

THESIS FOR THE DEGREE OF LICENTIATE OF ENGINEERING

**INTEGRATED PRODUCT AND PRODUCTION
PLATFORMS FOR PHARMACEUTICAL PRODUCTS**

DESIGN THINKING FOR THE DEVELOPMENT OF PERSONALIZED
MEDICINES

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Integrated Product and Production Platforms for Pharmaceutical Products
Design Thinking for the Development of Personalized Medicines

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Abstract

Treatments, when customized according to individual patient attributes, are in recent years referred to as personalized medicines. Personalized medicines aim at improving the therapeutic outcome of the patient. However, current pharmaceutical production is dominated by mass production in a batch manner, i.e. producing large volumes of identical products. Uncertainties prevail regarding the ability of current production to respond to the product customization need in an economically and technically realizable manner. However, without customized treatment reaching the patient the benefit of personalized medicines cannot be achieved. Hence, a mass customization-paradigm, i.e. economic feasibility when designing, producing and delivering customized pharmaceutical products, is desired.

Pharmaceutical product customization has been discussed from a product and production perspective. These discussions mainly focus either on product or production design. Additionally, the economic feasibility of suggested approaches is not fully explored. Mass customization requires joint consideration of product and production system design. Hence, the aim of this thesis is to explore integrated pharmaceutical product and production system design facilitating a shift toward mass customization-paradigm.

Methodologies to design the integrated product and production systems of pharmaceutical products supporting customization are proposed. Set-based concurrent engineering (SBCE) principles are adapted due to the ability of efficient product development. Platform-based design is adapted due to a successful approach to mass customization in manufacturing industry. Additionally, an integrated design approach to product value assessment is proposed to emphasize the customized pharmaceutical product value.

The methodology application is illustrated for oral dosage forms for the purpose of demonstrating refined approaches to integrated design of these. Knowledge regarding oral dosage forms as enablers for personalized medicines is generated.

Results show that the adaption of SBCE principles enables efficient consequence analysis of pharmaceutical product designs for production system designs and is accomplished by acquiring a set-based approach to simultaneous assessment of the performance of various designs. Platform-based design enables flexible pharmaceutical product and production system design, thus supporting mass customization. Finally, oral dosage forms embracing modularized designs provide substantial product design flexibility but affects manufacturing complexity and hence, the discussion of product and production system design cannot be separated.

Keywords: Personalized medicines, Mass customization, Integrated product and production platforms

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Maria Siiskonen
Gothenburg, Sweden, May 20, 2019

Appended Publications

The following publications are included in this thesis:

Paper A

Siiskonen, M., Malmqvist, J., Folestad, S., (2019), Product Architecture Management of Medicinal Products: An Integrated Function-Means Tree Approach to Customizing Oral Dosage Forms

Submitted to Journal of Design Research

This is a reworked manuscript of the paper “Applying Function-Means Tree Modelling to Personalized Medicines” published in *Proceedings of NordDesign 2018*. 14-17 August, 2018, Linköping, Sweden.

Distribution of work: Staffan Folestad first presented the idea of Set-Based Concurrent Engineering of pharmaceutical products. Johan Malmqvist supported with knowledge and tools of engineering design, such as product architecting. Maria Siiskonen developed the methodology and conducted the case studies. Maria Siiskonen wrote the manuscript. Johan Malmqvist and Staffan Folestad contributed with knowledge and critique to the papers concept and form.

Paper B

Siiskonen, M., Watz, M., Malmqvist, J., Folestad, S., (2019), Decision Support for Re-designed Medicinal Products: Assessing consequences of customizable product design on the value chain from a sustainability perspective

Paper accepted to the 22nd International Conference on Engineering Design - ICED19, 5 - 8 August, 2019, Delft, Netherlands

Distribution of work: Maria Siiskonen and Matilda Watz conceptualized the paper together. Maria Siiskonen contributed with the work regarding product design and value-modeling. Matilda Watz contributed with the sustainability life cycle assessment. Maria Siiskonen and Matilda Watz wrote the manuscript together. Johan Malmqvist and Staffan Folestad contributed with knowledge and critique to the papers concept and form.

Paper C

Siiskonen, M., Malmqvist, J., Folestad, S., (2019), Integrated Product and Production System Platforms in a Set-Based Manner Enabling Personalized Medicines

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”It’s far more important to know what person the disease has than what disease the person has.”

- Hippocrates

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CHAPTER 1

Introduction

The aimed value of *personalized medicines* is to enhance the therapeutic outcome of the patient, i.e. ensuring a safe and effective treatment [Ahmed *et al.* 2016, Meyer, 2004]. *Personalized medicine* can refer to the means to map the characteristics of a patient in order to guide therapeutic decisions of the patient. Another usage of the term *personalized medicines* refers to the means to provide treatment, i.e. the dosage form, tablet, capsule, inhaler and so forth, that is tailored according to individual attributes to optimize the treatment of the patient [Crommelin *et al.* 2011]. The former concept *personalized medicine* has made significant progress due to advances in diagnostics, nanotechnology and so forth, but the latter concept *personalized medicines*, i.e. tailoring the treatment according to patient attributes, remains at a more infant stage due to the lack of sufficient tools of developing tailored treatments, that can be designed according to patient characteristics, but also manufactured and distributed to an economically feasible manner [Gaspar *et al.* 2012]. To gain the full benefit of personalized medicines, these two concepts need to be connected when the maturity of each concept reaches a sufficient level. The therapeutic outcome of the patient cannot be improved if there are no customized treatments to enable this. Mass customization can be defined in the context of pharmaceutical products as designing, manufacturing and supplying customized products in an economically feasible manner [Govender, 2019]. Hence, the effort of this thesis is to advance the concept of personalized medicines focusing on the product and production design to enable treatment customization in an economically feasible manner, thus, into approaches contributing to a mass customization-paradigm of pharmaceutical products. The formulated drug product is intended throughout this thesis, when discussing pharmaceutical product design.

1.1 Background

Variable patient response to drugs has been a documented fact over the past six decades. Emerging research has shown that patient variability to drug response can be attributed to various biologically determined factors, but also to environmentally and behaviorally

determined factors [Vogenberg *et al.* 2010]. The understanding of underlying causes of various diseases started improving during the 19th century because of adequate advances in the scientific fields of chemistry, microscopy and so forth. Halfway through the 20th century, drug response could be mapped to individual metabolic characteristics. Finally, in the 21st century, the sequencing of human genomics emerged and hence the term personalized medicine was coined [U.S. Food and Drug Administration, 2013].

1.1.1 Problem analysis

Regardless of advancements in patient diagnostics, sequencing of human genomics and so forth, most pharmaceutical products still remain in the *one-size-fits-all*-paradigm. The *one-size-fits-all*-paradigm implies offering each patient the same type of medication to the same symptoms regardless of inter-patient variability.

On one hand, the current lack of tools predicting the patient response to treatments for most diseases gives doctors no choice rather than following the *trial-and-error* approach when prescribing a type of medication. In the event of unsatisfactory therapeutic effect, the medication is changed [U.S. Food and Drug Administration, 2013]. In addition, the existing production platforms are constraining the number of different product variants that are required to satisfy the therapeutic need of each stratified patient group [Wilson, 2016]. Pharmaceutical manufacturing is still governed by mass production in a batch manner with low flexibility and hence uncertainties lies in the level of customization that can be obtained with these platforms. Albeit, continuous production approaches are incrementally adopted by the pharmaceutical industry [Lee *et al.* 2015, Plumb, 2005].

A reason for batch-processing being the dominant approach to pharmaceutical production originates, at least partly, from the highly regulated production environment of pharmaceutical products. The time from drug discovery to market launch consumes a vast portion of patent time. Hence, the time of producing and selling the product on the market before exposed to low-cost competition is short. Additionally, making changes into the production processes of a filed product is a elaborate and complex process with respect to process validation and approvance, and simply, making changes to the production platforms of pharmaceutical products is not perceived as an economically sound business case [Suresh and Basu, 2008].

In response to breakthroughs in diagnostics, sequencing of human genomics and so forth, research regarding pharmaceutical product customization has been emerging. From a product design perspective, discussions of enablers for customization regard multiple unit dosage forms, such as modularized product designs, pellet-based dosage forms or mini-tablets, and have touched upon the topic of these dosage forms as being enablers for mass customization, directly or indirectly [Bonhoeffer *et al.* 2018, Aleksovski *et al.* 2015, Tissen *et al.* 2011, Yeleken *et al.* 2017]. However, literature verifying the full bene-

fits of these product designs cannot be found.

Furthermore, research has been focusing on experimenting with novel technologies of pharmaceutical product design. One such technology is additive manufacturing. By digital design, the material can be arranged as desired and by a layer-by-layer technique the product can be printed [Norman *et al.* 2017]. This provides customization on an individual level when functionalities of the product can be built to match individual patient attributes. The economic feasibility of handling the increasing number of product variants with such a technique currently lacks support. However, from a regulatory perspective, additive manufacturing might be an option for the future. The US Food and Drug Administration (FDA) recently approved a 3D-printed medicinal product [U.S. Food and Drug Administration, 2016].

Besides approaches to customized product design, research considering the management of an increasing number of product variants has been emerging. The focus has been to adjust the existing production platforms and supply chain networks to respond to the increased need for flexibility caused by an increasing number of product variants. For example, continuous production and integrated supply chain networks have been widely researched based on the hypothesis that continuous production provides more robust processes and eliminates difficulties regarding scaling the production. By adjusting the run time of the continuous processes the batch sizes can easily be varied [Plumb, 2005, Srini *et al.* 2015].

However, a relevant problem regarding the development of product and production systems for personalized medicines has been identified. The discussions have either focused on patient-centric product design, i.e. approaches to product designs enabling an enhanced therapeutic outcome of the patient such as multiple unit dosage forms, or on manufacturing technologies enabling a response to an increased number of product variants such as continuous production technologies. Additive manufacturing is a manufacturing technology and a candidate for patient-centric product design, however, the wider implementation of this technology lacks support. An integrated approach to product and production design supporting mass customization of pharmaceutical products is lacking.

1.1.2 Product and production development of pharmaceutical products

Not only is there a need for improvements in product development approaches of personalized medicines, but also for pharmaceutical products in general. The current pharmaceutical product development process acquires the nature of a sequential approach generally based on experimental laboratory work. From the discovery of a new molecular entity, a series of scale-ups follow to an extent depending on the success of clinical trials [Suresh and Basu, 2008]. Since the success rate of clinical trials is fairly low, numbers such as 10% success has been reported [Siew, 2017], the focus of pharmaceutical companies is to

produce pharmaceutical products sufficient, with respect to material amount and quality, for the clinical trials. Developing long-term, robust production systems have thus been a secondary focus. The consequence of not putting enough effort into the development of robust pharmaceutical production processes has been an accumulation of problems during the commercial production of pharmaceutical products. These problems have inevitably caused unnecessary costs for pharmaceutical production [Suresh and Basu, 2008].

There is a need, verified by the FDA, for science and engineering-based tools to improve the product development process of pharmaceutical products. The need is for tools to improve the efficiency of development work by shortening the time from discovery of a new drug entity to market launch. The tools should enable predictions of product behaviour and production system behaviour and hence, provide for robust pharmaceutical production [U.S. Food and Drug Administration, 2004]. Likewise, tools to predict product and production system behaviour hence seems a necessity to enable a mass customization-paradigm of pharmaceutical products as well.

1.1.3 Set-based concurrent engineering

Concurrent engineering is an organizational approach that has attributed many firms, mainly in the manufacturing industry, with successful results as it has shown effects regarding faster market launches of products matching customer needs and expectations [Wheelwright and Clark, 1992]. Concurrent engineering means cross-functional efforts in early product development, i.e. the work of various organizational disciplines is conducted in parallel and allows for information flow across these disciplines. Such disciplines are product design and production process development [Prasad, 1996]. Set-based concurrent engineering (SBCE) is an elaboration of concurrent engineering with the same philosophy of developing products in a cross-disciplinary manner. However, the main idea for SBCE as a product development philosophy is to work with sets of alternative solutions and push the decision-making regarding a final solution to a later stage in the product development process when solutions can systematically with increasing knowledge be narrowed down [Sobek *et al.* 1999].

1.1.4 Integrated product and production platforms

Platform-based product development is an approach to product development supporting industries with mass customization considerations. Platforms have been adopted by manufacturing industries, mainly for discrete part production, due to the ability to generate sets of derivative product variants, i.e. enabling product customization. Platforms have accomplished satisfying customization needs and are still retaining, on occasions even improving, the business [Wortmann *et al.* 1996, Ho and Tang, 1998]. Customization is seen as a strategy to compete on the market by offering product variety and thus, increasing the perceived benefit of a range of customers. From a company point of view, customiza-

tion can hence be perceived as a strategy to increase the overall value of the product by increasing the benefit for a range of customers. In the end, the core purpose of developing products should be to maximize the perceived value by the customer and improve the business.

1.2 Aims and goals

Inspired by successful product development approaches adopted in the manufacturing industry, the overall aim of this thesis is to explore opportunities of adapting integrated product and production platform thinking as design methods in the context of pharmaceutical mass customization. The goal is to find a remedy to the problems of the current tedious, sequential and experimental development procedure of pharmaceutical products where the production development is of secondary focus. Further, initial approaches of predictive tools to develop integrated product and production systems for customized pharmaceutical products are explored.

This exploration is aiming at addressing the gap of lacking integrated approaches to pharmaceutical product customization. SBCE principles are adapted in the product and production development process of pharmaceutical products enabling rapid generation and assessment of product and production system designs of pharmaceutical products. Further, to facilitate the emerging customization need of pharmaceutical products, platform-based design approaches are explored to generate pharmaceutical product families supporting a mass customization-paradigm. A support for product customization is aiming at facilitating an increase in the perceived value by the customer.

Within this thesis, SBCE is seen as a design philosophy supporting the development work and employed due to the proven efficiency achieved in several businesses [Prasad, 1996]. Since platforms have proven an enabler of feasible product customization [Wortmann *et al.* 1996, Ho and Tang, 1998], a platform-based design approach to product development is adapted to support the development of customized pharmaceutical products. Furthermore, throughout the thesis, several studies are conducted and as an illustrative example, the modularized tablet design will be used. The purpose of choosing the modularized tablet design throughout the thesis is to contribute to knowledge regarding the benefits of modularized tablet designs as enablers for personalized medicines.

The thesis aim is concretized into the following goals:

- To adapt platform-based design approaches in the context of pharmaceutical product development to facilitate mass customization of pharmaceutical products
- To propose methodologies by which to develop integrated product and production system designs supporting mass customization of pharmaceutical products and

also, by which to assess these designs

- To adapt SBCE in the context of developing pharmaceutical products to perform systematic evaluations of sets of design solutions efficiently
- To contribute to the knowledge of the benefits of modularized tablet designs as enablers for personalized medicines.

The primary context is mass customization of pharmaceutical products. The results shall be generalizable beyond the context of pharmaceutical product customization.

1.3 Research questions

The aim of this thesis is to explore methods of integrated platform-based design in the context of personalized medicines governed by SBCE principles. The following research questions are proposed for this thesis to guide research activities to achieve the research goals proposed:

RQ1: *How can pharmaceutical product designs be established to support product customization and the consequences of these designs for the production assessed?*

The first question aims at studying how pharmaceutical product designs supporting the customization need can be established in a systematic manner. Moreover, the consequences of these product designs supporting the customization need on pharmaceutical production are studied.

RQ2: *How can the value of pharmaceutical product designs supporting customization be assessed?*

The second question aims at studying how an assessment of product value can be performed in the context of pharmaceutical products supporting the customization need and more specifically, how the value of the pharmaceutical product is transformed when the product design is changed to support customization.

RQ3: *How can the product and production system be modeled so that the consequences of changing customer needs can be assessed?*

The third question aims to build on the first question but more specifically, to study the dynamic integration of the product and production system design.

RQ4: *How can modularized tablet designs enable personalized medicines?*

The fourth question aims at contributing knowledge of modularized tablet designs as enablers for personalized medicines.

1.4 Research scope and delimitations

The main context of studies is personalized medicines and hence, each methodology proposed has been developed with personalized medicines in mind. The result of this thesis is an exploration regarding methodologies to concurrently develop product and production system designs and hence, the proposed methodologies will embrace a prescriptive approach.

The methodologies proposed build highly on platforms. In this thesis, these platforms are perceived as means to design product and production systems; hence platform-based design approaches are exercised as the means of developing pharmaceutical products. The assessment of the platforms as products themselves, i.e. assessing the efficiency of these platforms to develop product and production systems, is outside the scope of this thesis.

This thesis will propose approaches contributing to a mass customization-paradigm of pharmaceutical products. This will be performed by suggesting flexible product designs aiming at supporting mass customization but the connection between patient characteristics and the design parameters of the product will not be studied.

