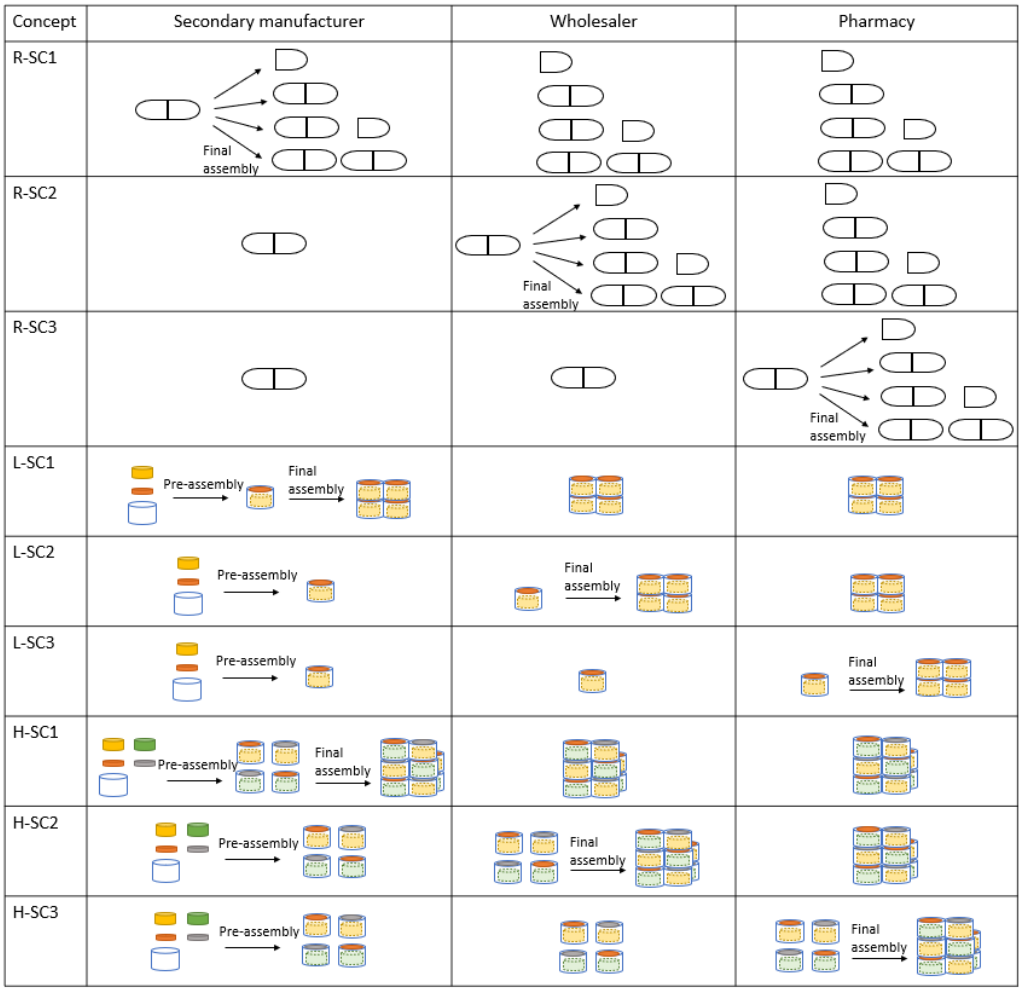

Figure 4.7: Integrated product and production system concepts for conventional product design (R-SC1, R-SC2 and R-SC3) and modular product designs for two degrees of modularization, lower-Np design (L-SC1, L-SC2 and L-SC3) and higher-Np design (H-SC1, H-SC2 and H-SC3)

Cost models of integrated product and production system concepts

Production cost models were developed based on the integrated product and production system concepts and are presented in Table 4.8 for respective SC archetype. It should be noted that the models are irrespective of the product design (R, L or H), but the performance of a concept regarding these cost models is affected by the product design. Furthermore, it is assumed that assembly costs are irrespective of the SC stakeholder performing the assembly.

In Table 4.8, $C_{sec,PDx}$, $C_{WS/Ret_{mod}PDx}$ and $C_{WS/Ret_{assm}PDx}$ are product variety management costs of the secondary manufacturer, wholesaler and pharmacy, which were already established in the **evaluative domain** but are described here for convenience. The product variety management cost of the secondary manufacturer is calculated using Equation 4.9, which is based on the production time of a component being two-or three-fold the fabrication time due to changeover processes (Wilson, 2016); thus, $Nt_{comp,PDx}$ is the number of components produced by the secondary manufacturer, and the term $3 * Nt_{comp,PDx}$ describes the change over time being threefold the fabrication time of the components. These components assume the nature of tablets for the conventional product design and parts for the modular product designs.

$$C_{sec,PDx} \sim Nt_{comp,PDx} + 3 * Nt_{comp,PDx} \tag{4.9}$$

Equation 4.10 describes the production cost of the wholesaler when managing modules $C_{WS_{mod}PDx}$, where $Nt_{WS_{mod}PDx}$ is the number of modules. Equation 4.10 likewise describes the cost of the pharmacy managing modules $C_{Ret_{mod}PDx}$, where $Nt_{Ret_{mod}PDx}$ is the number of modules.

$$C_{WS/Ret_{mod}PDx} \sim Nt_{WS/Ret_{mod}PDx} \tag{4.10}$$

Equation 4.11 describes the production cost of the wholesaler $C_{WS_{assm}PDx}$ when managing assemblies, where $Nt_{WS_{assm}PDx}$ is the number of assemblies. Equation 4.11 likewise describes the production cost of the pharmacy $C_{Ret_{assm}PDx}$ when managing assemblies, where $Nt_{Ret_{assm}PDx}$ is the number of assemblies.

$$C_{WS/Ret_{assm}PDx} \sim Nt_{WS/Ret_{assm}PDx} \tag{4.11}$$

Equations 4.10 and 4.11 are based on models by Thonemann and Bradley (2002) and Benjaafar et al. (2004), and they describe the cost product variety management and product variety as a linear relationship in inventory keeping and retailer type of operation.

To model the assembly cost, both the pre-assembly cost ($Ca_{pre,PDx}$, Equation 4.3) and final assembly cost ($Ca_{fin,PDx}$, Equation 4.4) are adopted.

Table 4.8: Cost models to assess production cost of the pharmaceutical supply chain

SC archetype	Secondary manufacturer	Wholesaler	Pharmacy	Assembly	
				Pre	Final
SC1	$C_{sec,PDx}$	$C_{WS_{assm}PDx}$	$C_{Ret_{assm}PDx}$	$Ca_{pre,PDx}$	$Ca_{fin,PDx}$
SC2	$C_{sec,PDx}$	$\frac{C_{WS_{mod}PDx}+C_{WS_{assm}PDx}}{2}$	$C_{Ret_{assm}PDx}$	$Ca_{pre,PDx}$	$Ca_{fin,PDx}$
SC3	$C_{sec,PDx}$	$C_{WS_{mod}PDx}$	$\frac{C_{Ret_{mod}PDx}+C_{Ret_{assm}PDx}}{2}$	$Ca_{pre,PDx}$	$Ca_{fin,PDx}$

Value model for cost-effectiveness

To model the value of integrated product and production system concepts, Equation 4.5 is adopted along with the approach described in Section 4.2.3. The value descriptions of the concepts are based on the patient benefit metrics established in the **evaluative domain** (i.e., B_{dose} and $B_{release}$) and the production cost models presented in Table 4.8.