This thesis will focus on oral dosage forms of medicinal products. Furthermore, the production system considerations are limited to the secondary production of pharmaceutical products and the consequences of customized product designs on these. Hence, stages in the product and production development process of pharmaceutical products such as the discovery of new molecular entities and production of the raw material, including the active pharmaceutical ingredient (API) and excipients, are outside the scope of this thesis. Additionally, considerations regarding regulatory aspects due to the proposal of new methodologies with which to develop pharmaceutical products are outside the scope of this thesis.

1.5 Academic and industrial relevance

This thesis should contribute to academic research but it should also have relevance from an industrial point of view.

The *academic purpose* of this research is to increase knowledge regarding the product and production development process of personalized medicines. A methodology of integrated product and production system design in an SBCE manner is facilitating the concurrent product and production system development of pharmaceutical products. Further, approaches to evaluating these new product and production system designs are proposed. The methodologies thus support knowledge increase regarding customized product designs and corresponding production systems. Moreover, the application of the methodologies are illustrated in a modularized tablet design context throughout the thesis to generate

knowledge regarding the benefits of modularized tablet designs as enablers for personalized medicines.

The *industrial purpose* is to perform groundwork for a tool to concurrently develop sets of product and production systems of pharmaceutical products in a predictive manner. This tool not only supports the work of R&D-engineers at pharmaceutical companies when new product designs are to be developed but also, facilitates an efficient evaluation of sets of designs simultaneously and can thus improve the quality output of new product and production system designs. Finally, this tool will contribute to forming the product development paradigm of pharmaceutical products from a sequential, laboratory-based procedure to a predictive modelling and simulation task to improve the quality output of the product and production systems.

1.6 Outline of the thesis

The thesis is organized as follows; **Chapter 1** provides an introduction to the topic and presents the problem as well as the research questions to be answered. **Chapter 2** describes the frame of reference, the relevant theory and concepts that this thesis is based upon and critically reviews existing theory and concepts and, consequently, identifies perceived research gaps. Further, approaches to address the perceived research gaps will be identified. A description regarding the research approach undertaken during the research work is provided in **Chapter 3**. Selected results, a collection of highlights from the appended papers, are presented in **Chapter 4**. **Chapter 5** provides answers to each research question stated in **Chapter 1** and discusses the quality of research outcomes. **Chapter 6** concludes the thesis and provides an outlook for future work. Finally, **Paper A, B and C** are appended.

CHAPTER 2

Frame of Reference

This thesis is not limited to a single scientific field but rather cuts across elements of several fields. The aim is to adapt design thinking and product development approaches, mainly thus far employed in the manufacturing industry, into the context of pharmaceutical product and production development of customized pharmaceutical products. Hence, relevant theories and concepts that this thesis builds upon originate in product design and development and personalized medicines. This chapter describes these relevant theories and concepts and concludes with the perceived gaps with respect to the development of personalized medicines.

2.1 Personalized medicines

[Govender, 2019] compiled the characteristics of a patient that shall be considered to enable customized product design, since these characteristics may cause a variability to drug response and, consequently, the therapeutic outcome. A conceptual illustration of the connection between patient characteristics and product design parameters can be seen in Figure [Govender, 2019]. These characteristics are divided into three main domains, namely the biological, behavioural and environmental. Biological characteristics refer to patient attributes such as gene encoding, allergies and intolerances or age. Behavioural characteristics refer to attributes including administration difficulties and adherence, and environmental characteristics refer to attributes including food and alcohol habits. However, the respective dimension cannot be considered in isolation and hence, [Govender, 2019] introduces a dimension crossing the other dimensions of characteristics, the *patient preference* dimension. The *patient preference* dimension is aiming at demonstrating the complex interaction between the different dimensions. [Govender, 2019] further explained this complex interaction by providing an example of an ageing population that require an ease of handling the drug product, but simultaneously, the drug product need to comply with physiological factors such as age and organ functions.

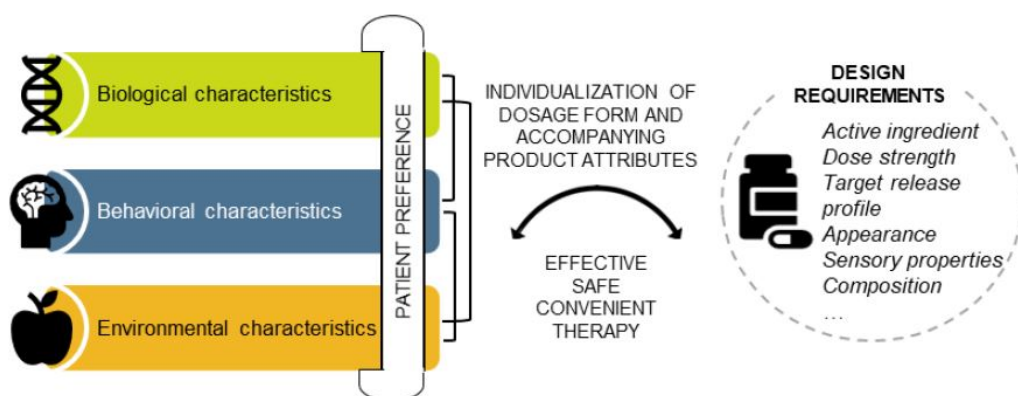


Figure 2.1: The dimensions of patient characteristics and the correlated design parameters of customized drug products [Govender, 2019].

This complex set-up of interacting patient characteristics should then be translated into design parameters of the drug product to enable customized treatments. These design parameters are the active pharmaceutical ingredient, the dose strength, the release rate of the drug from the product complex, the formulation, sensory attributes referring to, for example, the taste and smell of the drug product and finally, the dosage form appearance, i.e. a flexible product size.

By designing the product according to these design parameters for the individual patient, the therapeutic outcome can be enhanced, i.e. the safety and efficiency of the treatment. However, for these products to reach the patient, affordable manufacturing and distribution of these products is required. Flexibility is not only required from a product design perspective, referring to the design parameters to be considered for product customization but also, an evident consequence of product customization is the increasing number of product variants and the decreasing production volumes [Govender, 2019]. The following section will describe approaches to product design and production system design discussing customization.

2.1.1 Pharmaceutical product and production design approaches to customization

Pharmaceutical product design and production design research in the context of personalized medicines have been emerging as a response to opportunities of product customization.

Product design

Current commercial product designs, such as multiple unit dosage forms, i.e. modularized tablet designs, pellet-based dosage forms and mini-tablets, have been discussed as enablers for personalized medicines. These product designs have especially been studied as dosage forms facilitating treatment of pediatric and geriatric patients. Additionally, the enabled opportunity of flexible dosing has been discussed [Aleksovski *et al.* 2015, Tissen *et al.* 2011, Klingmann *et al.* 2013, Bonhoeffer *et al.* 2018]. However, studies of the full benefit of multiple unit dosage forms as enablers of a mass customization-paradigm of pharmaceutical products cannot be found.

Scored tablets, i.e. tablets with a cut on the face to make tablet splitting convenient, is another commercially available product design. These tablets are produced to offer patients the opportunity to adjust the dose and thus, enabling some level of customization. Tablet splitting is also facilitating administration difficulties as especially children and elderly have difficulties in swallowing tablets and capsules and as a result, tablets are split into halves [Standing and Tuleu, 2005]. Most scored tablets available may be split into two or four subunits [Quinzler *et al.* 2006]. However, splitting can lead to inadequate dosing or tampering with the embedded release properties built in the tablet and can thus lead to poisoning [Wening and Breitzkreutz, 2011]. In addition, [Wening and Breitzkreutz, 2011] argued that a tablet split into only four doses is uncertain to be sufficient for customization.

Novel product designs are emerging in the literature to enable personalized medicines, one such example being orodispersible films. Orodispersible films are solid state drugs designed to disintegrate in the oral cavity and hence, forming a solution or suspension in the mouth. These drug products suit pediatric and geriatric patients since the design facilitates a convenient administration [Slavkova and Breitzkreutz, 2015]. Additionally, orodispersible films are stable in their solid forms and can be cut into desirable pieces, hence supporting dose flexibility [Visser *et al.* 2015]. Widespread commercial implementation lacks evidence.

Production design

Additive manufacturing has been much studied as a technology of providing customized product designs. In a computer model, the matter can be arranged as desired [Goyanes *et al.* 2015]. Hence, product design can assume whatever form and [Norman *et al.* 2017] argued that there are hardly any limits to customization with an additive manufacturing approach. Additive manufacturing has proven to be a viable technology in the pharmaceutical production context. For example, FDA recently approved a 3D-printed product [U.S. Food and Drug Administration, 2016]. However, the success of commercial production in the context of personalized medicines lacks support.

Continuous technologies is another manufacturing technology on the rise and a considered viable for enabling customized pharmaceutical products. Continuous manufac-

turing technologies have been discussed advantageous from the ability to respond to variations in production volumes and variants, which will be a consequence of product customization. Further, the discussions have extended to the supply chain networks of the pharmaceutical products and continuous technologies as enablers for handling the increasing number of product variants [Lee *et al.* 2015, Srai *et al.* 2015, Mascia *et al.* (2013)]. These studies conducted still considered the product design remaining in the current *one-size-fits-all*-paradigm and focused on adjusting the current manufacturing platforms. There are uncertainties regarding how far the current mass production platforms can be stretched to enable satisfactory customization.

[Wilson, 2016] addressed limitations of the current manufacturing platforms of pharmaceutical products to enable customization in an economically feasible manner. The current manufacturing platforms are not designed nor optimized for customization paradigm. The process flow is inefficient due to various unit operations performed and the different efficiencies of these unit operations. Further, other crucial activities of pharmaceutical production, such as set-up, cleaning and quality assurance, strengthen inefficiency. Due to strict requirements of the quality of pharmaceutical product while still employing batch processing, tedious cleaning activities need to be performed to ensure no left-overs from a previous batch. Additionally, different types of products require varying types of processing and hence, set-up activities are performed to adjust processing equipment accordingly. Further, the quality assurance process which mainly consists of testing the quality of a sample off-line at a laboratory, additional activities besides product processing account for longer times and hence, a customized-paradigm in which the number of increasing product variants is coming down the pipeline cannot sufficiently be employing current manufacturing platforms. Customization to be technically realizable and economically feasible hence lacks evidence.

Current approaches to pharmaceutical product customization are mainly presented from two detached ends. Either, the product design is discussed as an enabler for personalized medicines, i.e. approaches to enhance the therapeutic outcome of the patient, or the production system design is discussed, i.e. approaches to respond to variable production volumes and the increasing number of product variants. However, to enable mass customization of pharmaceutical products, and integration of patient-driven product design, which optimizes the therapeutic outcome of the patient, and a production system design enabling the production of these products in an economically feasible manner is required. As [Wilson, 2016] pointed out, the strong connection between the pharmaceutical product formulation and manufacturing need to be thoroughly understood to enable pharmaceutical product customization.

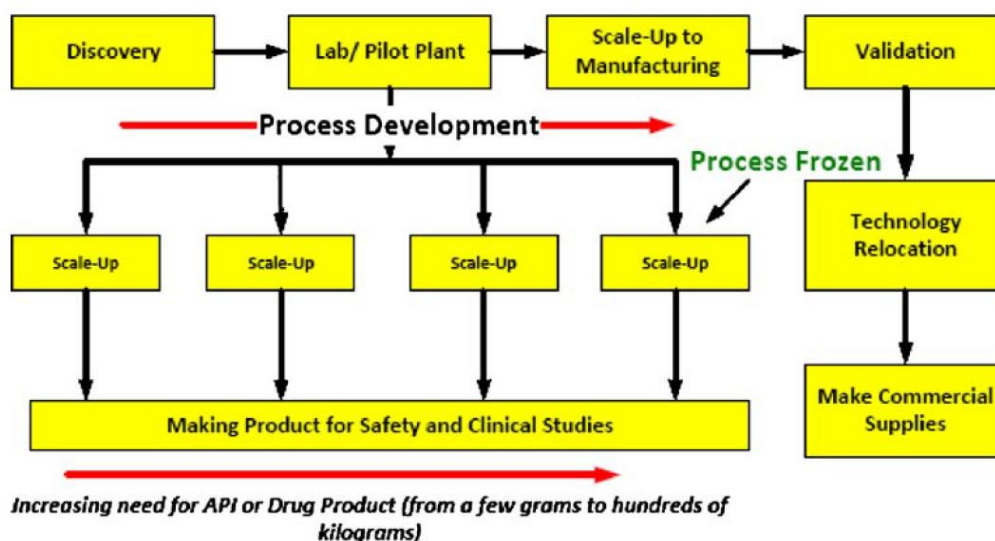


Figure 2.2: The product and production development process described by [Suresh and Basu, 2008].

2.2 Product and production development in the pharmaceutical industry

Even though the strong correlation between formulated drug product design and manufacturing process is required to be understood to enable pharmaceutical product customization according to [Wilson, 2016], the nature of the current pharmaceutical product and production development process might not support increasing this understanding. The current product and production development process of pharmaceutical products takes upon a sequential approach, see Figure 2.2 for an overview. A sequence of scale-ups is still a reality and performed according to the success level in clinical trials. Additionally, the product and production development process is governed by empirical laboratory work and hence, has been described as a tedious and resource consuming process [Suresh and Basu, 2008].

Some concurrency when developing the formulated drug product and the manufacturing process occurs at a laboratory scale. The production process is further developed as a scale-up procedure from an early safety assessment or clinical trial to finally reaching the commercial manufacturing level of production. The process is developed providing for the amount of material required at the current clinical trial phase. Sources report that about a 10% success rate can be expected from the clinical trials [Suresh and Basu, 2008, Siew, 2017] hence, making larger efforts of developing production systems is of secondary priority. Not only has scaling-up proven to complicate the development of pro-

duction processes, but the development of robust manufacturing processes has been left to a secondary focus. Additionally, once a sufficient production process has been found, it is frozen early to enable process validation and then starting to produce the product commercially. Making changes to validated production processes is also a tedious activity due to strict regulations of pharmaceutical production.

Not only is the product development process considered tedious for the current mass production paradigm but also, to enable development of customized product designs and the production systems of these, tools to support efficient product and production development is needed. [Suresh and Basu, 2008, U.S. Food and Drug Administration, 2013] has expressed a need for science and engineering-based tools to enable predictive and cost-efficient development of pharmaceutical product and production processes. The product and production process behavior needs to be predictable to facilitate the current product and production development process.

2.3 Product design and development

Product design is a process of creating, developing or constructing a product, system, component or process. The reason for conducting product design activities is to meet the desired needs of customers or stakeholders, and the product, system, component or process are the means through which to meet these needs. Product design is an interdisciplinary process where fundamental elements include activities such as defining, synthesizing, constructing, testing and assessing, and where science and engineering are applied to provide the means for meeting the needs defined [Pahl and Beitz, 1995].

Several authors have proposed frameworks for generic product design and development such as [Pahl and Beitz, 1995], [Roozenburg and Eekels, 1996] and [Ulrich and Eppinger, 2012], see Figure 2.3 for the product development process proposed by [Ulrich and Eppinger, 2012]. The common denominator of these frameworks is a proposal of a systematic approach to develop products. A generic product development process consists of activities including *product planning* where the market need is defined and the end result of the product development project is clarified. A *concept development* phase aims at developing sets of concepts to widely search for candidate solutions to satisfy the market need defined at the start of the product development project. This set is quite rapidly narrowed down to further detail a concept with elaborate information regarding product functions, architecture, subsystems and components, the product geometry and material choices. Activities such as product construction and testing is performed as well as final design refinements. The final activity is a production ramp-up to test the production of the product with the intended equipment. The ramp-up is usually a stage-wise procedure before reaching a final manufactured product.

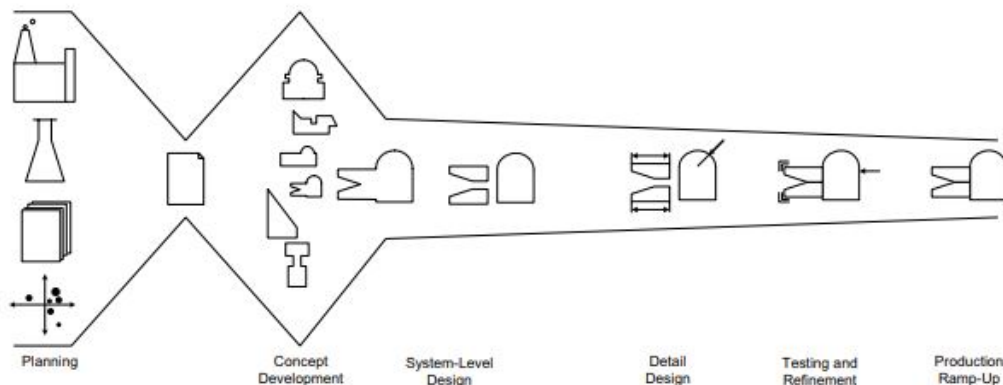


Figure 2.3: The generic product development process by [Ulrich and Eppinger, 2012].