4.5.2 Case study D

Case study D aimed to investigate the degrees of product modularization and postponement of the integrated production and production system concepts on cost-effectiveness; for this purpose, the nine concepts illustrated in Figure 4.7 were selected. Platform models were developed for these integrated product and production system concepts. Platform execution generated treatment portfolios manufactured and supplied throughout the respective reconfigured SC archetype for which the value was assessed. A case study was designed to generate and assess these treatment portfolios.

Two therapy archetypes were selected to represent two types of treatment regimens. For therapy archetype 1, a fixed regimen was selected using an SSRI treatment as a model therapy (the same as in case study A); for therapy archetype 2, a dynamic regimen was selected using an antiepileptic drug as a model therapy.

Based on the model therapies, patient populations were generated to describe the dose strength need of the patients and the dose strength window. For therapy archetype 1, the same approach to patient needs modeling is adopted as in case study A (see Section 4.2.4), but the execution bandwidth of the dose strength is set to 25 to 200 mg. For therapy archetype 2, because this model therapy follows a dynamic treatment regimen, a 10-week treatment period with dynamic treatment needs and dose strength windows was modeled. See Section 4.1.2 in paper D for details on the modeling.

The modular product design imitates that of case study A, which means that two API cores with dose strengths 10 and 5 mg respectively, two types of lids A and B and a single cup are used for treatment configuration; however, the filling module is disregarded as the design requirement size scalability exceeds the scope of this case study. To assess cost-effectiveness, the value model described in Section 4.5.1 was used.

The same three scenarios of weightings of w_B and w_C are assessed here similar to case study A, Section 4.2.4: *Value 50-50*, *Value 67-33*, and *Value 33-67*. The cost-effectiveness of an integrated product and production system concept embracing modular product design (i.e., L-SC1, L-SC2 and L-SC3 and H-SC1, H-SC2 and H-SC3) is assumed when their value scores exceed those of the reference designs (i.e., R-SC1, R-SC2 and R-SC3).

Case study results

Tables 4.9 and 4.10 display the results from assessing the value of the integrated product and production system concepts for both therapy archetype 1 and therapy archetype 2 respectively. These results are not cross compared since the aim is to find the integrated product and production system design for the therapy archetype generating the highest value within its context. The concepts are ranked based on their value scores to give an overview of how the concepts relate to each other.

Table 4.9: The value score for each integrated product and production system concept for therapy archetype 1. Based on the value scores, a ranking is given

		SC 1			SC 2			SC 3		
	Concept	R	L	H	R	L	H	R	L	H
Therapy 1	*Value 50-50*	2.99	3.02	3.00	3.00	3.02	3.20	3.00	3.03	3.60
	Ranking	9	4	6	6	4	2	6	3	1
	Value 67-33	2.32	2.84	3.68	2.32	2.84	3.81	2.32	2.84	4.07
	Ranking	7	4	3	7	4	2	7	4	1
	Value 33-67	3.67	3.19	2.32	3.67	3.20	2.59	3.68	3.21	3.12
	Ranking	2	6	9	2	5	8	1	4	7

Table 4.10: The value score for each integrated product and production system concept for therapy archetype 2. Based on the value scores, a ranking is given

		SC 1			SC 2			SC 3		
	Concept	R	L	H	R	L	H	R	L	H
Therapy 2	*Value 50-50*	2.80	3.26	3.00	2.80	3.26	3.20	2.80	3.26	3.60
	Ranking	7	2	6	7	2	5	7	2	1
	Value 67-33	2.19	3.12	3.68	2.19	3.12	3.81	2.19	3.12	4.08
	Ranking	7	4	3	7	4	2	7	4	1
	Value 33-67	3.41	3.40	2.32	3.41	3.40	2.59	3.41	3.40	3.12
	Ranking	1	4	9	1	4	8	1	4	7

The results in Tables 4.9 and 4.10 show that the best conditions for cost-effectiveness is achieved by combining product modularization and postponement, which is true for the scenarios *Value 50-50* and *Value 67-33*, where the modular product design with highest degree of modularization and postponement (H-SC3) results with the highest value score. If production cost is emphasized before benefit, referring to scenario *Value 33-67*, cost-effectiveness cannot be achieved for the modular product designs since the reference product design achieves the highest value score for each SC archetype.

The effect of postponement can be seen when comparing the same product design for respective SC archetype. Fixing the product design also thus fixes the patient benefit score. Comparing, for example, the concepts H-SC1, H-SC2 and H-SC3 with each other show that an increased degree of postponement increases the value score i.e., SC1 $\rightarrow$ SC2 $\rightarrow$ SC3. This means that the score for production cost must increase with an increasing degree of postponement. This can be seen in respective scenarios of weightings, *Value 50-50*, *Value 67-33* and *Value 33-67*.

The effect of product modularization is not as clear as the effect of postponement since an increased degree of modularization both increases the patient benefit score and the production cost score. Often, a higher degree of modularization leads to a higher value score, when fixing the

SC archetype. This can be seen when comparing, for example, R-SC3, L-SC3 and H-SC3 with each other. At times the cost of increased degree of modularization exceeds, however, the increase achieved in patient benefit. This is the case, for example, for therapy archetype 2, L-SC2 and H-SC2, see Table 4.10.

A valuable finding is that of therapy archetype 2, which already in its reference design poses a high product variety; in Section 4.5.2 it was described that this model therapy produces scored tablets in four dose strength variants. For the concepts L-SC2 and L-SC3, results show that the product variety management cost of the stakeholders in the SC before *point of variegation* is lower than for the same stakeholders managing the reference product design for the respective SC archetype, i.e., R-SC2 and R-SC3. These results are displayed in Paper D, Table A2. The reason is that the lower-Np design can produce and manage less components up to the *point of variegation* than the reference product design does and still generate a patient benefit score exceeding that of the reference design.

5

Discussion

In this chapter, each research question posed in the introduction chapter is answered. Furthermore, the quality of the research outcomes is discussed as well as the scientific and industrial contributions.

5.1 Answer to research question 1

RQ1: *How can product modularization support the design of customized pharmaceutical products?*

Two main approaches are presented to establish increased product variety for customization in a pharmaceutical product context: the *modular approach* and *scalar approach*. In the *modular approach*, components satisfying product design requirements for customization, formulated as product functions, are integrated into the product design. In the *scalable approach* to product variety, flexibility is built into the product design requirements. Scalability is achieved by scaling the number of components used to provide for a product function by using components with variant characteristics. The *modular* and *scalable* approaches are demonstrated as enablers of pharmaceutical product customization. In paper A, API cores are introduced to comply with the product design requirement dose strength. Dose strength scalability is achieved by scaling the number of API cores, where the smaller the dose content of the API, the larger the obtained dose strength scalability. Lids and cups are introduced to control the target release profile, where increased flexibility into target release profiles is achieved by incorporating an increasing number of lid variants with

various physical characteristics. Finally, filling modules are introduced to scale the treatment size, where variable treatment sizes are achieved by incorporating a varying number of filling modules into the product. Section 4.2 demonstrates the feasibility of product modularization as a strategy to establish customized pharmaceutical products.

Through product modularization, the desired product design requirements can be effectively adapted according to patient needs. Product parts that satisfy the respective design requirement can be produced as standardized components, which can then be assembled into treatments in the required ratio to satisfy individual patient needs. The advantage of product modularization is that a substantial increase in the external product variety can be achieved by producing a few different variants of a certain component. This finding is evident in Table 4.2, where modular product designs are compared to the reference product design.

Section 2.2.2 discussed commercial product designs that hold potential for customization, such as tablets enabling splitting or multiple unit dosage forms. In the case study of paper A creating variety through splitting, a portfolio of tablets were used as a reference design and point of comparison when evaluating the potential for external product variety of the portfolio created by the modular product designed for customization. The results displayed in Table 4.3 show that the ability to create external product variety using modular product designs substantially exceeds the ability to create it using the reference design. Multiple unit dosage forms can achieve dose strength scalability similar to product modularization; for example, Aleksovski et al. (2015) discuss mini-tablets as enablers for customized pharmaceutical products. Aleksovski et al. (2015) further suggest target release profile flexibility to be achievable by mini-tablets. In this case, the discussion solely concerns a dose-dependent release, which means utilizing the inherent release properties of mini-tablets. The discussion did not include creating release flexibility in a controlled manner, such as by using lids and cups as suggested in this thesis; nevertheless, the current discussions on commercial pharmaceutical products remain in a MP context with a product design which was neither intended nor designed for a customization context. Furthermore, no elaborate cost estimations can be found regarding cost-effective customization.

Cost-effectiveness, measured as a weighted sum between the increase in patient benefit and increase in production cost, however, is not solely obtained by product modularization. This finding is evident from Table 4.3

for scenario *Value 50-50*, where the reference design acquires a higher final score than any modular product design. The indication is that through product modularization, the relative production cost increases faster than the relative patient benefit.

For customization, the product design requirements of dose strength, target release profile and treatment size were addressed, which are not an exhaustive set of design requirements. Because Section 4.2 presented a general approach to establishing customized pharmaceutical product designs, the integration of the remaining design requirements can be performed by following the suggested approach. Future research should study the integration of these design requirements and their realization as components. While using the proposed approach to establish customized pharmaceutical products of specific therapies, the selection of the design requirements from the extended set should be based on the needs of the therapy and the final system model should be adapted accordingly, which enables eliciting the real trade-off between the patient benefit and production cost for a specific therapy.

5.2 Answer to research question 2

RQ2: *What challenges the cost-effective production of customized pharmaceutical products?*

Manufacturing system challenges

Paper B studied the process flexibility of the currently operating manufacturing system when operated in a customization context. The modeled manufacturing system comprised the tablet-punching process. In the case study presented, the current manufacturing system was adjusted to be able to operate in a customization context. The customization context was created by the product designs, which embraced a modular product design for the purpose of dose strength scalability. To enable fabricating these modular product designs, the tablet punch was changed from a single-tip punch, used for tablet fabrication, to a multi-tip punch, by which the modules ought to be fabricated. The results in Table 4.4 suggest that this adjustment does not achieve cost-effectiveness, which was described as the time of tablet punching being inferior to the acceptable time of tablet punching for modular product designs. This acceptable time was based

on the punching time of the conventional tablet design used as a reference case and increased by the quantity of treatment outcome increase (treatment quality) achieved by product modularization. The results from case study B suggest that the increase in tablet-punching time is not justified by the increase in treatment quality; thus, as a strategy to increasing patient benefit by improving treatment quality, product modularization entails feasibility challenges in manufacturing from a cost perspective.

Beyond the tablet-punching operation, the manufacturing system includes a set of unit operations to produce tablets, which have not been modeled and are thus, not accounted for. These unit operations are mainly batch based with low flexibility (Srai et al., 2015; Wilson, 2016); thus, accounting for these unit operations might promote a cost-effective production of modular product designs. The reason is that concerning the case study presented in Section 4.3.3, for example, instead of producing three tablet variants (i.e., the reference design), a single module is produced (i.e., the modular product design), and thus fewer changes are applied between fabricated product variants during production.

Change-over times were not considered in the model but can be two- to three-fold the production time (Wilson, 2016). Accounting for change-over times will influence the final result and benefit modular product designs before conventional product designs. A change-over is required between every produced tablet variant (or module variant); thus, if comparing modular product designs to the conventional design, to create the same level of customization for both designs, fewer modules need to be produced for the modular product design than tablet variants of the conventional product design. This is because for the modular product design, a few standardized modules can establish a substantial increase in the level of customization, whereas for the conventional product design, each customized product variant needs to be separately produced. The number of change-over processes for the modular product design is thus likely to decrease compared to the conventional product design. In a customization context, however, a sufficient increase in product variety is expected, and achieving this variety might require producing an increased number of module variants which might exceed the capacity of the manufacturing system offered by cost-effective means. The challenge becomes identifying the level of customization required and how the product and manufacturing system should be designed to be able to offer this level of customization to achieve an acceptable increase in production cost.

The assembly process is also not accounted for but significantly affects the results. When modular products are manufactured, they need to be assembled into treatments. Whether to fill modules in capsules or glue modules together, adding this process will increase the production cost of modular product designs and challenge the cost-effective manufacturing of customized pharmaceutical products.

After defining the overall manufacturing system for modular product fabrication and the assembly process, the model to assess the cost-effectiveness of manufacturing should be expanded. A comprehensive system model that includes these unit operations beyond the tablet-punching operation and incorporates change-over processes provides a better basis to conduct trade-off analysis between the benefit of product modularization and cost of production from a customization perspective.

Supply chain challenges

Paper C analyzed the currently operating pharmaceutical SC or "as-is" design from the perspective of its operation in a customization context. The consequence of a customization context is increased product portfolio complexity, which challenges the cost-effectiveness of the SC operation. The challenging factors are:

- Production process capacity utilization
- Inventory levels
- Material consumption
- Economies of scale
- Operational lead time
- Delivery complexity
- Quality control
- Risk of errors
- New working procedures

The capacity utilization rate of the production processes decreases due to increased equipment downtime, which is caused by the increasing number of changeovers during production caused by an increased product portfolio complexity. Inventory levels are increased due to an

increased number of product variants, which induces an increase in the stock levels of the total inventory (even if the stock levels per product variant were kept unchanged). An increase in material consumption is a consequence of the increased need for material purchases for a larger variety of product variants, and a consequential risk is the accumulation of waste and unnecessary material consumption due to an increased risk of material expirations. Decreased economies of scales are a consequence of producing an increased product variety since smaller volumes of an increased number of product variants need to be produced. An increased operational lead time is caused by more frequent interruptions to the production flow due to an increased product variety, and additional handling and moving of parts and products are required. The delivery complexity of the products to the subsequent SC stakeholders is increased since an increased number of product variants in lower volumes is delivered instead of bulks of product variants. The effort in quality control is increased due to an increasing number of batches produced with product variety, because the quality is controlled for each batch using the current quality control approach. An increased risk of errors is a consequence of an increasing number of processes, operations and work tasks throughout the supply chain that must be performed due to an increase in product variety. Finally, an increased product variety requires an increased number of new working procedures of SC stakeholders since additional support tools and education are needed to manage the SC.