2.3.1 Integrated product development

The sequential product development process induces a risk of prolonged lead-times. In the sequential approach, usually an activity is finished before moving on to the next one. This type of progress may require iterative loops to previous activities when increasing knowledge about the production, market and product design is acquired and hence, the choices made early are not sufficient anymore. [Andreasen and Hein, 1987] proposed an integrated product development process, see Figure 2.4, to facilitate a parallel conduction of development activities between the product design, production design and marketing disciplines. An integrated approach enables a continuous monitoring of the market need and the customer, simultaneously as the product and production system is designed and thus, promotes a continuous information flow across these disciplines. Hence, information from a discipline becomes faster available to be addressed by another discipline.

2.3.2 Concurrent engineering

Concurrent engineering (CE) is a philosophy with which to perform product design and is strongly related to the integrated product development process by [Andreasen and Hein, 1987]. CE is mainly an organizational approach but can describe the product development approach as well. CE thinking to design parallelizes the activities of product design and production design disciplines. Concurrently performed design has proven beneficial to a sequential approach because of promoting simultaneous decisions regarding, and mismatches in-between these disciplines can be avoided [Prasad, 1996].

[Sapuan and Mansor, 2014] emphasized the importance of introducing CE into composite product design. Not only is CE regarded important because of the frequent customization need of composite products, which requires early decisions regarding materials and manufacturing-specific considerations, but also because a thorough understanding

* INTEGRATED PRODUCT DEVELOPMENT

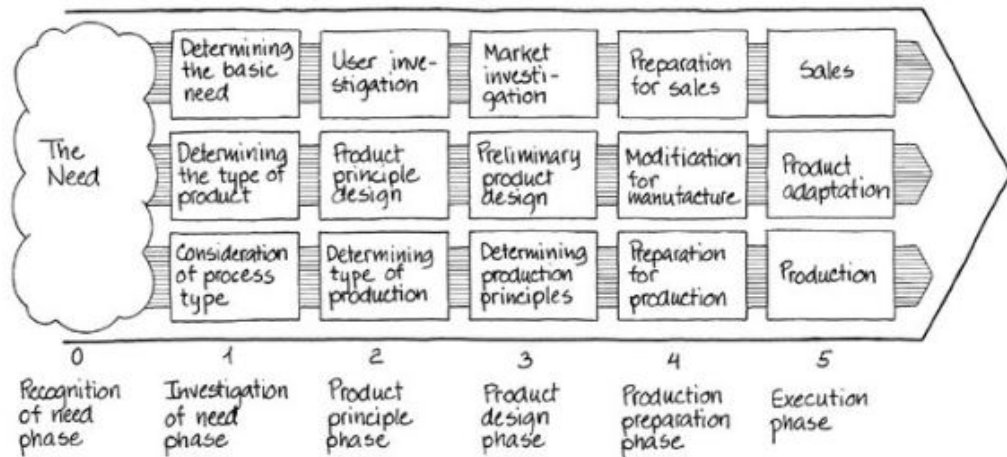


Figure 2.4: The integrated product development process by [Andreasen and Hein, 1987].

of material properties and the impact of these properties on production processes are required. [Sapuan and Mansor, 2014] further provided a review of CE implementation in the industries of composite products and concluded that implementation into these industries has been performed to a limited extent. No references to the pharmaceutical industry could be found.

Set-based concurrent engineering

Set-based concurrent engineering (SBCE) is a product development philosophy which adopts the concurrent approach to design. However, in contrast to the conventional product design and development, an early choice of a single design solution which is iterated until it meets the specifications of the product, system or process, the set-based design philosophy emphasizes the establishment of sets of alternative design solutions which are with increasing information systematically narrowed down until a single feasible solution is found [Sobek *et al.* 1999]. Figure 2.5 provides a conceptual illustration of the difference between a generic product development process of [Pahl and Beitz, 1995, Ulrich and Eppinger, 2012] and the set-based approach by [Sobek *et al.* 1999]. The illustration is trying to emphasize that both approaches work with sets of solutions until the concept development phase, but the approach of [Sobek *et al.* 1999] works with sets of solutions further into the product development process, whereas the generic product development process makes an early choice of concept that is refined in iterations. The product development process in the pharmaceutical industry resembles the generic product development process from the product development phase of product formulation.

The SBCE has received attention in the past decades as the philosophy of product development that enables a fast process resulting in a qualitative end product [Kennedy *et al.* 2008, Ward and Sobek, 2014]. [Bernstein, 1998] proposed a concrete approach to SBCE and suggested activities including defining the design space of respective discipline, finding the intersections between the design spaces of respective disciplines and further, expanding the design space through collaboration between disciplines. The design space should systematically be narrowed down when increasing information about the intersecting design space has been gained. And as a last activity, the feasible solution shall be defined. [Raudberget, 2010] studied the practical implementation of SBCE in industry and suggested a set of guidelines and activities supporting SBCE. These guidelines and activities include avoiding freezing a design solution early in the design process and making a distinction between important and unimportant product specifications. Broad targets for specifications considered important should be set, and the unimportant specifications should be left unspecified. Further, solution alternatives shall be eliminated on the sound basis when enough information has been acquired. Finally, tools such as trade-off curves, technical data and simulations should be used throughout the process on which to base elimination decisions.

2.3.3 Platform-based design and product variety

Platform-based design is an approach to developing products with the same goal as SBCE, i.e. to generate knowledge about sets of design solutions. However, SBCE is rather a philosophy, whereas platform-based design is an approach with hands-on activities to develop product platforms. Further, product platforms have been frequently adopted for the purpose of generating sets of derivative products, i.e. product families instead of a single feasible solution [Michaelis *et al.* 2013]. Product platforms have proven to accelerate business by increasing the value to the customer. A customized product can be offered, which makes the product attractive to the customer, but the customized product is configured from a defined set of components and hence, economical feasibility is achieved [Meyer and Lehnerd, 1997, Wortmann *et al.* 1996, Ho and Tang, 1998]. Product platforms form a technology grounded in a common structure, the product architecture, and sets of defined subsystems and components. The product architecture is a scheme informing how the functions of a product are allocated to physical components and how these interact with each other to provide for the overall function of the product [Ulrich and Eppinger, 2012], hence, the architecture informs how the components of the product should be organized in the configuration in order to generate a product variant. The components used for configuring product variants can vary to provide derivative products, but the structure is kept rigid [Meyer and Lehnerd, 1997].

Two types of product architecture are widely discussed as enablers of product variety. A modular product architecture, that is a product configured of modules that embed product functions. These modules are defined with standardized interfaces and by adding, subtracting or exchanging modules, product variety can be achieved [Fujita, 2002]. Scalar

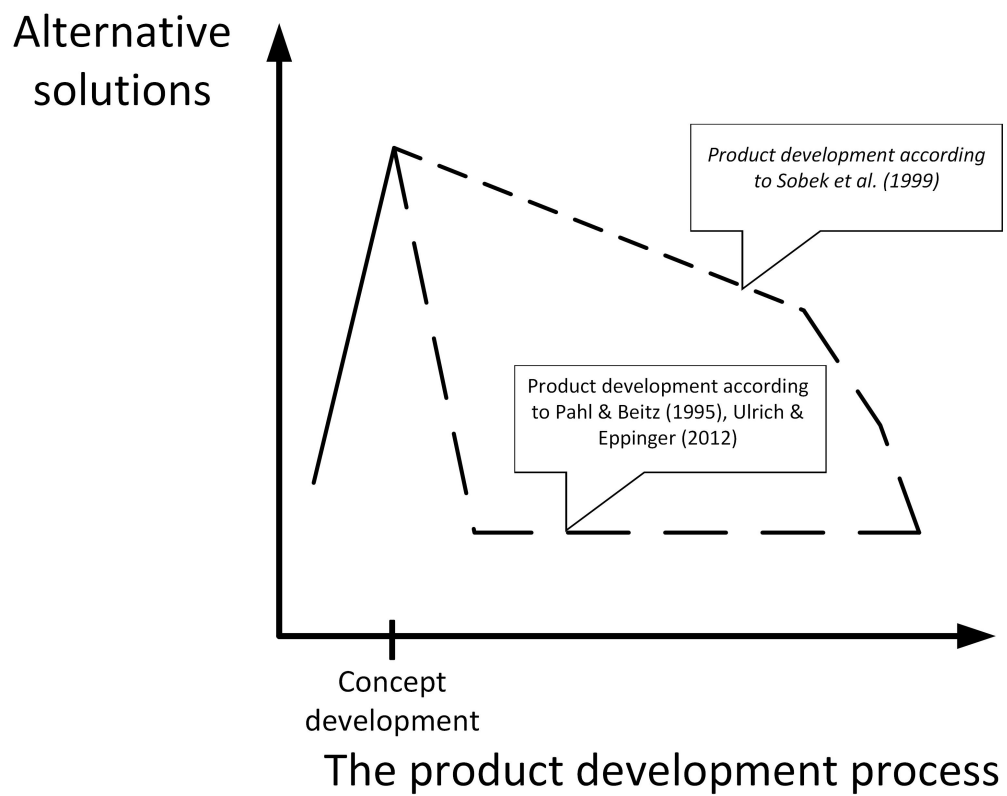


Figure 2.5: An illustration of the difference between a generic product development process by [Pahl and Beitz, 1995, Ulrich and Eppinger, 2012] and a set-based product development process [Sobek *et al.* 1999].

product architecture is the second type of architecture enabling product variety. A scalar product architecture has a rigid architecture and the components of the product are frozen into a structure. However, a scalar architecture allows for adjusting the design parameters of specific components, inside a defined functioning bandwidth of the component, and hence, product variety can be achieved [Simpson, 2001].

Functional modeling

As described, the product architecture is the scheme of allocation of product functions into components realizing the functions. Hence, functional modelling is an approach by which to describe the architecture of products. A functional model describes what a product is supposed to do which is the *intended* behaviour of a product [Gero and Kannengiesser, 2004].

EF-M tree modelling is an approach to functional modelling and builds on Function-Means modelling originally developed by [Tjalve, 1976]. The overall function of the product is expressed as a functional requirement (FR) to which a design solution (DS) is defined. The DS realizes the function. Further, this DS can be described in its FRs and similarly, DSs are found to the respective FRs. The FR and the DS follow a one-to-one cardinality, but alternative DSs to an FR can be proposed. By doing so, alternative approaches to realize the functions of the product is achieved, thus creating variants of a product, i.e. establishing sets of design solutions to a product. Function-means modeling has been evolving over time and the EF-M tree modelling approach by [Schachinger and Johannesson, 2000] adds an element of constraint (C). The purpose of the Cs are to limit the functioning region of the FRs, thus informing the design space of the DSs realizing the FRs. Function-Means Modeling can be used as a scalar approach to product variety by defining a functioning bandwidth of the FRs and by adjusting the DS realizing the FR to satisfy the functioning bandwidths, a variety of solution alternatives.

The **CC method** presented by [Claesson, 2006] is based on EF-M trees but encapsulates the FRs and the DSs of the EF-M tree into independently functioning subsystems, or CC objects. By introducing independently functioning subsystems, such subsystems can be perceived as modules. Hence, a modular architecture is achieved. These modules can be added to, subtracted from and exchanged. Similar scalar approach to product variety, as with the Function-Means modelling, can be achieved with the CC method.

Both [Levandowski *et al.* 2014] and [Michaelis *et al.* 2015] connected the CC objects to the component tree of the product. The component tree describes the physical components (CO) of the product that provides for the desired functions. The information regarding the physical realization of the product is embedded in the CC objects, but by expressing the component tree with respect to the COs dimensions, geometry and so forth the product architecture can be better understood. Figure 2.6 shows a conceptual model of the CC method redrawn from [Michaelis *et al.* 2015].

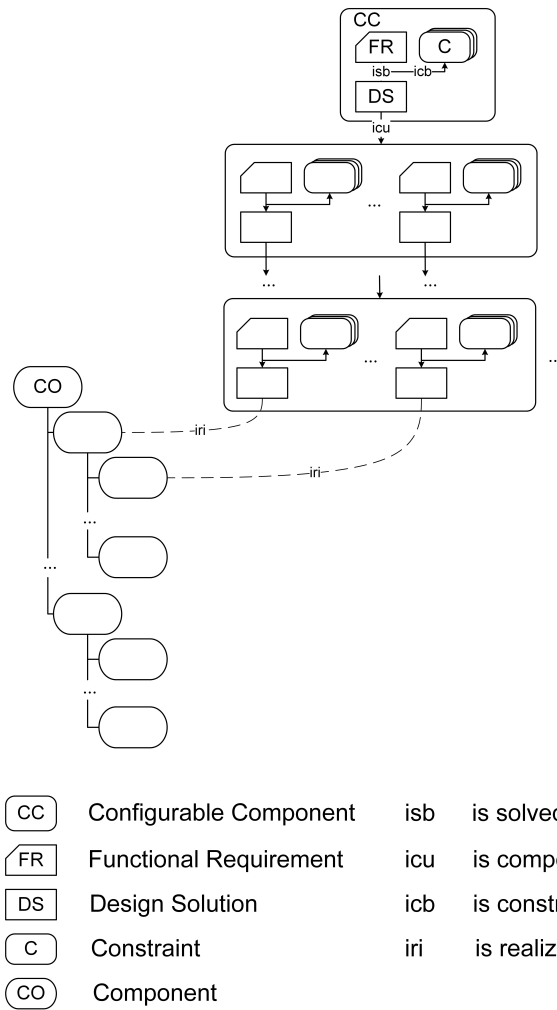


Figure 2.6: An illustration of the CC method by [Claesson, 2006], redrawn from [Michaelis *et al.* 2015].

2.4 Product value

The core of developing products shall be to increase the perceived product value of the customer or some other stakeholder. There are numerous definitions and approaches to describe product value. As mentioned, product customization can be seen as an approach by which to increase the value to the customer, by offering a product tailored to customer needs. [Lindstedt and Burenius, 2003] defined product value as the ratio between the perceived benefits to the customer and the expenditure of the customer, expressed in time, money or effort. Simply, a product offering additional benefits to a customer at a lower cost is considered embracing a higher value.

The concept screening matrix by [Ulrich and Eppinger, 2012] developed from the concept selection method first introduced by [Pugh, 1990] is a more concrete approach by which to describe the value of the product compared to the approach by [Lindstedt and Burenius, 2003]. The concept screening method is an approach by which to perform a qualitative relative comparison of concepts toward a reference concept. The performance of a concept is compared to the reference concept with respect to chosen performance criteria. These performance criteria can be seen as criteria indicating the relative value of the respective concepts. However, the choice of value-indicating criteria is left to the researcher. Value assessment as proposed by [Pahl and Beitz, 1995] and the related approach of concept scoring matrix by [Ulrich and Eppinger, 2012] suggests further describing the value-indicating criteria on quantitative scales and developing scoring systems to assign each concept scores depending on how well these concepts perform on each value-indicating criteria. Further, [Pahl and Beitz, 1995] and [Ulrich and Eppinger, 2012] suggests assigning weights to the value-indicating criteria to enable the promotion of concepts performing better on criteria judged more important. These approaches require further developed concepts to enable sufficient performance assessments of the concepts with respect to the criteria compared to the development level required for the concept screening matrix. However, the approaches by [Pahl and Beitz, 1995] and [Ulrich and Eppinger, 2012] can provide for more accurate comparisons between concepts than the concept screening matrix can.

The feasibility of customized pharmaceutical products have been assessed but these approaches have mainly acquired a narrow economic focus. The cost-efficiency of pharmaceutical product customization has been discussed for example by [Hatz *et al.* 2014] and [Srai *et al.* 2015]. However, the core purpose of the pharmaceutical product, which is to treat people and hence, bring human and societal benefits, is overshadowed by this narrow economic focus. Approaches with which to assess the value of products expanding beyond the narrow economic perspective has been proposed by studies conducted in the aerospace industry by for example [Bertoni *et al.* 2015] and [Hallstedt *et al.* 2015]. The proposed approach to value assessment integrates a full sustainability perspective as value indicators, that is including the social, environmental and economic dimension when assessing the value of products. Hence, the societal benefits of the products is incorporated

into the product value.

2.5 Results of literature analysis

A review of existing literature on approaches to pharmaceutical product customization and pharmaceutical product development resulted in a number of research gaps, which are presented below. Further, theoretical elements to address these gaps have been identified through the literature review, considering product development approaches in the manufacturing industry. These theoretical elements identified will be presented.