These challenges were elicited through an analytical assessment applying the premise that a customization context requires an increased product portfolio complexity. This analysis was performed using literature from the pharmaceutical production field and non-pharmaceutical production research, including topics such as product variety management and MC. In addition, the assessment assumed a qualitative nature. The magnitudes of decrease in the performance criteria were not elicited but should be addressed in the future. Future research should also include verifying the challenges regarding real production data.

5.3 Answer to research question 3

RQ3: *What reconfiguration strategies can support the cost-effective production of customized pharmaceutical products, and what challenges appear when trying to implement these strategies?*

Strategies

Reconfiguration strategies to support cost-effective production were identified in paper C. Two strategies to mitigate product portfolio complexity and reduce production cost are applicable when placing the *point of variegation* at the wholesaler or later in the SC, such as SC 2, SC 3 and SC 4:

1. Bulks of standardized DPs in intermediate (IM) packaging can be manufactured and supplied through more stages of the SC.
2. Identical drug products (DPs) from different manufacturers can be considered the same DP, decreasing the number of product variants.

When manufacturing and supplying bulks of standardized DPs, instead of a product portfolio consisting of customized pharmaceutical products, fewer batches of larger quantities are managed throughout the SC up to the *point of variegation*; thus, the operational effort is decreased due to a decreased complexity of the product portfolio to be managed up to the point of variegation in the SC. This finding was also showed by Nolan and Ploszczuk (2021), who suggested postponement scenarios in the pharmaceutical SC to reduce lead-times and inventory levels. Furthermore, identical DPs from different manufacturers could be considered the same DP, which would decrease the number of product variants to be managed throughout the SC. The same product, categorized according to its clinical benefits, are manufactured by several manufacturers. Even though the final formulation of the products might differ, these products must at least contain the same active ingredient, have the same strength and dosage form and route of administration (U.S. Food and Drug Administration, 2021a). If these DPs could be treated as the same product, the product portfolio complexity could be decreased. This aspect could especially be advantageous if the product assumed a modular product design, as established throughout Section 4.2; for example, the API core or active ingredient and dose-determining part of the product could be standardized, and the diverting portion of the dosage forms (which diverts the DPs of different manufacturers) could then be realized as modules of their own.

Another strategy to improve patient benefit is:

3. By direct delivery or SC 4.

By delivering the prescriptions directly to the patient as illustrated in SC 4, the patient benefit can be increased by eliminating their effort of

acquiring prescriptions at the pharmacy. Studies on prescription-filling rates have shown that 30% of first-time prescriptions of some medications are left on the pharmacy shelf in the US (The Network for Excellence in Health Innovation, 2014); pediatric patients discharged from the emergency department displayed a prescription-filling rate of 65% in the US (Kajioka et al., 2005); and a case study on historical data of prescription-filling rates of a healthcare service provider in the US showed an overall rate of 72.3% (Chang et al., 2017). A direct delivery could be a solution for improving adherence by relieving the effort of acquiring the treatment.

Challenges

When reconfiguring the pharmaceutical SC, the following challenges emerge in connection to moving the *point of variegation*

1. The position of *point of variegation*
2. Reallocation of the packaging process

A key challenge is to investigate where the *point of variegation* should be placed and thus where the final assembly is performed. Performing the final assembly requires technology, education and resources of the stakeholder, and the challenges include deciding, for example, which stakeholder is the most suitable to perform the assembly process, what type of assembly process to use and what level of customization is required in the pharmaceutical products.

In addition, the packaging process need to be reallocated while moving the point of variegation, which includes considering the responsibility, scope and location of this process. As described in paper C (see Figure 4), packaging and labeling requirements by various regions and countries are responsible for introducing complexity into the product portfolio (Wilson, 2016; Govender et al., 2020c), which could be a ten-fold increase in product variety in an MP context. Distributing the operation of packaging and labeling close to the respective market served thus enables mitigating the complexity arising from the requirements in different regions and countries (Savage et al., 2006; Verhasselt and Friemann, 2012).

The following challenges are connected to a direct delivery scenario, which poses a more drastic reconfiguration to the SC since the pharmacy is eliminated (i.e., SC 4):

3. Increased complexity in prescription delivery to the point of the patient.
4. Elimination/reallocation of pharmacy functions.

The challenge of prescription delivery to the point of the patient increases complexity since instead of supplying products through established channels to the pharmacy, the prescriptions are delivered to each individual. Considerations should include who performs this deliver and how a safe and timely delivery can be assured. Furthermore, eliminating the pharmacy from the SC eliminates the operations of the pharmacy, which might indicate an overall increase in the operational performance of the SC by, for example, decreasing operational lead time; however, this change also eliminates vital functions performed by the pharmacy, such as ensuring patient safety, and these activities thus must be provided by other means.

Costs are also induced by adopting the complexity mitigation strategies via reconfiguration, where the real trade-off between the gains and losses is not yet completely understood. This gap calls for future research directions to establish system-level quantitative models clarifying the trade-off between reconfigurations and the resulting impact on production cost.

In addition, the SC reconfigurations have not considered the scenario of placing the *point of variegation* by the patient, which could reduce the operational effort of the remaining SC stakeholders since the patient becomes responsible for performing the final assembly of the treatment. The challenge of ensuring a sufficient quality of the final treatment arises, however, and future research should investigate how much operational effort can be reduced by placing the *point of variegation* by the patient and whether the emerging challenge with that is technical, psychological, regulatory and so forth.

5.4 Answer to research question 4

RQ4: *How can a later point of variegation support a cost-effective production of customized pharmaceutical products?*

As discussed in answer to RQ3, strategies to decrease product portfolio complexity can increase the operational performance of the SC since bulks

of DPs in IM packaging can be managed throughout the SC. The product portfolio reaches its full complexity at the *point of variegation*; thus, the later the *point of variegation* is placed in the SC, the more the operational performance of the SC stakeholders can be improved. The results in the case study of paper C suggest that the reconfigured SCs show a gradual improvement in cost-effectiveness with a later *point of variegation*, (i.e., SC 1 $\rightarrow$ SC 2 $\rightarrow$ SC 3). An increased performance for the criteria *capacity utilization*, *operational lead time*, *delivery complexity*, *effort in quality control* and *risk of errors* is thus expected with a higher degree of postponement along with an increasing overall economy of scale is expected. Post-*point of variegation*, a fully complex product portfolio needs to be managed downstream the SC. An increased degree of postponement decreases the *time to patient* due to minimizing the number of stakeholders managing the product before it is acquired by the patient, which enables the fastest response to patient prescriptions.

The results of the case study in paper D verify the conclusions of Paper C, which is that practicing postponement can keep the production cost low in the SC until the *point of variegation*, as indicated by results in Tables 4.9 and 4.10 and by results on the performance of production cost in Tables A1 and A2 in Appendix A in paper D. Manufacturing and supplying a low number of product parts keep the costs of the secondary manufacturer, wholesaler and pharmacy low until the *point of variegation*, where the product portfolio reaches its full complexity in product variety. The results in paper D reveal that an increased degree of postponement is a key factor for a decreased production cost compared to production costs of scenarios with lower degrees of postponement. The patient benefit can be improved by increasing the degree of modularization in the final treatment variant; hence, a strategy which combines postponement and product modularization provides the conditions to achieve the cost-effective customization of pharmaceutical products. The conclusions drawn from the results in paper D are based on simulation models for integrated product and production system concepts which have been adapted based on two real-life therapy archetypes, for which simulations concerning cost-effectiveness have been performed. This means that the conclusions are implications based on the selected therapy archetypes.

A challenge with an increased degree of postponement is the increased inventory levels required to be kept before and at the *point of variegation* if a timely response to patient needs is desired (given that a timely response to the patient need is prioritized before low inventory levels). Similar

conclusions were reported by Nolan and Ploszczuk (2021) in their study on pharmaceutical postponement, where they suggested keeping a safety stock to increase the response to order fulfillment and hence decrease lead-times. This timely response to patient needs can, however, also lead to unnecessary material consumption and an increased risk of stock expirations, because safety stock is produced to be responsive to a fluctuating demand of patient needs.

The trade-off between the decreased operational effort and increased inventory and material consumption is a consequence of the assumption made when establishing designs for the suggested reconfigured SC archetypes. These archetypes were designed under the premise that the *point of variegation* aligns with the position of the *prescription statement*. This thesis has not considered an unaligned *point of variegation* and *prescription statement*, which would result in other trade-offs, for example, by placing the *prescription statement* by the secondary manufacturer to match the production to the treatment need, and the *point of variegation* by the pharmacy to minimize the product portfolio complexity would inevitably increase the time to patient since the produced components would need to be supplied throughout the SC after placing the prescription statement. Future research should address the trade-off between the operational effort and the inventory levels and material consumption and should address the point of *prescription statement* in relation to the *point of variegation*.

5.5 Validation and verification

This section evaluates the outcomes of the research conducted in this thesis. As described in Section 3.3.4, the validation square by Seepersad et al. (2006) is used as a framework to systematically evaluate the research outcomes presented in this thesis.

Supports are proposed in each appended paper, and the measurable success criteria for their evaluation were outlined in Section 3.3.4 and are repeated below:

(A) From a *process* perspective, the supports developed in the PS stage should:

  i enable the design of customized pharmaceutical products by enabling the integration of product design requirements complying to patient needs;

ii enable the design of pharmaceutical products with adaptable product design requirements according to individual patient needs;

iii enable the integrated design of products, manufacturing systems and SCs;

iv enable the assessment of the patient benefit, production cost and value of the established product, manufacturing system and supply chain designs.

(B) From an *outcomes* perspective, by applying the supports developed in the PS stage, cost-effective designs for pharmaceutical product and production systems in a customization context should be achieved.

5.5.1 Theoretical structural validity

Examining theoretical structural validity consist of two steps: validating individual constructs and validating the consistency of the assembled support based on the individual constructs.

Construct validity

According to Seepersad et al. (2006), construct validity can be proven by the wide acceptance of these constructs in the literature. For product and manufacturing system design in papers A, B and D, the EF-M and elaborated CC method were used, which are methods based on function-means modeling. Using function-means modeling for product architecture design has a long tradition tracing back to, for example, (Tjalve, 1976), and this modeling approach has since evolved in various directions. Representing evolvements to the function-modeling approach, EF-M and CC methods have been more recently illustrated by, for example, (Michaelis et al., 2013; Levandowski et al., 2014; Michaelis et al., 2015; Müller et al., 2020; Borgue et al., 2021). These studies have demonstrated that these methods work for product and/or manufacturing system designs within non-pharmaceutical contexts, such as aerospace and automotive. This finding suggests that EF-M and CC methods are accepted and well tested by the research community for product and/or manufacturing system design.

In papers A and D, the concept scoring approach by Ulrich et al. (2020) was adapted as an approach to describe concept value. Similar approaches

found in the literature are presented in Section 2.5.1 and include the concept design analysis (CODA) method by Eres et al. (2014) or the elaborated approach Early Value Oriented design exploration with knowledgE maturity (EVOKE) by Bertoni et al. (2018), both of which were demonstrated as value-driven design approaches in the context of an aeronautical SC. Another approach called the multi-criteria decision-making process by Bertoni (2019) is based on the CODA method but integrates a larger sustainability perspective for decision-making, which was demonstrated in the context of designing an electric site for mining operations. In paper C, the concept screening approach by Ulrich et al. (2020) was used for concept evaluation. The concept screening matrix is based on Pugh's method of controlled convergence and literature from, for example, Harris et al. (2016) in a power train context and Rondini et al. (2020) in a product service system context for low voltage products, which illustrated the usage of this approach for concept screening. The concept scoring and screening approaches are thus suggested to be accepted by the research community to describe concept value.

Internal consistency

To build confidence in the internal consistency of a support, Seepersad et al. (2006) suggest the usage of flow schemes, mathematical models or logical arguments. Papers A, B and D proposed design methodologies assembled from constructs and hence documentation on the logical buildup of each methodology to build confidence in their internal consistency has been provided in respective paper. This documentation describes the logical links between the individual constructs, meaning the information input to a construct, the transformation of this information in the construct and the output of the construct, which then serves as an input into the next construct. In paper A, this documentation is provided in Section 3. Papers B and D provide flow schemes illustrating the flow of information to support the logical arguments of the links between the constructs, which is presented in Section 3.1 in paper B and in Section 3.2 in Paper D.

5.5.2 Empirical structural validity

According to Seepersad et al. (2006), the empirical structural validity can be proven by showing that the selected case examples are similar to the intended use cases of the constructs by describing the adequateness of the case examples as representing actual problems for which the supports

are intended and by proving the appropriateness of the data collected to support conclusions.

1. Similarity of case examples to general usage of constructs

In the design methodologies proposed in this thesis, the CC and EF-M methods are used for the purpose of integrated product and/or manufacturing system design of pharmaceutical products and are intended to be used in the following way:

- to integrate product/manufacturing system design requirements by using them as functional requirements of the product/manufacturing system in function-means structures;
- to realize the features of the product parts and the machinery of the manufacturing system in the function-means structures by establishing a component tree structure;
- to integrate the product domain and manufacturing system domain in production processes by identifying the interaction between the product and manufacturing system;
- to establish product/manufacturing system platforms from which concept variants can be generated.

Michaelis et al. (2013), Levandowski et al. (2014) and Michaelis et al. (2015) used CC for integrated function modeling of product and manufacturing systems establishing function-means structures and furthermore to establish component domains for the feature realization of these function-means structures. These integrated models were developed into platforms whose execution generated sets of integrated product and manufacturing system concepts. In addition, the product and manufacturing system domain interaction in manufacturing operations were demonstrated by the approaches of (Michaelis et al., 2013; Levandowski et al., 2014; Michaelis et al., 2015). An elaboration of the interaction modeling in manufacturing operation, called the producibility model, is illustrated in the works by Madrid et al. (2016), Landahl et al. (2017) and Landahl et al. (2021), which has been adapted in this research to model the interaction of the product and manufacturing system domains. Müller et al. (2019) used EF-M for the purpose of design space exploration to generate sets of alternative design concepts to create a new product variant. All the mentioned approaches to applying CC and EF-M methods focus on generating sets of

variants to explore and choose a single product/manufacturing system design. In this thesis, however, the CC and EF-M methods are used to generate product portfolios, which means generating alternative product variants of a product portfolio from a defined platform. The approach to generating these sets of product variants is similar, although the end goal of using these approaches differs; nevertheless, the usage of the CC and EF-M methods in this thesis represents an intended usage and is similar to previous uses of these constructs.