The following research gaps have been identified:

- The approaches to address the emerging need for mass customization of pharmaceutical products are either focusing on product design or production system design. To enable mass customization of pharmaceutical products the connection between the patient-centric product design and production system needs to be thoroughly understood.
- There is a need for science and engineering-based tools enabling the development of pharmaceutical products and the corresponding production systems in a predictive manner. The current product and production system development approach of pharmaceutical products is mainly based on a sequential, experimental procedure from scale-up to scale-up. Not only is this a tedious and time-consuming process for pharmaceutical product development in the current mass production paradigm, but also a process such as is not believed to be sustainable for a mass customization paradigm.
- The value of pharmaceutical product and production system designs supporting customization have embraced a narrow economic focus. This overshadows the core purpose of a pharmaceutical product, i.e. to treat people and hence, bring societal benefits.
- Finally, multiple unit dosage forms have been discussed as enablers for personalized medicines but the full benefit of these product designs as enablers for a mass customization-paradigm has not been clarified.

Literature analysis

[Wilson, 2016] stated that to enable pharmaceutical product customization, the connection between the product formulation and the production need to be thoroughly understood. Integrated approaches to product development such as CE have proven beneficial in the manufacturing industry for ensuring a sufficient understanding of the product and production system design simultaneously, and most importantly, the interaction in-between these processes [Prasad, 1996]. Hence, concurrent engineering principles will be adapted

in this thesis to explore the opportunity of providing a connection in-between the product and production system design of pharmaceutical products.

As described by [Suresh and Basu, 2008, U.S. Food and Drug Administration, 2013] a need for science and engineering-based tools are required in the pharmaceutical product and production development to improve a tedious, sequential and laboratory-based development process. The desire is for tools provide for predictive simulations to enable efficient concurrent development of pharmaceutical product and production system. SBCE has been a successful product development philosophy in the manufacturing industry with regard to the ability to develop qualitative products fast [Ward and Sobek, 2014]. Platform-based design has supported mass customization in the manufacturing industry, and even improved business [Wortmann *et al.* 1996, Ho and Tang, 1998]. Hence, SBCE principles and platform-based design approaches are adapted to develop methodologies by which to design integrated product and production system platforms for pharmaceutical products to support customization and simultaneously enable prediction of product or production system behaviour.

To enable product design assessment of pharmaceutical products, supporting customization, that incorporates considerations of societal benefits, inspiration from approaches by [Bertoni *et al.* 2015] and [Hallstedt *et al.* 2015] will be taken. [Bertoni *et al.* 2015] and [Hallstedt *et al.* 2015] proposed approaches by which to integrate a full sustainability perspective, including the social, environmental and economic perspectives, to perform value modelling. However, the approaches by [Bertoni *et al.* 2015] and [Hallstedt *et al.* 2015] employed the concept of net present value, and hence, required a translation of value criteria into monetary metrics. Thus, the concept screening matrix, allowing for a qualitative comparison between product concepts will be adapted in the context of pharmaceutical products to eliminate the need for translation into monetary metrics.

Since the multiple unit dosage forms have been discussed as enablers for customization [Aleksovski *et al.* 2015, Tissen *et al.* 2011, Klingmann *et al.* 2013, Bonhoeffer *et al.* 2018], each study will incorporate multiple unit dosage forms as a case to generate knowledge about these in the context of pharmaceutical product customization.

CHAPTER 3

Research Approach

Design can refer to an object or product, tangible or intangible, such as a chair or a webpage. Design can also refer to activities a researcher performs to create objects as well as generate knowledge about objects. In the latter case, the objective of generating knowledge as an activity is to change an existing situation of an object to a desired one [Simon, 1996]. To achieve a change in the existing situation of an object into a desired one a support is required. The knowledge acquired when performing design activities in order to generate knowledge about objects can be transformed into practical implementation to develop such designs (such *designs* referring to objects or products). This transformation is achieved with the aid of the developed support.

Design research can be defined as "generating knowledge about design and for design" [Horváth, 2001]. On a comprehensive level, design research has two aims. The first aim of design research is to establish the support, i.e. methods, methodologies, tools and so forth to improve the performance of design activities, a practical outcome of design research. The second aim of design research is to increase the understanding of design. Ideally, these two aims, the establishment of practical tools to support the conduct of design activities and the activities leading to an increased understanding of design, are integrated and considered jointly. The integrated conduct of activities supports the achievement of the overall aim of design research [Blessing and Chakrabarti, 2009].

3.1 Frameworks for design research

As design research has a two-fold purpose of both understanding design and practically improving designs, an integration of multiple fields of science is not only required, but also a vast cognitive and psychological effort. Hence, structuring design research is essential for the researcher to advance understanding [Eckert *et al.* 2003]. For design researchers, a few research frameworks have been established to support the researcher in the research activities to maximize the probability of successful outcomes from research projects. A successful outcome of design research implies a valid result in a generic, the-

oretical and practical sense [Blessing and Chakrabarti, 2009, Eckert *et al.* 2003]. This section will provide an overview of different frameworks for design research and clarify the research approach taken to conduct research in this thesis.

3.1.1 Paradigms of Design Research

[Warell, 2001] described two types of design research paradigms which were originally presented by [Jørgensen, 1990]. These two design research paradigms, problem-based and theory-based, and respective approach are illustrated in Figure 3.1. The origin of the research topic initiation differentiates these design research paradigms. The researched topic may have been initiated by a practical problem during the conduct of design work and thus, a problem-based research approach is suggested as research approach. On the other hand, the researched topic might have also been initiated by an insufficient availability of theories and methods with which to conduct design work and thus, a theory-based research approach is suggested. Both approaches aim for the same final goal regardless of the point of research initiation, that is to acquire new scientific knowledge, develop methods into which to implement this acquired knowledge and finally, transfer the acquired knowledge into practical results.

According to [Jørgensen, 1990], the problem-based research approach starts with a practical problem of conducting actual design work and is followed by empirical work to discover structures of causalities. The problem-based approach is governed by empirical research activities to gather external, real-world knowledge of design processes and products. The theory-based approach is highly characterized by theoretical activities, such as combining existing theoretical elements into new theories, theories that are perceived to be lacking, and hence, promotes development of theoretical constructs [Warell, 2001].

The steps of each research approach are rarely conducted in a sequential manner, but the approaches are rather iterative and research activities are conducted in several loops. Further, according to [Warell, 2001], most design research projects collect elements from both paradigms to various degrees depending on the project, i.e. a constant ongoing interplay between the problem-based and theory-based approaches occur. This interplay is illustrated by the arrows pointing in various directions in Figure 3.1.

3.1.2 Design Research Methodology

[Blessing and Chakrabarti, 2009] developed the Design Research Methodology (DRM), a framework with which to conduct design research. The framework consists of four distinct stages with various research activities performed at each stage. Figure 3.2 presents the stages of DRM and further, the means of conducting research and the main outcome of each stage is clarified. A short description of each stage follows.

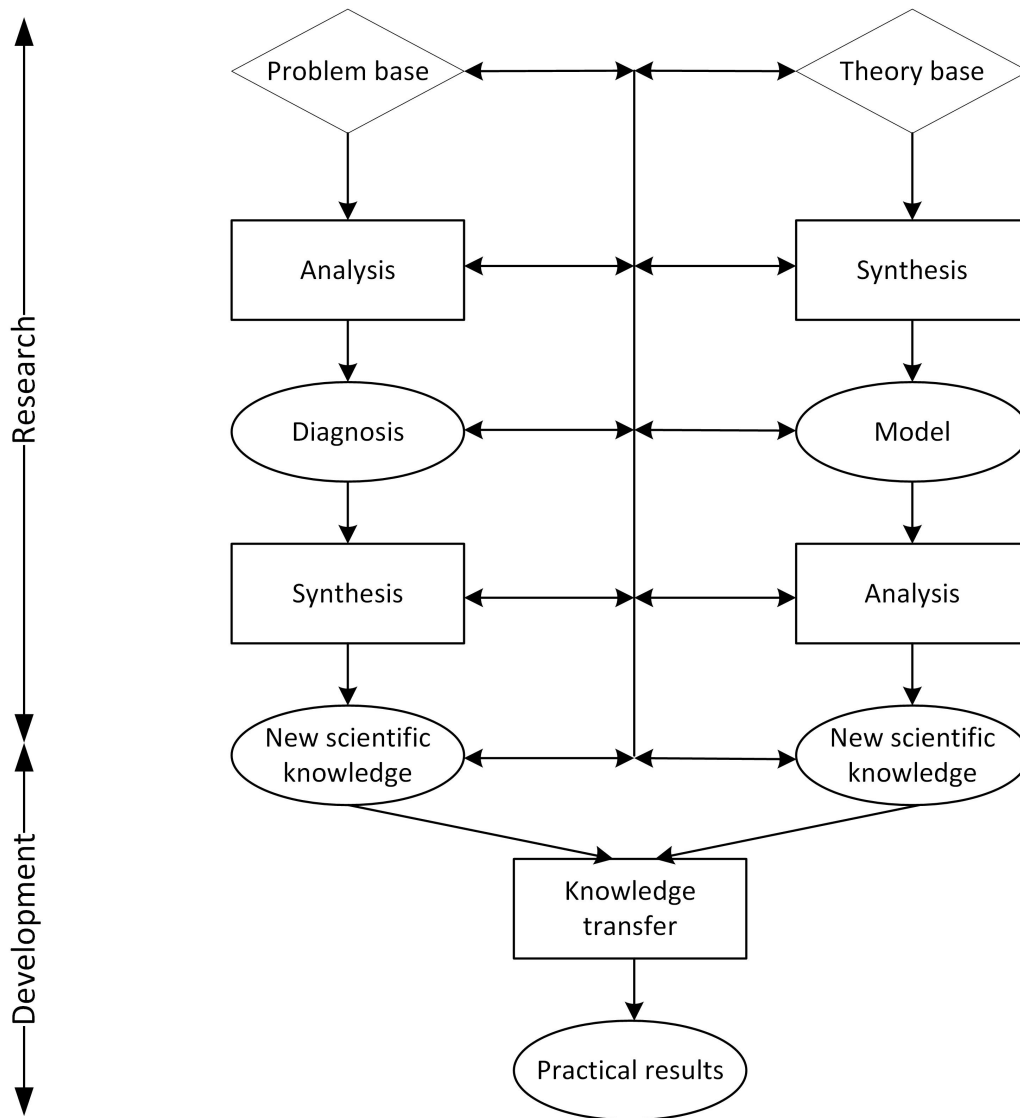


Figure 3.1: The two types of research processes according to [Jørgensen, 1990], redrawn from [Warell, 2001].

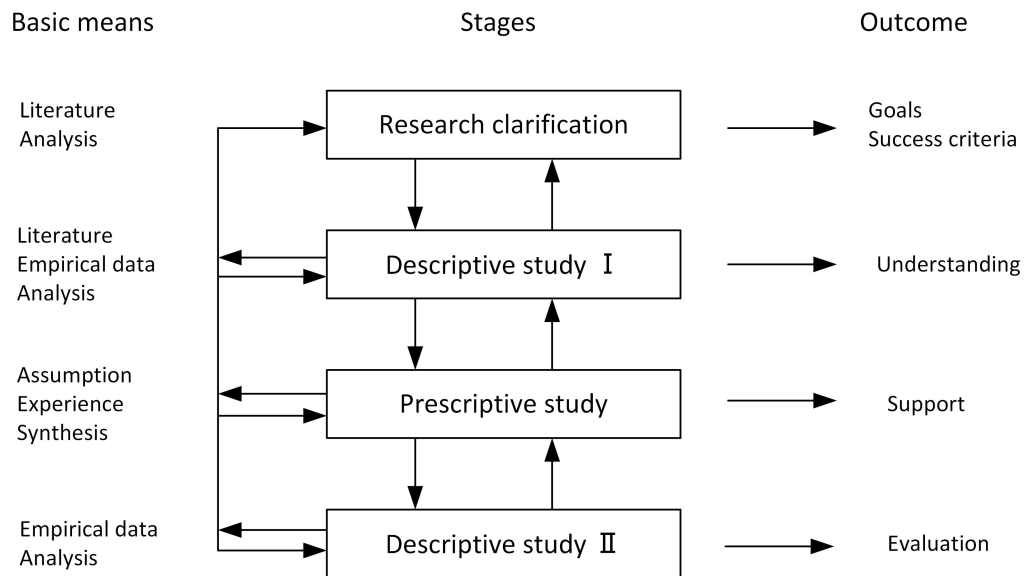


Figure 3.2: The Design Research Methodology, redrawn from [Blessing and Chakrabarti, 2009].

Research clarification

The first stage of the DRM is the *research clarification* stage. The main outcome of the *research clarification* stage is a formulated overall goal of the design research project and a further elaboration of goals into criteria. These criteria will assess the success of the research project. At this stage, research questions are formulated.

To formulate the goal of the research project, an understanding of the initial stage to be changed is required. Further, a vision of the desired stage to aim for when conducting design research activities is specified. This stage is governed by literature studies and analysis.

Descriptive study I

The second stage of the DRM is the *descriptive study I* stage. The main outcome of this stage is a better understanding of the research goal and criterion to determine the success of the research project. By complementing the analysis performed during research clarification with additional literature studies and empirical data analysis, the knowledge of the current situation and the criteria to be studied is increased. This stage can embrace a comprehensive or review-based nature depending on the research project.

Prescriptive study

The *prescriptive study* stage has the purpose of establishing the support to facilitate design work both in practice but also as a means of increasing the understanding of design. Preferably, this support contributes to both practical applications and to increased knowledge about design. This support can assume the nature of a tool, method, methodology and so forth.

At the *prescriptive study* stage the researcher's creativity, assumptions and experiences play a fundamental role, from which the support is established. This support should provide the means of achieving a change of the existing into the desired situation as formulated in the *research clarification* stage.

Descriptive study II

The final stage of the DRM is the *descriptive study II* stage. The main outcome of this stage is an evaluation of the support established in the *prescriptive study* stage. An evaluation of how the existing situation has been changed to the desired situation is performed.

The *descriptive study II* stage has two objectives: to evaluate the applicability of the support and to assess the success of the support. The success of the support is assessed with regard to the success criterion formulated in stage *research clarification* and refined in stage *descriptive study I*. This assessment is performed by conducting empirical studies to test the support.

DRM is presented stage-wise but it is a highly flexible framework. As illustrated in Figure 3.2, arrows are pointing in several directions. The researcher is given the freedom of executing each stage in the preferred order and iterate stages several times if desired. Stages can be left out if judged unsuitable to the nature of the research project.

3.1.3 Other design research frameworks

[Eckert *et al.* 2003] proposed a framework to design research which to a large extent corresponds to the DRM framework by [Blessing and Chakrabarti, 2009]. However, [Eckert *et al.* 2003] not only suggested a separation of the DRM stages into additional stages depending on the nature of the research activity performed during a stage. For example, a separation of *descriptive study I* into activities, such as empirical studies and theory formation, was proposed. Additionally, [Eckert *et al.* 2003] chose the perspective of stressing the importance of evaluating each outcome of research activities conducted and hence, integrated an additional element of evaluation of each research activity as a primary activity. The aim of developing this framework was to better address the perceived problem of design research, meaning the multidisciplinary nature of design research leading to the difficulty of predicting the consequences of implementing research findings in

an industrial context. Hence, the validity of each research activity is continuously monitored throughout the stages of research. Naturally, the element of evaluation is included in the DRM framework but embedded in the stages of the framework.

The *interactive model* by [Maxwell, 2013] is a framework for qualitative research design which emphasizes a parallel approach to research and which argues that research activities, such as collecting and analyzing data, developing theories, refining research questions and so forth, each affect one another and are also more or less are conducted in parallel. Moreover, the interactive model is a model both *of* a research project and *for* a research project, i.e. a model that facilitates researchers' understanding of their research projects but that likewise facilitates the conduct of the research project. Other frameworks generally express how to conduct activities within a research project.

3.1.4 The applied research approach

This licentiate thesis fits into the theory-based paradigm as described by [Jørgensen, 1990]. It is argued that the current product and production development process of pharmaceutical products is a sequential, mainly laboratory-based, time and resource-consuming approach and hence, new theories regarding engineering-based development approaches of products proven efficient shall be brought in. This research project takes inspiration from theoretical elements regarding product and production development processes in other fields, mostly the manufacturing industry, and combines these theoretical elements into new theories that are applied in the context of product and production development of pharmaceutical products.

The research activities performed can be aligned with the parallel research approach as described by [Maxwell, 2013], i.e. activities have not been conducted in a sequential manner but the activities have instead been ongoing simultaneously and affected one another. However, to structure the research conducted, the DRM framework is used to conveniently communicate each research activity performed but also to remind oneself of the possible types of activities that must be performed in order to maximize the probability of a successful outcome of the research project.