The concept scoring approach was adapted as a value-driven design approach to select the most value-creating pharmaceutical context for customization. The purpose of this approach was:

- to establish a link between concept performance and stakeholder needs (patient needs and production cost considerations) by describing criteria for concept scoring;
- to enable weightings of the criteria and thus enable the simulation of alternative business strategies;
- to comprehensively enable describing the value of a concept.

Similarities in the intended usage of the approach can be identified with the CODA matrix by Eres et al. (2014), the EVOKE approach by Bertoni et al. (2018) and the multi-criteria decision-making process by Bertoni (2019). Each of these approaches build on the CODA matrix, whose purpose is to link the various engineering characteristics (or concept performance) with the customer and stakeholder needs translated into value criteria (criteria) as well as to assign weights to these value criteria for the purpose of simulating various business strategies. Finally, the CODA matrix allows assigning each concept a merit score, which aims to describe the value of this concept and thus facilitates selecting the concept embracing the highest value. The intended usage of the concept scoring matrix in this thesis thus far aligns with established usages of similar approaches; however, the CODA matrix uses a quantitative variant of quality function deployment to additionally describe the correlation between each engineering characteristic and value criteria and thereby establish internal weightings of engineering characteristics, where engineering characteristics with a stronger correlation to value criteria are more visible in the final merit score. This approach has not been used in this thesis but could be considered in future research to incorporate such internal weightings. In this thesis, the criteria are assigned equal weights since the relative importance between the value criteria was not

studied; for example, this research did not investigate whether the benefit of a product from a dose strength perspective is more important for the therapeutic outcome than it is from a target release profile perspective.

In paper C, the concept screening approach by Ulrich et al. (2020) was used for qualitative concept comparisons. The concept screening matrix was selected to screen early-phase concepts of the reconfigured SC designs in this thesis and to allow visualizing the connection between the concepts and value criteria. This approach is based on relative comparisons and suits early design concept screening and does not require detailed data, which was not readily available in paper C. This usage is similar to that of Harris et al. (2016) and Rondini et al. (2020), where this approach was used as an early concept screening method and visualization of customer needs in an early-design phase where detailed data are not available.

2. Similarity of case examples to actual problems

To illustrate the usage of the supports, case studies have been performed in respective papers. For each case study, therapy archetypes have been selected based on real-life therapies. Regardless of the disease, some level of customization is desired in the treatments, whether with respect to dose, release, size or other design requirements (Aleksovski et al., 2015; Govender et al., 2020c). The real-life archetypes selected can thus be considered as realistic examples and accurate representations of a design problem for which the methodologies proposed in this thesis are intended. In paper B, a diabetes treatment was selected as a model therapy for the case study due to the proven manufacturability of this treatment as mini-tablets (Goh et al., 2017). An SSRI treatment was selected to represent a fixed regimen therapy, representing a treatment which is not changed during its course, which was used both in the case studies of papers A and D. In paper D, an antiepileptic drug was also selected to represent a dynamic regimen, which means a treatment that changes during its course. A second reason for selecting the antiepileptic drug was that this drug is already available in a high variety on the market. The model therapies selected for paper D were intended to represent two extremes of product variety. Furthermore, the selected therapies in each case study regard oral dosage forms, specifically tablets. The tablet was selected as a representative dosage form due to being the most common dosage form (Plumb, 2005; Nagashree, 2015; Wilson, 2016).

In paper B, the tablet-punching system and tablet compression unit

operation were selected to represent the manufacturing system and the unit operation studied in the case example for two reasons: Firstly, if the manufacturing were adjusted to produce modules instead of tablets, the adjustment would likely affect the tablet punching operation since, secondly, multi-tip punches are available that can be used in the tablet-punching system to punch minitablets or modules, which also aligns with the geometrical properties defined for the modular products in the case study.

Papers C and D studied reconfigured SC archetypes and selected business models operating in mass customization/high product variety environments to be adapted into a pharmaceutical context. SC 2 is based on the retail corporation Walmart, SC 3 is based on the fast-food chain Subway and SC 4 is based on Dell. These business models were selected based on their already successful operation.

3. The data collected to support conclusions shall be proven appropriate

Simulation models were established for the case studies along with simplifications and assumptions, whose validity is discussed below.

Patient populations were modeled in the case studies of papers A, B and D. These populations describe patient needs and were used to inform the product variants to be configured for each treatment portfolio and were used to assess the quality of these treatments with respect to patient benefit metrics. Patient needs were described through their dose-strength needs, and due to the absence of this data, these needs were modeled as a normal distribution over the dose-strength range defined by the selected therapy archetype. A normal distribution was selected because natural phenomena can acquire a normal distribution such as blood pressure, IQ and height Frost (n.d.); however, it remains unverified whether this is the best distribution to describe patient needs, which might challenge the generalizations of the conclusions drawn from the simulation results.

Modular product designs were proposed for the case studies of papers A, B and D. To verify the manufacturability of such product designs with respect to product dimensions, these designs imitated commercially manufactured product designs such as minitablets as well as cores, lids and cups fabricated in laboratory environment (Goh et al., 2017; Govender et al., 2020a,b). The manufacturability of such product designs is therapy-archetype specific, however, and dictated by the product's material com-

position. While adapting the methodology to any therapy archetype for which customized pharmaceutical products are to be designed, the manufacturability must be verified with respect to size, shape, dose strength, material composition and so forth.

In the value modeling in papers A and D, metrics for patient benefit and production cost were consolidated into a single value score. The metrics use different measurement units, and to overcome this difference, each concept was compared regarding each metric in isolation and assigned a score on a normalized scale. This normalization process risks losing the magnitude of increase or decrease in respective relative metric. A high value score of a concept might indicate that the relative patient benefit increases faster than the relative cost but does not describe the increases in absolute terms. Future research should study how patient benefit and production cost can be assessed in absolute terms.

Two categories of production cost were modeled, namely assembly cost and product variety management cost. To model the assembly cost in papers A and D, the complexity factor by Pugh (1990) was adapted and is based on the number of parts, types of parts and interfaces between parts. This approach cannot be used to provide absolute numbers of the assembly cost and was thus instead used to perform relative comparisons of various product concepts. After outlining the technical assembly process, whether it is gluing modules or filling modules in a capsule, better cost models can be created to describe this process. In paper D, product variety management cost was described for the secondary manufacturer, wholesaler and pharmacy. These cost models are based on the number of product variants to be produced and managed in stakeholder operation to indicate the production cost and were collected from literature in pharmaceutical manufacturing (Wilson, 2016) and product variety management (Thonemann and Bradley, 2002; Benjaafar et al., 2004). These metrics similarly cannot describe production cost in absolute terms, and hence relative comparisons were performed between the concepts and for respective stakeholder in isolation. Furthermore, normalized scores of these costs were used in value modeling. There is a risk of production cost accumulation throughout the SC, which means that considering stakeholder costs in isolation might overestimate or underestimate the overall production cost.