[Blessing and Chakrabarti, 2009] presented seven types of research projects, which differ from each other with respect to the stages treated in the DRM framework, but also differ from each other with respect to the nature of the stages treated. Each appended paper resembles the research project type proposed by [Blessing and Chakrabarti, 2009] outlined in Figure 3.1.4. The stages of the DRM framework treated in each paper consist of the *research clarification*, *descriptive study I* and *prescriptive study*.

This type of research project, as described in Figure 3.1.4, was judged to describe the research conducted in each appended paper due to the nature of the research project. As mentioned, this research is judged to fit into the theory-based paradigm approach as

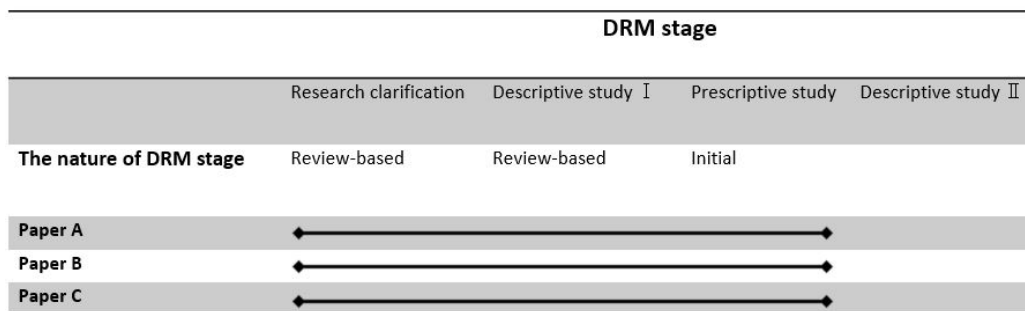


Figure 3.3: The applied research approach, redrawn from [Blessing and Chakrabarti, 2009] and complemented by each paper to illustrate the extension of studies regarding the DRM stages.

described by [Jørgensen, 1990]. Further, the research questions aim at answering the question of *how* rather than describing an as-is stage answering the question of *what*, thus taking on an exploratory nature. The theory-based research approach paradigm of synthesizing theoretical elements into new theories and the exploratory nature of the research questions are considered justifying the review-based *descriptive study I* stage, which aims at reviewing theories of product development in other fields of research. Further, a more extensive *prescriptive study* stage, creating new theories, establishing models and so forth, is considered justified for this type of research project.

So far, the models developed are still at an infant stage and hence, the *prescriptive study* stage is marked as "initial" but more elaborate work on this stage will be performed later and further, the *descriptive study II* stage shall be addressed in the future. A description of the applied research approach of each paper follows.

The applied research approach of Paper A

Paper A addresses initially RQ1, *How can pharmaceutical product designs be established to support product customization and the consequences of these designs for the production assessed?* The *research clarification* stage was comprised of a broad literature review and as a result, a two-fold research gap was established. First, a gap of methods to systematically designing pharmaceutical products to support mass customization in a concurrent manner was defined. The second gap addressed the lack of explored benefits of modularized tablet designs as enablers for personalized medicines.

The next stage of execution of the DRM framework was the *descriptive I* stage. This stage consisted of theory developing activities. Theoretical elements of systematic modelling of product design approaches in the context of product customization in manufacturing industry were studied, i.e. platform-based design approaches. Hence, the configurable component (CC) method, i.e. a platform-based design approach founded on

product architecture modelling by [Claesson, 2006] was chosen as a theoretical element. The CC method was adapted into the context of pharmaceutical products to establish customized product designs by expressing the architecture of these products and further developing them into platforms. Further, studies regarding approaches with which to assess these product designs from a production point of view were conducted and the complexity factor by [Pugh, 1990] was adopted to provide an indication of product design consequences for production.

The *prescriptive study* stage was conducted by synthesizing the theoretical elements adapted in the theory development-study into a methodology of proposing systematically designed pharmaceutical products by expressing the architectures of these and further developing the product architectures into product platforms. Hence, product designs supporting customization can be established. Further, this methodology proposes an approach to assess the consequences of these product designs for production. The purpose of this methodology is to contribute to a design tool for pharmaceutical products to be later implemented in industry. Lastly, the applicability of this methodology was tested in an exploratory manner to simulate and understand the benefits of modularized tablet designs. The purpose of the methodology application was to contribute to knowledge regarding modularized tablets as enablers for personalized medicines and hence, addressing RQ4, *How can modularized tablet designs enable personalized medicines?*

The applied research approach of Paper B

Paper B addresses RQ2, *How can the value of pharmaceutical product designs supporting customization be assessed?* The study in Paper B builds further on the approach of developing product platforms for pharmaceutical products by applying the CC method proposed in Paper A. The study was initiated by a realization that no existing methodologies emphasizing the benefits of pharmaceutical product designs supporting customization could be found. The *research clarification* stage comprising a literature review aimed at defining pharmaceutical product designs from a value-perspective confirmed the lack of methodologies with which to conduct an assessment of pharmaceutical product designs satisfactorily. Assessments of pharmaceutical product designs were mainly performed from an economic point of view disregarding the core purposes of pharmaceutical products, i.e. to treat people, hence bringing human and societal benefits.

Hence, a *descriptive study I* stage aimed at studying theoretical elements from manufacturing industries to be inspired by approaches defining product value. Methods with which to assess value from a full sustainability perspective, i.e. social, economic and ecological, were adopted as theoretical elements. More specifically a framework for sustainable product development, SLCA2.0 by [Villamil *et al.* 2018], was adapted to perform a life cycle assessment of pharmaceutical products from a full sustainability perspective. Additionally, methods for value modelling were studied and finally, the concept screen-

ing matrix by [Ulrich and Eppinger, 2012] was adapted to enable comparative studies of pharmaceutical product designs.

The *prescriptive study* stage further synthesized the methods into a methodology that proposes an approach with which to develop pharmaceutical product designs supporting customization and assess the value of these designs from a full sustainability perspective, i.e. including the economic, environmental and social sustainability dimension. The applicability of this methodology was tested in the context of modularized product designs. Simulations were performed to assess the consequences of modularized tablet designs on perceived product value. Hence, these simulations aimed at addressing RQ4, *How can modularized tablet designs enable personalized medicines?* , by generating knowledge regarding the value of modularized tablet designs.

The applied research approach of Paper C

Paper C addresses further RQ1, *How can pharmaceutical product designs be established to support product customization and the consequences of these designs for the production assessed?* , as well as RQ3, *How can the product and production system be modeled so that the consequences of changing customer needs can be assessed?* The study of Paper C was initiated by a desire to further develop an approach to concurrent engineering of pharmaceutical products by focusing on a more elaborate integration of production system design. A *research clarification* stage, governed by literature studies regarding product development of personalized medicines and approaches to product customization by adopting concurrent principles, resulted in a perceived gap of non-existing methods to systematic concurrent engineering of customized pharmaceutical products.

The *descriptive study I* stage was comprised of literature studies to study theoretical elements regarding concurrent engineering approaches for product customization. The manufacturing industry was studied to acquire inspiration for approaches to concurrent engineering and product customization. The SBCE approach to platform-based development by [Levandowski *et al.* 2014] was adapted. A model of integrated product and production platforms for pharmaceutical products was developed by adapting the approach to SBCE and platform-based development. Further, a proposal for an approach to respond to changing customer needs was developed by applying the producibility model by [Landahl *et al.* 2017, Madrid *et al.* 2016]. Hence, a dynamic model for developing customized product and production system designs was established.

The *prescriptive study* stage consisted of activities of synthesizing the methods studied in the *descriptive study I* stage into a methodology. This methodology aims at facilitating the development of integrated pharmaceutical product and production system platforms in a set-based manner and described an approach to respond to changes in customer needs. The application of the methodology was presented in the context of a

modularized tablet design to generate knowledge regarding the benefits of modularized tablet designs as enablers for personalized medicines, hence addressing RQ4, *How can modularized tablet designs enable personalized medicines?*

3.2 Research methods

This section describes the primary methods to conduct research. In this thesis, the primary methods employed have been reviewing the literature and synthesizing theoretical elements into methodologies. Further, simulations have been performed to test the applicability of the methodologies and to generate knowledge regarding modularized tablet designs as enablers for personalized medicines. Thus, illustrative case studies have been carried out in the context of modularized tablet designs.

3.2.1 Literature review

Literature review has been used as a data collection method in the research project. Literature reviews have been conducted stepwise in each study of Papers A, B and C. The aim of the literature reviews has been to create a comprehensive understanding of the problem of customized pharmaceutical product and production development activities either being focusing on the patient-centric product design or on the production system design. Successful approaches to mass customization of pharmaceutical products are not fully explored. Further, studies to understand the product development process of pharmaceutical products, being governed by experimental laboratory work in a sequential manner and the modest focus directed towards production system development have been performed. Hence, literature regarding pharmaceutical product development was analyzed for the purpose of establishing research gaps.

Literature regarding product development in the manufacturing industry was reviewed and analyzed with respect to phenomena describing successful product development philosophies and approaches. Further, the analysis conducted included an assessment of these philosophies and approaches ability to be adapted in the context of mass customization of pharmaceutical products.

3.2.2 Methodology development

The collection of theoretical elements were synthesized into methodologies to address the research gaps proposed as results of the literature reviews. SBCE principles were chosen as a product development philosophy to enable the efficient assessment of sets of product and production system variants. Methods synthesized into methodologies included, the CC method [Claesson, 2006] and the EF-M tree modelling approach [Schachinger and Johannesson, 2000]. The functional modelling nature of these methods was perceived

advantageous for flexible product and production system design as well as the ability to use these methods for platform modelling. Platforms have been proven to support mass customization in the manufacturing industry. SLCA2.0 method [Villamil *et al.* 2018] was collected to support an integrated approach for sustainable product development of pharmaceutical products. And finally, the concept screening matrix [Ulrich and Eppinger, 2012] was adapted to enable a value description of customized pharmaceutical product designs.

3.2.3 Simulation based case studies

Simulations have been employed to mainly illustrate the application of the developed methodologies and hence provide initial validation by confirming that the behaviour of the methodologies is sufficient according to the defined goals for developing the methodologies. Simulation studies have also been conducted to understand the opportunities provided for the product and production development process of pharmaceutical products by applying approaches employed in the manufacturing industry. For example, applying SBCE principles to develop product and production system designs for pharmaceutical products allows for rapid cause-and-effect simulations of various product designs and the consequences for production. The main focus has been to develop platforms for product and production systems of pharmaceutical products and hence, the software CCM [Claesson, 2006] which is a platform modelling software and enables modelling and simulation of platforms, has been used. Due to the restricted capabilities of CCM [Claesson, 2006], simulation support has additionally been provided by MATLAB .

Each study conducted, as described in the appended papers, demonstrates the applicability of the methodology synthesized by performing an illustrative case study. These case studies have been conducted in the context of modularized tablet designs to generate knowledge about these designs as enablers for personalized medicines. The illustrative case studies performed are of a qualitative nature, for example the application of methods require qualitative studies, such as employing the CC method [Claesson, 2006] to design flexible pharmaceutical products. The illustrative case studies are also of a quantitative nature, experimental simulations have been conducted to generate knowledge about the *cause-and-effect* of various design choices of modularized tablet designs and the consequences of these designs on predefined criteria. The data used for the experiments have both been of a fictitious nature and data gathered from empirical studies found in the literature.

3.3 Research outcome quality criteria

Empirical validation of design theories has been proven a difficulty of conducting design research [Roozenburg and Eekels, 1996, Buur, 1990]. [Roozenburg and Eekels, 1996] described that the process of designing products cannot be repeated, and this can be un-

derstood when considering the inter-disciplinary nature of design research that relies to a large extent on the researchers knowledge, experience, creativity and the ability to connect various scientific fields. [Roozenburg and Eekels, 1996] thus highlighted the consequences of a non-repeatable design process; firstly, to prove that better research outcomes would have been obtained with another research approach is a difficulty, and secondly, proving that the research outcome by precise virtual repetition in a mathematical manner is a difficulty due to the various number of factors affecting the result. [Roozenburg and Eekels, 1996] even argued that proving the research outcome in a mathematical manner might even be irrelevant.

Approaches to validation of design research has been proposed by numerous sources [Creswell, 2014, Buur, 1990, Yin, 2009]. Two fundamental guiding questions that are connecting most of the validation approaches are *did we do the right things?* and *did we do things the right way?* The first question relates to the *validity* and the second question to the *reliability* of the design research outcome.

[Creswell, 2014] described *validity* as considerations of the research outcomes ability to describe the measured phenomena, including the trustworthiness and credibility of the research outcome. [Almefelt, 2005] suggested *transferability*, i.e. the degree to which the results can be generalized beyond the setting, an important concept to consider when assessing validity of research outcomes. [Almefelt, 2005] further elaborated that, the researcher has the ability to enhance the transferability by providing a careful description of the study, the context, hypothesis proposed and so forth. *Reliability* of the design research outcome considers concepts such as the consistency of the approach proposed and hence, the *reproducibility* of research outcome [Creswell, 2014].

[Creswell, 2014] described procedures to ensure the validity of research outcomes when performing quantitative research activities or rather, described threats to validity. Thus, to ensure valid research outcomes, evidence supporting validity threat elimination becomes important. Eliminating validity threats imply that the research conducted affects the objective of research in an intended way and does not affect anything else. [Creswell, 2014] divides validity threats into two groups, *internal* and *external validity* threats. *Internal validity* threats consider threats to the procedure of performing experiments, for example, the sampling procedure and drawing correct inferences from results and so forth. *External validity* threats consider threats to the generalizability of research results from the experiment beyond the chosen sample.

[Buur, 1990] addressed the difficulty of validating design research by suggesting a two-fold design research validation approach. The first part, denoted *logical verification*, consists of activities including ensuring no internal conflicts between the theoretical elements synthesized into new theories and ensuring that the method derived from the theory is consistent with the theory, i.e. consistency. Further activities include the ability of explaining all relevant phenomena, observed in literature or empirically, with the theory

proposed, i.e. completeness of theory. And final and last activity, the theory should be able to explain the observations of the case studies performed. The second part of the research validation approach by [Buur, 1990], denoted *verification by acceptance*, suggests that theories proposed, and the methods or models derived from the theories, are valid if accepted by experienced designers.

[Sargent, 2013] proposed a model for stepwise validation of simulation models. The model by [Sargent, 2013] aligns with the intention of ensuring the *validity* and *reliability* of research outcomes. Further, Sargent described the element of credibility as a part of model validation, that is the confidence that the users of the model have in the model, as well as the confidence in the information retrieved from the model. The level of credibility should increase with proper validation of the simulation model.

According to [Sargent, 2013], the aim of simulation model validation, i.e. activities such as model verification and validation, is to ensure that the information retrieved from simulation models are correct for their usage context. Verification implies that the simulation model is doing what the model is intended to do. Validation implies confirming that the model performs according to a sufficient accuracy as intended in the predefined context. Hence, the validity of a model is strongly linked to the context of model application. If the model has been developed to answer certain questions, the model validity is decided from the ability of the model to answer these questions.

The model for stepwise validation of simulation models by [Sargent, 2013] incorporates three vital elements to the development procedure of the simulation model and further, the validation and verification in-between each developed element. The first element is the *problem entity*, which is the system, product or phenomena for which a simulation model is to be developed. The second element is the *conceptual model*. The conceptual model can be a graphical, mathematical or logical representation of the problem entity defined. The final element is the *computerized model*, which is the conceptual model implemented into a computer. The validation procedure in-between each element of the developed model consists of the following steps, *conceptual model validation*, *computerized model verification*, *operational validation* and *data validity*.

Conceptual model validation is the procedure by which to validate the conceptual model, i.e. to ensure that the conceptual model developed solves the problem entity for which the model has been created. Activities of this step aim to ensure that the underlying theories and assumptions for the model are correct and reasonable for the problem entity defined. *Computerized model verification* is the procedure to ensure that the implementation of the conceptual model in a computer has been conducted in a correct manner. The *operational validation* procedure ensures that the computer model used for simulations can describe the model behavior to a reasonable extent in order to provide a solution for the problem entity defined. Finally, the *data validity* step aims to ensure that the data necessary for the three elements of model development are adequate and correct to solve

the problem entity, i.e. data for model building, conducting experiments on the model and finally, providing a solution for the problem entity.

3.3.1 The applied research quality assessment procedure

A short summary will be provided to elaborate on which of the research quality criteria described above are adopted to assess research outcomes of this thesis. The research performed, as mentioned, has embraced a quantitative nature and to some extent qualitative nature, hence the quality criteria for assessing research outcomes will be described separately for qualitative and quantitative criteria.

Adopted qualitative research quality criteria

The criteria adopted in this thesis to assess the quality of research outcomes of qualitative research is *validity* and *reliability*. The proposed methodologies are results from qualitative studies and are perceived as models but also as design theories and hence, validity and reliability criteria proposed by [Creswell, 2014], [Sargent, 2013], [Almefelt, 2005] and [Buur, 1990] is adopted.