To assess the benefit from a dose strength perspective in papers A, B and D, the concept of *quality decay* by Blackenfelt (2001) was used to

describe the distance between the optimal dose strength need of the patient and the dose strength of the treatment that can be configured using a treatment portfolio. To verify the adequateness of this approach, comparisons of real data regarding the therapeutic outcomes of the patients to modular treatment designs should be performed. There is a lack of existing modular product designs offering tailored dose strengths to patients, which results in a current lack of data describing therapeutic outcomes of patients.

From a target release profile perspective (papers A and D) and treatment size perspective (paper A), the number of choices available for the patient, given their fixed dose strength (and target release profile for treatment size), was used as a proxy for an increased patient benefit. Product variety is accepted as a proxy measure for customization; however, customer involvement in product specification is required for true customization (Lyons et al., 2020); thus, these metrics might overestimate or underestimate the patient benefit. Future research should focus on developing models that describe the target release profile of patients and the patient preference with respect to treatment size. Developing these models to assess the quality of treatments from target release profile and treatment size enables better assessing the patient benefit from these perspectives.

5.5.3 Empirical performance validity

This section discusses the usefulness of the design methodologies proposed in papers A, B and D. The usefulness evaluation is performed regarding the requirements stated at the beginning of this section.

Regarding the *process*-related requirements (A):

i Paper A demonstrated that by using CC method product design requirements, complying to patient needs can be incorporated in a pharmaceutical product design by function-means modeling.

ii Paper A demonstrated that incorporating non-functional requirements to define bandwidths for product design requirement flexibility enables establishing product portfolios with product designs adaptable with respect to product design requirements, which has been further shown by the execution of the platform model which is based on the function model established in (i).

iii Paper B demonstrated that integrated product and manufacturing system designs using EF-M modeling can be established for pharmaceutical products and the corresponding manufacturing system. Paper D demonstrated that integrated designs of product and supply chain concepts can be established.

iv Based on the design methodologies and the resulting designs for product, manufacturing system and supply chain designs, computational models were developed to enable assessing the value of the developed product, manufacturing and supply chain designs for a pharmaceutical customization context. Furthermore, simulations demonstrated that these computational models can assess the patient benefit, production cost and value of the product, manufacturing system and supply chain concepts.

The evaluation of the design methodologies with respect to the design processes was conducted from the perspective whether the methodologies can be used for the design task for which they were intended.

From an *outcomes perspective*, the measurable success criterion is that the design methodologies proposed throughout this thesis can establish product, manufacturing and SC design concepts that are better suited for a customization context than reference designs, which are based on the commercially available product designs. This means that the design methodologies should enable established concepts to display cost-effectiveness.

The case study of paper A aimed to use the design methodology to establish product portfolios consisting of treatments embracing a higher degree of customization compared to the reference product design. Table 4.2 shows that the product portfolios established with the intent of customization displayed a substantial increase in external product variety compared to what can be achieved by the reference product design. Despite this substantial increase in product variety produced, the results in Table 4.3 suggest that cost-effectiveness cannot be achieved since the production cost increases along with the increase in patient benefit. The results of the case study in paper D, however, suggest that the design methodology proposed in paper D, which integrates the approach to modular product design for customization with the reconfigured SC archetypes applying postponement, enables achieving integrated product and production system concepts for cost-effective customization. This finding is shown in Tables 4.9 and 4.10, where the final value score, serving as a proxy for cost-effectiveness, is higher for each modular product design (L

and H) and for any SC configuration (SC1, SC2 and SC3) compared to the reference product design operating in their reference SC designs (R). This finding is true for the scenarios *Value 50-50* and *Value 67-33*, representing when the patient benefit criteria are weighted equal to the production cost, or when the patient benefit criteria are prioritized before the production cost criteria. In addition, the same results are achieved for both therapy archetypes of a static and dynamic treatment regimen.

5.5.4 Theoretical performance validity

Function-means modeling, used to establish customized pharmaceutical product and manufacturing system designs, is a general approach to establish product architectures and hence this approach is generalizable beyond the case studies for which application was demonstrated in this thesis, i.e., beyond the tablet and the tablet punching system. The proposed approach to product and/or manufacturing system design can be adapted to any pharmaceutical or medicinal product and/or its manufacturing system as long as the design requirements of these are known by translating these design requirements into functional requirements, establishing design solutions to these, constraining the functional bandwidths, defining the design solutions as realizable components and so forth. The proposed approaches to value modeling for concept selection, i.e., the concept screening and concept scoring methods, are likewise generalizable beyond the case studies demonstrated in this thesis. These value modeling approaches can be adapted by identifying case specific customer/stakeholder needs which should be serving as concept selection criteria and by identifying the links between the concept performance and the satisfaction of these stakeholder needs.

5.6 Scientific and industrial contribution

The contributions of this thesis can be divided into scientific and industrial contributions.

5.6.1 Scientific contribution

From a scientific perspective, this thesis aimed to adapt strategies and methods from the production and engineering design fields into a new context. This thesis adapted MC principles in a pharmaceutical context. Product modularization was demonstrated as a novel design strategy to

establish customized pharmaceutical products. The function-modeling methods EF-M and CC were applied to establish product architectures for customized pharmaceutical products, representing an original approach to translate patient needs for customization into functional requirements of the pharmaceutical product, to propose novel product designs for customized pharmaceutical products. To the best of my knowledge, no approach to function modeling of pharmaceutical products for customization has been previously demonstrated.

This thesis has demonstrated the applicability of the CC and EF-M methods for the generation of product portfolios of customized product variants. Previously these methods have been used for set-based product development with the purpose to configure alternative product variants and then to choose a single variant for further development.

This thesis demonstrated the integrated design of the pharmaceutical product and its manufacturing system using the EF-M method as well as a requirement change propagation approach for redesign of product and production systems. This approach enables the consequent assessment of product design changes to manufacturing systems and vice versa. To the best of my knowledge, no such approach to the integrated design of product and manufacturing systems of pharmaceutical products can be found.

This thesis demonstrated the adaption of the principle of postponement in a pharmaceutical SC. Previous studies have researched postponement in the pharmaceutical context, such as (Savage et al., 2006; Ladsaongikar and Martinez, 2016; Verhasselt and Friemann, 2012; Nolan and Ploszczuk, 2021). These studies consider an optimization of the currently operating pharmaceutical SC in an MP context, however, rather than exploring opportunities for pharmaceutical MC. To the best of my knowledge, no studies integrating product modularization and postponement as an approach to pharmaceutical MC can be found.

This thesis also adapted value-driven design approaches to the pharmaceutical context to facilitate decision-making between concepts for pharmaceutical customization. To the best of my knowledge, no value-driven design approaches to evaluate pharmaceutical products from a value perspective can be found that integrate a wider patient benefit and production cost perspective connected to customization needs.