To assess the **validity** of the proposed methodologies the ability of the methodologies to solve the problem entity that the model has been created for is assessed, described as the *conceptual model validation* activity proposed by [Sargent, 2013]. Ensuring the model sufficiency, aligns with the completeness criteria proposed by [Buur, 1990], i.e. ensuring that the relevant phenomena observed can be explained by the proposed theory. The *transferability* criteria, as proposed by [Almefelt, 2005], is used to evaluate the transferability of the proposed methodologies beyond the context for which the methodologies were created. *Credibility*, i.e. the confidence the model user has in the model as well as the information retrieved from the model as described by [Sargent, 2013], is used to assess the methodologies. The *verification by acceptance* activity suggested by [Buur, 1990], i.e. the acceptance of the theories and models proposed by experienced designers, is considered correlated to the *credibility* criteria and is discussed in this thesis.

Reliability is the second criteria according to which the proposed methodologies are assessed. The *reproducibility* criteria as suggested by [Creswell, 2014] is discussed and the correlated concept of *consistency* by [Buur, 1990], i.e. ensuring the synthesis of theoretical elements has been performed correctly and the methods are in agreement with the theory. *Computerized model verification* as proposed by [Sargent, 2013] correlates to these previously mentioned criteria as it emphasizes the importance correct implementation of the model into the computer thus this criteria will be addressed in this thesis.

Adopted quantitative research quality criteria

As mentioned, the case studies performed during research adopts partly a quantitative nature with experimental simulations conducted. Hence, criteria chosen to assess the quantitative research outcomes are *internal* and *external validity*.

To discuss **internal validity** the sampling procedure of the population used for case study simulations is assessed, which [Creswell, 2014] suggested as a threat to *internal validity*. [Sargent, 2013] discussed the *operational validity*, i.e. the ability of the computer model to describe behaviour of phenomena sufficiently according to the problem defined, which is considered correlated to *internal validity*. A correctly performed experimental set-up shall reflect a correct behaviour of the model.

To assess the **external validity** the *generalizability* of the case study results beyond the sample is discussed.

The quality of the research outcomes are discussed in Chapter 5.

CHAPTER 4

Results

This chapter presents the results of the thesis within the scope of the aim and goal of this thesis. A short summary of each study in the respective appended paper is provided with the main motivation behind conducting the study. The important results of each Paper, A to C, are highlighted. Complete descriptions of studies conducted and results obtained are provided in the appended papers.

4.1 Summary of studies conducted

This section presents a summary of each study conducted paper-wise and the main motivation behind the studies.

Paper A addresses RQ1, *How can pharmaceutical product designs be established to support product customization and the consequences of these designs for the production assessed?* The focus is to explore how pharmaceutical product designs supporting customization can be established. The motivation behind conducting the study was the lack of engineering-based design methodologies with which to develop pharmaceutical product designs supporting customization and assessing the consequences of these designs for pharmaceutical production.

The key contribution of Paper A is a proposal for a methodology to develop pharmaceutical product designs by establishing the architectures of pharmaceutical products, developing these architectures into product platforms and assessing the consequences of these product designs with respect to manufacturing complexity. The architecting approach builds on the CC method presented by [Claesson, 2006] and the complexity factor by [Pugh, 1990] serves as an indicator of manufacturing complexity. Further, the application of the methodology is illustrated in the context of modularized tablet designs to address RQ4, *How can modularized tablet designs enable personalized medicines?*

Paper B addresses RQ2, *How can the value of pharmaceutical product designs supporting customization be assessed?* and focused on the means to assess the value of a re-designed pharmaceutical product supporting customization. The idea for Paper B was initiated by the results of Paper A. In Paper A the performance of the pharmaceutical product designs was assessed with respect to the number of product variants and the complexity factor, but more elaborate approaches to assess the performance of customized pharmaceutical products was a desire. Additionally, the narrow focus on an economic perspective when assessing pharmaceutical product performance found in literature, further confirmed the need for better value assessment approaches. This study focused on performing more elaborate analyses on the value of pharmaceutical product designs, emphasizing the importance of treatment customization.

The key contribution of Paper B is a methodology to support design decisions regarding pharmaceutical product designs from a value perspective. Furthermore, the methodology suggests a value-modelling approach where a full sustainability perspective, i.e. including the social, economic and ecological sustainability dimensions, is adopted as value assessment criteria. The applicability of the methodology is illustrated in the context of modularized tablet designs to address RQ4, *How can modularized tablet designs enable personalized medicines?*

Paper C addresses RQ1 and RQ3, *How can the product and production system be modeled so that the consequences of changing customer needs can be assessed?* and further elaborates on the research gap defined in Paper A regarding the need for engineering-based design methodologies to concurrently develop pharmaceutical product designs and corresponding production systems. The idea of Paper C was initiated by the desire of elaborate approaches to consequence analysis of pharmaceutical product designs on the production system.

The key contribution of Paper C is a methodology to concurrently develop integrated product and production system platforms for pharmaceutical products to support the consequence assessment of pharmaceutical product design choices for the production system. Additionally, the methodology allows for dynamic platform modelling, i.e. responding to changes in the established integrated platform that might occur due to a change in customer needs. Further, the applicability of the methodology is illustrated in the context of modularized tablet designs to address RQ4, *How can modularized tablet designs enable personalized medicines?*

4.2 Paper A: Product Architecture Management of Medicinal Products - An Integrated Function-Means Tree Approach to Customizing Oral Dosage Forms

The purpose of Paper A was to develop a methodology for managing product architectures of pharmaceutical products. A literature review showed emerging research addressing personalized medicines. The research focus thus far has been directed towards empirical attempts to customized product design or towards production system design assuming a product design of the *one-size-fits-all*-paradigm. Concurrent approaches to product and production system design supporting mass customization of pharmaceutical products are lacking.

The methodology proposed in this Paper A focuses on a systematic approach to establish customized product designs of pharmaceutical products and suggests an initial approach to assess the consequences of established product designs for manufacturing complexity. Furthermore, the application of the methodology is illustrated in the context of modularized tablet designs to generate knowledge on modularized tablet designs as an enabler for personalized medicines.

4.2.1 Proposed methodology

The proposed methodology is presented in Figure 4.1. Traditional product design from the *one-size-fits-all*-paradigm, such as a fully integral tablet design, provides the foundation for the product architecture, i.e. a description of the product in terms of its functions. Further, patient attributes serve as input and are refining the established functional model of the product by translating these attributes into product functions. This translation is performed by logical reasoning and supported by the literature. The CC method [Claesson, 2006] is applied to establish the architecture of the pharmaceutical product. The product platform of the pharmaceutical product is modelled by complementing the product architecture with design parameters. For platform modelling and execution, the CCM [Claesson, 2006] and MATLAB softwares are used. The output of the methodology is a product platform for pharmaceutical products. Additionally, through the execution of the product platform, sets of product families are generated for which the performance is calculated. In this study, the complexity factor by [Pugh, 1990] was used as an indicator of product family performance with respect to manufacturing complexity.

4.2.2 Illustrative case study

To illustrate the application of the methodology, a modularized tablet design is introduced. Further, the consequence for production from various modularized tablet designs is as-

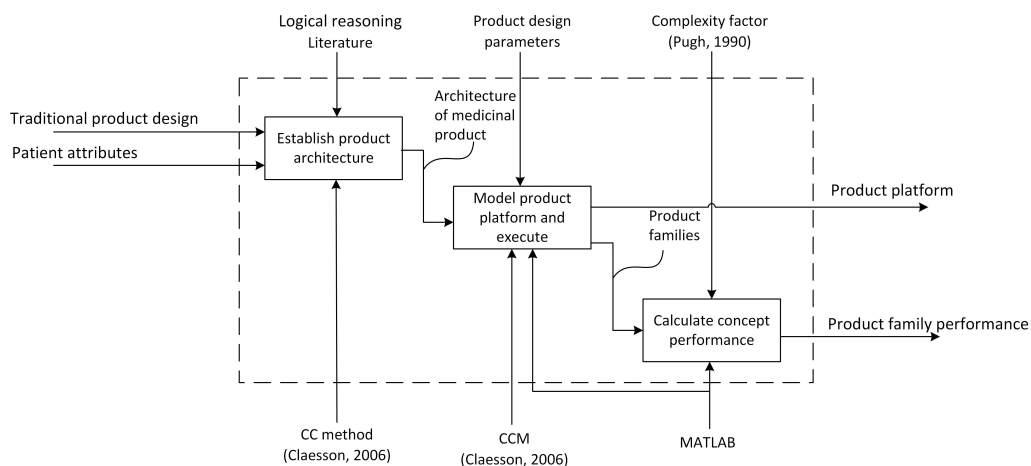


Figure 4.1: The proposed methodology of Paper A to develop customized pharmaceutical product designs and assess the performance of these designs.

sessed. Cases were prepared to generate product families by platform execution. These cases use various sizes of API modules from which to configure product variants, Case A configures product variants of API modules of size 1 mass unit, Cases D and E use two sizes of API modules, 1 & 5 mass units and 1 & 10 mass units, respectively, and case G uses three sizes of API modules, 1, 5 & 10 mass units from which to configure product variants. Each case uses filling modules of a single size for product variant configuration purposes. The execution space of the product platform is defined as each dose step in-between 1 and 100 mass units.

Figure 4.2 presents the results of the product family performance calculation. This performance is displayed as the *number of product variants* on the primary axis (to the left) for product families A, D, E and G. Additionally, to give an indication of the cost-benefit of introducing modularized tablet designs and further, configuring product variants from various sizes of modules, the results of performance calculations are presented as the ratio between the *number of product variants* and the *complexity factor* on the secondary axis (to the right). In Figure 4.2 the product families A, D, E and G have been organized according to an increasing customization level (the number of product variants).

Conclusively, Paper A has successfully presented an approach to concurrent engineering of product and production system designs of pharmaceutical products supporting customization. This has been conducted by proposing a methodology for managing product architectures of pharmaceutical products, developing these into platforms and assessing the consequences of these established product designs on manufacturing complexity. Further, the application of the methodology was illustrated in the context of modularized tablet designs to generate knowledge regarding modularized tablet designs as enablers for personalized medicines. Results in Figure 4.2 indicate that by the introduction of a few

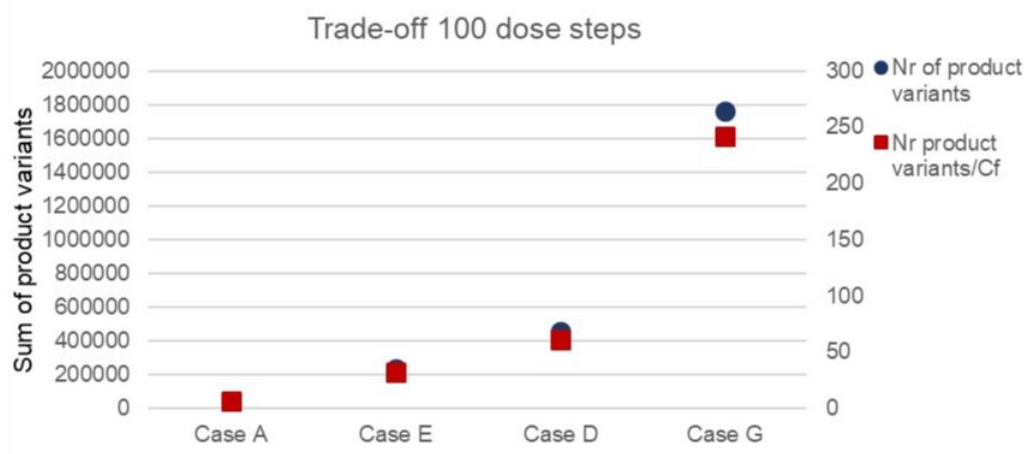


Figure 4.2: Trade-off between *the number of product variants* and the ratio between *the number of product variants* and *complexity factor* in Paper A.

standardized modules from which to configure product variants, the number of product variants increases rapidly. Further, the ratio between the *number of product variants* and the *complexity factor* indicates that even though the complexity factor would be increasing by introducing several modules as product configurational means, the complexity factor is not increasing as fast as the number of product variants.

4.3 Paper B: Decision Support for Re-designed Medicinal Products

- Assessing consequences of customizable product design on the value chain from a sustainability perspective

The purpose of Paper B was to establish a methodology with which to evaluate the value of pharmaceutical product designs, more specifically, assessing the value change when a customizable product design is introduced. A literature review showed that value modelling approaches have not been applied in the context of personalized medicines. Value assessments of pharmaceutical products have in general been limited to economic perspectives. Additionally, environmental assessments of pharmaceutical products were found. Furthermore, literature studies showed that these studies of pharmaceutical product value conducted from an economic or environmental perspective were limited to a single value chain phase, as no studies assessing the consequences of introducing customizable product designs on the whole pharmaceutical value chain could be found.

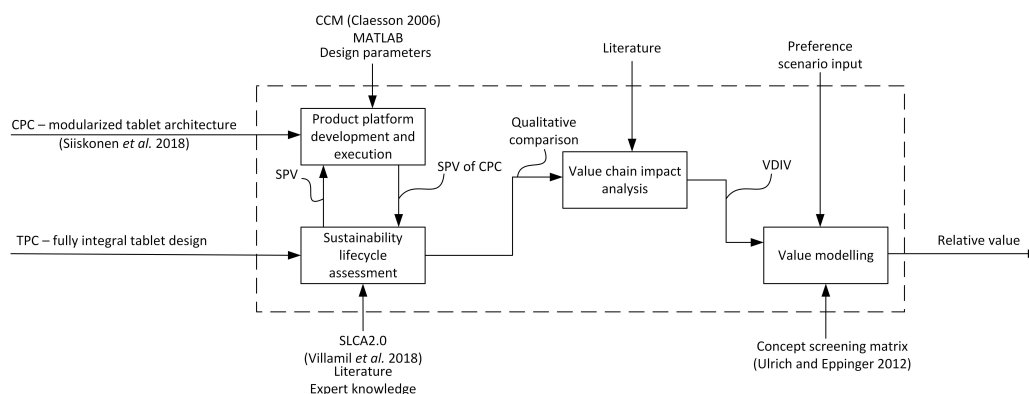


Figure 4.3: The proposed methodology in Paper B to assess the value of pharmaceutical products from a full sustainability perspective.

The methodology proposed in Paper B suggests an approach by which to assess the value of pharmaceutical products by integrating a full sustainability perspective, including the social, economic and ecological sustainability dimensions, as value assessment criteria. The assessment is performed by studying the consequences for the pharmaceutical value chain of changing product design.

4.3.1 Proposed methodology

Figure 4.3 presents the proposed methodology of Paper B. The product platform approach of Paper A is adapted to generate customizable product designs. A sustainability lifecycle assessment, using SLCA2.0 [Villamil *et al.* 2018], is performed on customizable product design, but also on a traditional product design to generate reference data. A qualitative comparison with respect to sustainability criteria is performed between the customizable and the traditional product design. The qualitative comparison is elaborated by studying the pharmaceutical value chain and phases of the value chain prone to change due to a change in product design. Variables in each value chain phase changing value-wise due to a customizable product design are identified, quantified and categorized according to the sustainability dimension affected from the value change. A model of value simulations was established, where sustainability dimensions are acquiring weight, and hence, can be used to give information regarding the sustainability dimension promoted by the respective product design.

4.3.2 Illustrative case study

To illustrate the application of the methodology, a commercial treatment for hypertension is adopted to serve as a foundation for developing the product platform for the customizable product design. The traditional product embraces a fully integral tablet design. The

Table 4.1: Scenarios for value modelling as performed in paper B.