5.6.2 Industrial contribution

From an industrial perspective, this thesis presented and demonstrated design strategies, methodologies and models for product, manufacturing system and SC design for a pharmaceutical customization context. This thesis proposed a novel design methodology that guides the systematic development of customized pharmaceutical products. To the best of my knowledge, no such methodology exists. This thesis also suggested product designs, i.e., modular product designs which can increase the quality of the products, where quality concerns the increased compliance with individual patients needs concerning dose strength, target release profile and treatment size.

Furthermore, this thesis proposed an original design methodology for the integrated design of product and manufacturing systems. Consequence analysis can be performed, for example, by changing the product design (for customization), the refined requirements on the manufacturing system as well as the consequences on production can be assessed. In this thesis, this consequence assessment approach was demonstrated in the context of product redesign (for customization) and the effect on production time. To the best of my knowledge, no such methodology exists which allows for system-level simulations to assess the consequences on production cost of alternative product and manufacturing system concepts in a pharmaceutical context.

Reconfigured pharmaceutical SC archetypes were proposed for the purpose of reducing production costs in the SC. These SCs were reconfigured for the purpose of mitigating the product portfolio complexity, which is a consequence of operating the SC in a customization context. This thesis has further identified challenges emerging due to these SC reconfigurations.

Furthermore, a novel design methodology was proposed for the integrated modeling and design of product and production system for pharmaceutical product customization. This design methodology enables developing integrated concepts of modular product designs for customization and reconfigured SC archetypes. Furthermore, this design methodology enables the development of simulation models that allow system-level assessment of the consequences of integrated product design and SC archetype selections on product quality and production cost. In addition, realizations of the integrated product and SC archetype concepts were suggested to simultaneously increase the product quality, concerning the

customization of the product to individual patient needs, while reducing production costs to enable producing customized pharmaceutical products at an acceptable cost. To the best of my knowledge, no system-level models exist that integrate an end-to-end SC perspective for simulations of the consequences of various degrees of product modularization for customization and various degrees of postponement for cost reduction.

6

Conclusions and future research

This chapter concludes the thesis and proposes future research directions.

6.1 Conclusions

To address the challenge of unsatisfactory therapeutic outcomes for patients due to mass-produced, *one-size-fits-all* pharmaceutical products, this thesis explored the cost-effective design, manufacturing and supply of pharmaceutical products that are customized according to individual patient needs. The mass customization (MC) principles of *product modularization*, *process flexibility* and *postponement* were addressed and adapted into a pharmaceutical context for cost-effective customization. The results suggest:

Key finding 1: *Product modularization* can establish pharmaceutical products adaptable to individual patient needs. Furthermore, an increased degree of product modularization is the major factor affecting increased patient benefit and increased production costs.

An increased degree of modularization enables the flexibility of product design requirements to satisfy individual patient needs and thus provides the means to rapidly adapt the pharmaceutical product to the patient. An increased degree of modularization requires the manufacturing, management and assembly of an increased number and variety of parts, modules and assemblies, however, which generally leads to increased

production costs.

Key finding 2: In their current mass production (MP) context, the production platforms do not display the *process flexibility* required to produce an increased product portfolio complexity, which challenges the cost-effective production of customized pharmaceutical products.

Using current MP platforms, the production cost of manufacturing modular pharmaceutical products exceeds the increase in patient benefit achieved through pharmaceutical product modularization. Furthermore, operating the "as-is" design of the pharmaceutical SC in a customization context leads to a high product variety and low volume challenge with consequences such as increased operation costs, delivery time to patient, effort in quality assurance activities and degree of process changes.

Key finding 3: Production-process reconfiguration can support the cost-effective production of customized pharmaceutical products.

One cost-reducing strategy that can be adopted by moving the *point of variegation* by the wholesaler or later in the SC is to manufacture and supply bulks of components in IM packaging further in the SC, thereby reducing product portfolio complexity before the *point of variegation*. In addition, identical components from various manufacturers can be viewed as the same component, thereby decreasing the product variety in the product portfolio. Finally, direct delivery of prescriptions to the patient eliminates patient effort in acquiring them at the pharmacy. These reconfigurations require SC stakeholders to operate new processes and to reallocate and/or adjust their processes; however, and the final trade-off between benefits and costs of production process reconfiguration was not elicited.

Key finding 4: An increased degree of *postponement* is mainly responsible for the decreased production cost of customized pharmaceutical products.

Postponing the *point of variegation* provides conditions for reduced production costs; for example, instead of a complex portfolio of customized treatments bulks of product components can be manufactured and supplied further downstream the SC; however an increased degree of postponement to ensure a timely response to *prescription statements* leads to increased inventory levels and increased material consumption.

Key finding 5: Integrating *product modularization* and *postponement* provides the conditions for cost-effective pharmaceutical product customization.

As a product design strategy, product modularization supports integrating product design requirements into treatments and can, furthermore, do so by standardizing components that are produced and supplied, thereby generating opportunities from a production cost perspective compared to customizing the conventional product design. Postponement can be used to push the *point of variegation* later in the SC, thereby enabling the management of a product portfolio of lower complexity up to the *point of variegation*. This approach provides opportunities for decreased production costs in the pharmaceutical SC compared to if the final customization was performed early in the SC.

6.2 Future research

Several research directions could be adopted to advance the field of MC in a pharmaceutical production context, and a few are described below:

- For pharmaceutical product customization, the design requirements of scalable dose strength, flexible target release profile and scalable treatment size were addressed. This is not an exhaustive set of design requirements for customization, and thus future research should consider integrating further design requirements into the product design.

- Pharmaceutical product designs embracing various degrees of modularization were suggested, and their impact on the patient benefit and production cost were explored. No optimization of product components was performed to find the design that maximizes the trade-off between patient benefit and production cost. Future research can develop optimization models for pharmaceutical product and production system design.

- As an MC principle, process flexibility was mainly studied in the current MP context to elicit challenges. Future research can study novel technologies for pharmaceutical production to increase process flexibility within production.

- The assembly process was not studied from a process or technological perspective; however, modularizing pharmaceutical products requires an assembly process, and thus future research should investigate such an assembly process and related models to estimate the cost of assembly.
- The suggested reconfigured SC archetypes are based on the traditional pharmaceutical SC design and its stakeholders. Other drastic reconfigurations should be investigated, and the consequences of such reconfigurations on cost-effectiveness should be assessed. In addition, a simplified model of the SC was studied which excluded stakeholders such as the hospital. Future research should embrace a wider perspective of the societal challenges of pharmaceutical product customization.
- A few approaches were suggested to determine the cost-effectiveness of product and production system design for customized pharmaceutical products. Future research should address how cost-effectiveness should be described in a pharmaceutical customization context.
- The feasibility of the methodologies and the associated simulation models was demonstrated by using case studies based on real-life therapies as model therapies while using theoretical data. Further validation using industrial production data should be performed.
- The simulation models describing patient benefit and production cost are simplified. More elaborate models should be investigated along with models capturing the patient and societal benefits as well as production and societal costs of customization with respect to a wider time horizon.
- Pharmaceutical regulations were delimited from the scope. A research challenge is to understand the changing role of regulations in an MC context of pharmaceutical products from product and production system perspectives.

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