Scenario	1	2	3	4	5	6
w_{social}	0.67	0.67	0	0.33	0.33	0
$w_{ecological}$	0.33	0	0.67	0.67	0	0.33
$w_{economic}$	0	0.33	0.33	0	0.67	0.67

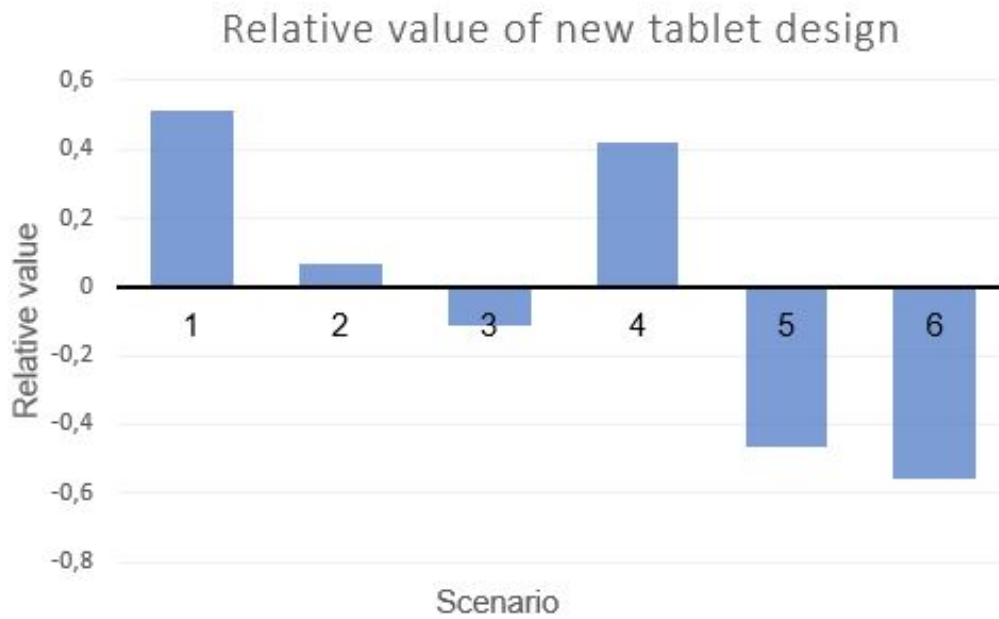


Figure 4.4: The value simulation results in Paper B of each scenario prepared in Table 4.1.

customized product design embraces a modularized tablet design. This commercial treatment also contributes reference data of traditional product design, when performing the sustainability lifecycle assessment. The results of value simulations are presented in Figure 4.4. The value increase or decrease of the customizable product design compared to the traditional product design is displayed. The scenarios simulated emphasize respective sustainability dimension differently, hence weights are assigned to each sustainability dimension according to Table 4.1.

Conclusively, Paper B has suggested an approach by which to assess the value of pharmaceutical product designs from a full sustainability perspective and by evaluating the consequences of product designs on the pharmaceutical value chain. The results in Figure 4.4 indicate that customizable product design is the preferred choice of product

design if value is to be created from a social and ecological dimension. Furthermore, the scenario emphasizing the social dimension the most and thereafter the economic dimension, still indicates that customized product design is the preferred product design choice.

4.4 Paper C: Integrated Product and Production System Platforms in a Set-Based Manner Enabling Personalized Medicines

The purpose of Paper C was to explore the adaptability of SBCE principles to develop product and production system platforms for pharmaceutical products. The study was initiated by the perceived gap of lacking SBCE approaches to product and production system design of customized pharmaceutical products. Since an initial proposal of an approach to concurrent engineering of pharmaceutical products was made in Paper A, this study builds on it. A further elaborated methodology to concurrently develop product and production system platforms, with a more detailed approach to production systems modelling compared to Paper A, is proposed. Further, an approach to extend the established integrated product and production system platform, when the functional bandwidth of these platforms are judged insufficient, is proposed. This approach to platform extension allows the platform to respond to changing customer needs. Furthermore, the applicability of the methodology is tested in the context of modularized tablet designs to generate knowledge regarding modularized tablet designs as enablers for personalized medicines.

4.4.1 Proposed methodology

The methodology consists of three major domains, the *platform preparation*-, *platform extension*- and *platform execution*-domains. Each domain will be described in succeeding sections.

Platform preparation-domain

Conducting the activities in the *platform preparation*-domain, see Figure 4.5, results in an integrated product and production platform. Sets of patient attributes and sets of manufacturing equipment specifications are translated through logical reasoning and literature into EF-M trees of the product and the manufacturing equipment, respectively, by applying the EF-M tree modelling approach [Schachinger and Johannesson, 2000]. The EF-M tree is complemented with component trees of the product and the manufacturing equipment and hence, the product and manufacturing equipment architectures have been established.

The functional bandwidth of the unit operation which joins the product architecture with the manufacturing equipment is controlled by the respective architecture. Likewise,

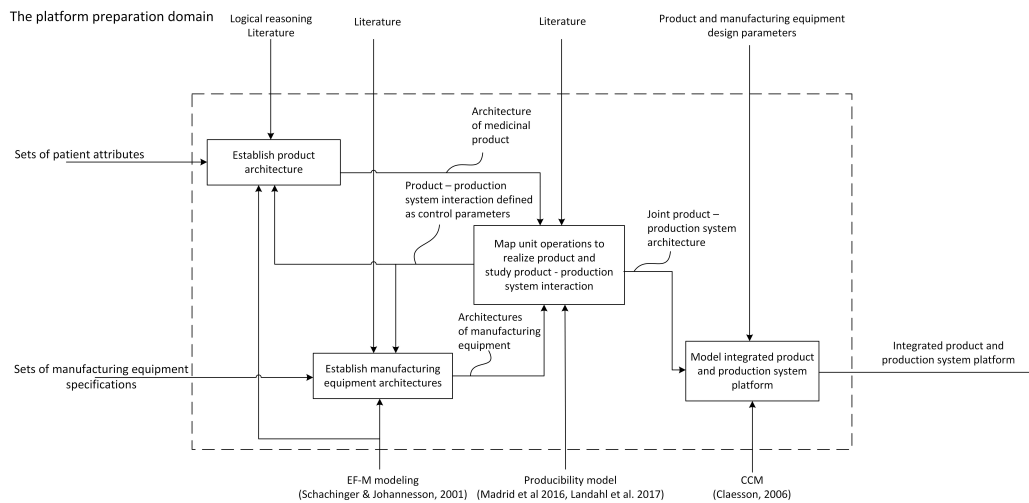


Figure 4.5: The activities of the *platform preparation*-domain in Paper C.

the joint functional bandwidth of the unit operation controls the architectures. The modelling of the functional bandwidth of the joining unit operation is performed by applying the *producibility model* by [Landahl *et al.* 2017]. The joint functioning bandwidth is modelled by identifying control parameters of respective architecture and by studying the interaction of these control parameters. This joint product - production system architecture is further developed into an integrated product and production system platform by complementing it with product and manufacturing equipment design parameters. The platform modelling is performed in the CCM software [Claesson, 2006].

Platform extension-domain

The activities in the *platform extension*-domain, see Figure 4.6 are accurate to execute when the functional bandwidth of the integrated platform is judged insufficient and needs an extension. Hence, extension activities create a platform variant.

An insufficient integrated platform is the result of either changing customer needs or changing manufacturing resources. As the sets of patient attributes or manufacturing equipment specifications are updated, an update is required of either platform to cover the new functional bandwidth. An update of either platform further updates the joint functional bandwidth of the unit operation joining the platforms, and this change further propagates to the remaining platform. Hence, an updated integrated product and production system platform variant with an adjusted bandwidth has been established.

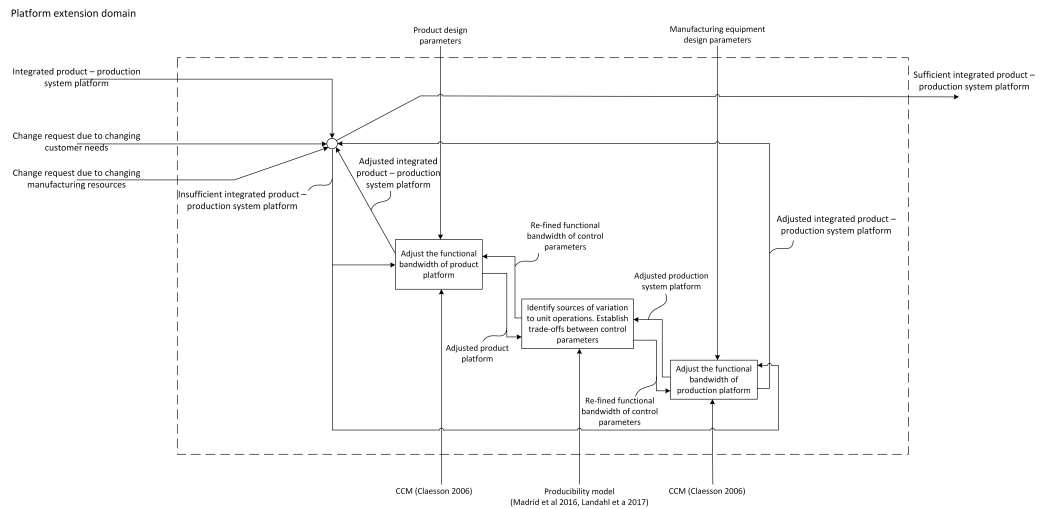


Figure 4.6: The activities of the *platform extension*-domain in Paper C.

Platform execution-domain

Figure 4.7 outlines the activities in the *platform execution*-domain which are performed to study the performance of the integrated product and production system platform variants.

A Bill-of-material (BOM) defines the execution space of the integrated product and production system platform variants by informing what is needed in terms of product and production system variants. Execution of the integrated platform variants generates feasible sets of product and production system variants for which the performance is calculated. The performance indicator is chosen according to the information to be acquired from platform variants.

4.4.2 Illustrative case study

The proposed methodology was applied to a commercial treatment of diabetes. An integrated product and production system platform variant for the traditional product design of the treatment, i.e. a fully integral tablet design, was established. Further, a modularized tablet design of the same treatment was introduced and hence, another platform variant was established. The consequence of design on the tablet compression process was studied by platform execution. The tablet compression time was used as a performance indicator. For tablet compression, a tablet punching tool consisting of a single tip was used to compress tablets of the traditional product design and two types of tools were used to compress tablets of the modularized product design, *tool1* consisting of 8 tips and *tool2* consisting of 14 tips. Table 4.2 summarizes the increase in tablet compression time when introducing a modularized tablet design.

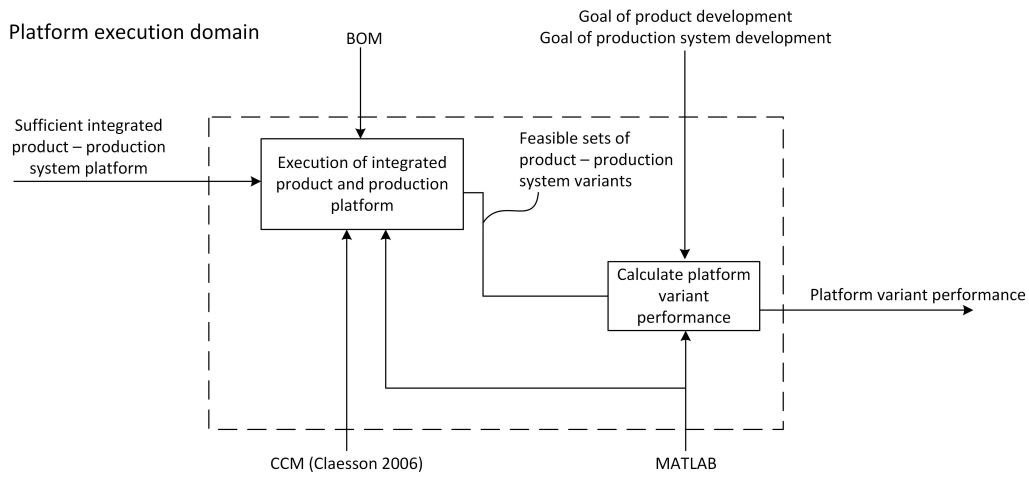


Figure 4.7: The activities of the *platform execution*-domain in Paper C.

Table 4.2: Increase in tablet compression time in Paper C.

Case	t_{Tool1}	t_{Tool2}
Traditional product design	-	-
Modularized product design	95%	1%

Conclusively, Paper C has successfully presented the first approach to set-based concurrent engineering of product and production system designs of pharmaceutical products. Furthermore, the results show that a modularized tablet design increases the tablet compression time; however, a multiple tip tool consisting of 16 tips achieves break-even in tablet compression time for the modularized tablet design and the traditional tablet design. This result illustrates the application of the methodology to inform design decisions regarding product or production system design (here, the tablet punch design) to achieve the desired performance (here, measured as the tablet compression time).

CHAPTER 5

Discussion

This chapter answers the research questions proposed in Chapter 1, as well as discussing the quality of research results. Furthermore, the main scientific and industrial contribution of the thesis is discussed.

5.1 Answering the research questions

The research questions posed in Chapter 1 will be answered in this section.

RQ1: *How can pharmaceutical product designs be established to support product customization and the consequences of these designs for the production assessed?*

RQ1 is primarily addressed in Paper A and Paper C. By applying the CC method [Claesson, 2006] to functional modelling, architectures of pharmaceutical products supporting flexible product designs can be established. Thus, designs that support product customization. To assess the consequences of flexible pharmaceutical product designs for production the complexity factor by [Pugh, 1990] can be used. Further, an integrated approach to product and production system modelling by applying the EF-M tree modeling [Schachinger and Johannesson, 2000] to describe the architectures of the product and production system, respectively, allows establishing customized product designs an assessing the consequences for production. The integration of respective architecture requires the producibility model by [Landahl *et al.* 2017] to model the interaction between the product and production system in joining unit operations.

The CC method [Claesson, 2006] is an approach to functional modelling, i.e. expressing the product according to its functions. Functional modelling as an approach to establish pharmaceutical product architectures was judged beneficial, since the focus could be re-directed from a fixed solution space and physical realizations of product to rather consider the functions that the product should embed. Later, when considering alternative solutions to the functions, the design space is kept open and hence, allows assessing sets

of solution alternatives. Further, these product architectures were developed into product platform variants by complementing the architecture with product design parameters. The CCM software [Claesson, 2006], which is based on the CC method [Claesson, 2006], is a platform modelling software and was used to develop the product platform variants of pharmaceutical products. Further, CCM allows execution of the platform generating product variant sets, product families, grounded in the developed platforms. Hence, establishing product designs by employing the CC method [Claesson, 2006], support product customization.

To assess the consequences of customized pharmaceutical product designs for production, the complexity factor was adopted in Paper A. The complexity factor was used as a proxy to provide the indication of production consequences. The complexity factor is a measurement of product complexity, and hence, can provide indicate increasing production complexity. More complex product designs might pressurize production systems, for example in the sense of additional functionalities embedded in a product might require new production equipment to be installed to provide for this product function. The complexity factor was thus used to indicate additional costs that might arise due to more complex product designs. However, the complexity factor describes the complexity of the product, but does not describe the real consequences for the production system. Hence, more elaborate approaches to assess the consequences for production shall be studied. Thus, the study of Paper C was conducted to provide a remedy for this desire of elaborate modelling approach to production system consequence assessment.

Paper C adds an element of an approach to establish the architecture of the manufacturing equipment in parallel to establishing the architecture of the product. The EF-M tree modelling by [Schachinger and Johannesson, 2000] was applied as an architecting approach, which the CC method [Claesson, 2006] is built on. Further, the *producibility model* by [Landahl *et al.* 2017] is proposed to be used to model the joining of the product and manufacturing equipment architectures. The producibility model studies the interaction of the product and manufacturing equipment in the production unit operation that is aiming at transforming the product into the desired state by using the manufacturing equipment. In the unit operation, a joined functioning bandwidth of the product and manufacturing equipment is defined and hence, these entities are joined. The result is a combined product and production system architecture. This joined product and production system architecture is further developed into an integrated product and production system platform by complementing the architecture with product and manufacturing equipment specific design parameters. The modelling of the integrated platform is performed in CCM, similarly to Paper A. The execution of the integrated platform generates sets of feasible product and production system platform variants and thus, information regarding various choices of product design and the feasible production system with which to produce this product design can be acquired. Hence, the consequences for production due to changes in product design can be assessed.

RQ2: How can the value of pharmaceutical product designs supporting customization be assessed?

RQ2 is mainly addressed in Paper B. By applying the CC method [Claesson, 2006] to establish flexible product architectures, as described above, product designs supporting customization can be established. The SLCA2.0 method by [Villamil *et al.* 2018] provided sustainability criteria according to which the value of customized pharmaceutical product designs can be described from a full sustainability perspective. Studying the consequences of product customization for the value chain, the set of value driving criteria can be complemented. Finally, employing a concept screening matrix by [Ulrich and Eppinger, 2012] the value of customized product designs can be value criteria-wise compared to a reference concept and thus, the value of customized product design can be assessed.

The methodology proposed in Paper B employs the SLCA2.0 method [Villamil *et al.* 2018] to perform sustainability assessment of pharmaceutical products. The SLCA2.0 method [Villamil *et al.* 2018] allows for a qualitative comparative sustainability assessment of two product designs. The comparative sustainability assessment was used as a basis to assess the consequences of a product design change for the pharmaceutical value chain. Further, studies on the pharmaceutical value chain were performed, to complement the information from SLCA2.0 with established literature. Benchmarking of variables of the pharmaceutical value chain that are affected due to a change in product design was conducted. These value chain impact variables were categorized according to sustainability dimension affected, due to a change in product design. Finally, a concept screening matrix [Ulrich and Eppinger, 2012] was adapted as a method by which assess the value of the product designs. The identified impact variables of the value chain were used as value criteria. The concept screening matrix was complemented with weightings on the value chain impact variables with respect to the sustainability dimensions. Scenarios promoting each of the sustainability dimension was created and hence, product design choices guided by the preferred sustainability dimension was promoted. Hence, an approach by which to assess the value of pharmaceutical product designs supporting customization was proposed that incorporated a full sustainability perspective as value criteria.

RQ3: How can the product and production system be modeled so that the consequences of changing customer needs can be assessed?

RQ3 is addressed in Paper C. The consequences of changing customer needs for the production system can be modelled by an approach to dynamic integrated product and production platform modelling. This dynamic modelling is performed by extending the current integrated product and production system platform. Updating the product architecture and, consequently, the product platform according to updated customer needs provide a product platform responding to changing customer needs. The product platform is updated by adjusting the product design parameters of product platform and the mod-

elling of this update is performed in CCM. The updated product platform then causes a change in the joint functioning bandwidth of the unit operation, that combines the product and production system. The feasible joint functioning bandwidth in the unit operation is updated in CCM. The updated joint functioning bandwidth of the unit operation might require an adjustment in the functioning bandwidth of production system platform, and hence is updated accordingly to the requirements set by the joint functioning bandwidth of the unit operation. This updated functioning bandwidth ensures that the manufacturing equipment, of the production system, providing for the unit operation, is able to produce the updated product design according to changing needs. The update in the production system platform is performed in CCM by updating the manufacturing equipment design parameters. The process described provides for a new integrated platform variant. Execution of the integrated product and production platform model in CCM generates variants of product and production system designs. Criteria, to indicate the performance of each platform variant, shall be defined to assess the platform variants.

RQ4: How can modularized tablet designs enable personalized medicines?

RQ4 is addressed in Papers A, B and C. By introducing a few standardized modules of various sizes as configurational means for tablets, substantial flexibility on a product level can be achieved. By combining a few standardized modules in all possible combinations the number of combinations increases rapidly and, consequently, the number of unique product variants that can be established. Further, a modularized tablet design shows an increase in value from a social and environmental sustainability perspective. The reason for the increase in value is mainly due to the ability of modularized tablet designs to offer flexible doses, and hence, the treatment dose can be adjusted according to the patient need. Further, an accurate dose might relieve side effects, the release properties can be adjusted due to modularized product design and the administration effort is judged to decrease. All these effects are believed to improve the efficiency and safety of the treatment. From an environmental perspective, a modularized tablet design can promote a decrease in raw material consumption and a decrease in end-of-life waste. Finally, even though the tablet compression time of modularized tablet designs was longer than for the traditional tablet design, the increase in time was not extensive. Additionally, it is believed that by incorporating change-over times, an advantage from a modularized tablet design perspective can be achieved.

Simulations performed in Paper A showed the consequences from combinations of different module sizes on the level of customization and manufacturing complexity. The number of unique product variants, if only using a few module types to establish product variants from, is rapidly increasing since the size and shape of the product has proven to affect the release rate of the API. Thus, product variants with different release rates can be configured by introducing various assembly sequences of a few different types of modules. Further, adding a module consisting of solely filling material as configurational means, with the purpose of giving a flexible size to the product, additional product vari-

ants of unique sizes can be generated. The manufacturing complexity increased linearly with an increasing level of customization. The translation of manufacturing complexity to manufacturing cost shall be further studied to clarify the affordability of modularized tablet designs.

From a social sustainability perspective, an increasing value of customizable product design is mainly due to a flexible dose, and hence, the treatment dose can be adjusted according to the patient need. Further, an accurate dose might relieve side effects, a modularized product design allows for adjustment of the release properties, using the same reasoning as described above regarding product size and shape, and finally, the administration effort is judged to decrease due to the opportunity of adjusting the size and the shape of the product variants. From an environmental perspective, a modularized product design can promote a decrease in raw material consumption, which mainly is a consequence from the accurate dosing offered to patients. Similarly, offering accurate dosing to patients promotes the decrease of end-of-life waste, which might originate from both the fact that a more accurate dosing is available and hence, any surplus substances leaving the body ending up in the nature in vain is eliminated. Additionally, an increasing adherence with a customized product design might decrease the waste generated.

5.2 Quality of research outcomes

This section will discuss the quality of research outcomes. The proposed methodologies of Papers A, B and C and the outcomes of the illustrative case studies will be described. The proposed methodologies are perceived as design theories in the context of pharmaceutical products and hence, quality criteria proposed by [Buur, 1990] will be used to discuss the research outcomes. Further, the proposed methodologies are perceived as simulation models and thus, the quality criteria by [Sargent, 2013] will be used to discuss the research outcomes. Finally, quality criteria defined by [Creswell, 2014] for qualitative and quantitative studies as well as the specific criterion *transferability* proposed by [Almefelt, 2005] to assess outcomes of qualitative studies will be used to assess the quality of research outcomes.

5.2.1 Proposed methodologies

The proposed methodologies of paper A, B and C will be assessed with respect to the criteria *validity* and *reliability*.

Validity

The validity of the proposed methodologies of papers A, B and C are assessed with respect to the criteria of *conceptual model validation* proposed by [Sargent, 2013] and the

completeness criteria proposed by [Buur, 1990]. The core of these criteria is to assess if the models or theories are sufficient for the question that these models or theories are set to answer. As described by answering the RQs 1, 2 and 3 the proposed methodologies were able to answer the research questions. Further, these methodologies were established guided by these RQs and hence, are judged to be able to provide an answer to these research questions sufficiently. The sufficiency is judged due to the prescriptive nature of the research questions, i.e. the questions posed aims at answering the question of *how* design can be conducted in the context of personalized medicines. Proposals for approaches of *how* design can be conducted in the context of personalized medicines are suggested.

Transferability, as suggested by [Almefelt, 2005] a criteria for valid research outcomes of qualitative studies is evaluated for the methodologies proposed. The methodologies presented in paper A and C are transferable into other contexts and are performed by simply adjusting the architecture established by the CC method [Claesson, 2006] or the EF-M tree modelling approach [Schachinger and Johannesson, 2000] to the product and the corresponding production system desired. The methodologies proposed are transferable beyond pharmaceutical products since evidence to application of the approaches to product and production system design have already been illustrated in other contexts, such as in the context of aerospace products [Levandowski *et al.* 2014, Michaelis *et al.* 2015]. Further, product architecting and product complexity has been and should be co-discussed since it is evident that the product architecture affects the complexity of the product. The complexity factor by [Pugh, 1990] is a widely used concept and a suitable approach to give an indication of product complexity, as long as discrete parts and product structural complexity is considered. The methodology of Paper B is transferable into other contexts and is performed by adjusting the product platform generating customized products according to the desired product, i.e. the same reasoning regarding transferability of product architectures into other contexts applies here as described for Paper A above, since the platform approach in paper B adopts the approach from paper A. Further, the SLCA2.0 method by [Villamil *et al.* 2018] is a general approach to life cycle assessment and hence, is straightforward to be transferred into other contexts. The usage of SLCA2.0 has already been demonstrated in the context of the aerospace industry by for example [Villamil *et al.* 2018]. Moreover, for the final value assessment, the modelling was performed by employing the concept screening matrix by [Ulrich and Eppinger, 2012]. The concept screening matrix is an established and valid method to use when comparing concepts with each other towards defined criteria. Overall the proposed methodology of Paper B is thus transferable into contexts beyond the pharmaceutical industry.

Credibility, defined by [Sargent, 2013] as the confidence the user of a model has in the model as well as the information retrieved, and the correlated concept *verification by acceptance* by [Buur, 1990], is evaluated for the proposed methodologies. The credibility of the theoretical elements of each methodology such as CC method [Claesson, 2006], E-FM tree modeling [Schachinger and Johannesson, 2000], complexity factor, SLCA2.0 [Villamil *et al.* 2018] and concept screening matrix [Ulrich and Eppinger,

2012] can be judged to pose some level of credibility due to the widespread usage of these methods in research and industrial applications [Levandowski *et al.* 2014, Michaelis *et al.* 2015, Villamil *et al.* 2018, Raudberget, 2015]. However, the criteria *verification by acceptance* as proposed by [Buur, 1990] cannot be fulfilled since these methodologies, i.e. the synthesized methodologies from the collection of theoretical elements, have not been applied or evaluated beyond the researchers conducting the study.

Reliability

The *reproducibility* criteria as described by [Creswell, 2014] and the correlated concept *consistency* as described by [Buur, 1990] will be used to evaluate the proposed methodologies. An attempt to the fulfillment of these criteria has been performed by careful documentation of each step conducted while developing the proposed methodologies. Careful documentation is an activity suggested by [Yin, 2009] to ensure the reliability of research outcomes. Further, each chosen theoretical element to be synthesized into the proposed methodologies has carefully been motivated, as well as the application of the methods has been demonstrated. However, the choice regarding the theoretical elements used in the methodologies are largely affected by the judgment of a suitable approaches made by the researchers conducting the study, and also largely biased to the tradition of the research group regarding the methods to work with. For example, the CC method [Claesson, 2006] and the EF-M tree modeling approach [Schachinger and Johannesson, 2000] were chosen as methods to describe the architectures of product and production systems which are largely employed in the research group. However, a choice of a functional modeling approach is motivated due to the ability of these approaches to keep the design solution space wide but, another researcher might have chosen another approach.

5.2.2 Illustrative case studies

The applicability of the methodologies proposed are demonstrated through illustrative case studies in the context of modularized tablet designs. The demonstrations of the applicability of the methodologies have a two-fold purpose. The first purpose is to implement the methodology into a computer and to perform simulations to study the behaviour of the methodology, even perceived as a model. The second purpose of demonstrating the applicability of the methodologies was to use these to generate knowledge about modularized tablet designs.

Validity

The *validity* of the case selection should be discussed. Modularized tablet designs have been discussed as enablers for personalized medicines [Bonhoeffer *et al.* 2018, Aleksovski *et al.* 2015, Tissen *et al.* 2011, Yeleken *et al.* 2017], and hence, performing case studies in this context is judged valid as several researchers in the field has seen the potential in this type of product design.

Resulting architectures, described by the EF-M tree modeling approach [Schachinger and Johannesson, 2000] and CC method [Claesson, 2006] of the product can be used for other pharmaceutical products. This is done by adjusting the functional requirements and the design solutions to suit the product in question, however, the structural description of the architecture is still general. This *transferability* has been analytically described in paper B for insulin medication. No application in other pharmaceutical product context has been demonstrated and shall be addressed in the future. Thus, the *credibility* of this approach cannot be verified through acceptance by experienced designers, since this was a first approach to apply these methodologies in the pharmaceutical product context. Similarly, the SLCA2.0 method [Villamil *et al.* 2018] a first application in the pharmaceutical product context and hence, need further verification to increase the credibility of using this method in the pharmaceutical context.

Reliability

The criteria *computerized model verification* as described by [Sargent, 2013], i.e. the procedure of ensuring correct implementation of the model into a computer is evaluated. A correct implementation has been tried to achieve by describing the modeling and execution procedure of throughout the research activities. However, the *credibility* of such an implementation would increase with a third-party verification according to [Sargent, 2013]. A third-party verification has not been performed.

Applying the EF-M tree modeling [Schachinger and Johannesson, 2000] and CC method [Claesson, 2006] as approaches to establish product and production system architectures poses a difficulty of the *reproducibility* of the results. If the architecture of an existing product or manufacturing equipment is modelled and the functions and means are carefully defined, no difficulty of reproducing the results should exist. Even though, the resulting EF-M tree might divert in between researchers the interfaces of the physically realized components and modules should remain the same. However, to carefully define the functions and means of a product or manufacturing equipment is in itself a difficulty because, this activity is much depending on the researchers' knowledge, experiences and preferences. Further, if new functions are to be introduced to a product or alternative means to solve the functions are considered, the reproducibility of the results appears since, likewise, the modelling of the new functions and allocation of the functions into means are much up to the researchers' preferences, previous knowledge, available literature and so forth.

The sustainability assessment of pharmaceutical products performed by SLCA2.0 method [Villamil *et al.* 2018] was applied for the first time in the context of pharmaceutical products. The application of SLCA2.0 implies a sustainability analysis which is guided by a set of questions to be answered for the product studied. Hence, the relevant questions chosen from the pre-defined set of guiding questions to assess the sustainability of pharmaceutical products, were judged by analyzing literature on sustainability studies

of pharmaceutical products as well as by the previous knowledge of a group of experts in the field of sustainable product development. Hence, the chosen guiding questions for the sustainability assessment were purely based on researchers' knowledge, experiences, preferences and the literature studied and thus, another researchers ability of reproducing the same results is uncertain. Conclusively, the reproducibility of the study becomes a difficulty and hence, the reliability of the research outcome is threatened.

In Paper B the consequence analysis of customized product designs on the pharmaceutical value chain was performed by identifying variables prone to change due to a change in product design. These variables originated from the sustainability assessment conducted but also, from additional literature on pharmaceutical value chains and change impact analysis performed when introducing new manufacturing technologies into the value chain. Hence, deducing the value chain impact from this information was relying on the logical thinking of the researchers conducting the study and hence, the reproducibility of this activity is a clear difficulty for this study and further, threatens the reliability of the research outcome.

Internal and external validity

In general, the case studies were mainly of a fictitious nature. The possibility of actually producing such modules need to be further studied, to clarify the requirements of enabling the production of such modules. Further, the ability of producing such modules need to be empirically verified. In Paper C, the case was adopted from an empirical study by [Goh *et al.* 2017] where the production of mini-tablets was demonstrated. However, the resulting quality of the modules, a module dose inside the required tolerances, produced through the studied tablet compression equipment was not discussed. Hence, the reliability of the research outcomes need further validation.

The case study of Paper A, aiming at generating knowledge about the design of the modules and the consequences of the module design on the level of customization and the manufacturing complexity, required a sample of various API modules. These modules were different regarding the design of the modules, more specifically, the size of the modules and the sample of the API modules was produced by the researchers conducting the study. An *internal validity* threat is hence identified, that is the sampling of the case data. The cases, the sample of modules, are defined with characteristics such as module diameter, dose and so forth, that predispose the outcome of the experiments conducted on this sample. The nature of the experiment was an exploration of the design space, more specifically, explore the consequence of different sized modules on the level of customization and manufacturing complexity. Further, the idea was to see the trends from a decreasing module size or combinations of different sized modules with respect to the level of customization and manufacturing complexity. Hence, the sample is considered valid to be used for this purpose and hence, a threat to internal validity is judged to be

eliminated in this case.

Likewise, sample selection can pose a threat to the *internal validity* of the research outcomes of Paper B. A population was generated to represent a treatment need and, consequently, represent the need of various product variants to be generated. For Paper B, the population was assumed to be treated in a surplus manner, i.e. a patient of the population was offered a treatment dose that was closest to the dose need of the patient, but a larger dose than needed was offered (if a product variant embedding the dose of the patient did not exist). Hence, the need of material to produce all the product variants of the population might be overestimated when calculating the material consumption of production. This overestimation becomes especially crucial for the material consumption when producing the traditional product design, since only three product variants were produced and hence, the majority of the population was assumed to receive a treatment of a higher dose than needed. The customized product design was assumed to be produced at a more accurate dose and hence, a surplus treatment is eliminated. Further studies should be conducted to clarify how a population with a traditional product concept is treated to draw more accurate conclusions.

Considering *external validity* threats, the generalization of the results beyond the experimental setting might pose a threat to validity of the research outcomes of Papers A, B and C. Results regarding the benefits of modularized tablet designs from a level of customization point of view, value perspective and production consequences might be applicable to products beyond the pharmaceutical industry as long as modularized product designs are considered. However, the findings regarding the benefits of modularized product designs, i.e. the rapid increase in product variants by introducing a few standardized modules for configurational means, draws upon the opportunity that the release rate of the pharmaceutical product is depending on the size and the shape of the product. If the consideration of release rate is applicable in other industries is evidently questionable. However, findings indication toward an increased adherence and decreased administration difficulty due to flexible size and shape of the product variants might be generalizable to the food industry for example, where similar problems of food administration could be an issue. Additional experiments in the desired context to enable a transfer of results would hence need to be conducted if knowledge were to be generated from modularized product designs in other contexts.

5.3 Thesis results contribution impact

As described in Chapter 1 this thesis should have relevance from both an academic research and industrial point of view. Hence, this section will discuss the main scientific and industrial contribution, respectively.

5.3.1 Main scientific contribution

Known theories widely used in the manufacturing industry such as SBCE and platform-based design has been demonstrated in a new context, the pharmaceutical product context. This shows the transferability of these theories and further, that these are applicable and effective in a wider context. To the pharmaceutical context, new evidence of the benefits of modularized tablet designs has been provided as enablers for personalized medicines. It has been shown that a vast increase in a number of product variants can be obtained from a few standardized components and hence, can support a shift towards a mass customization-paradigm of pharmaceutical products.

5.3.2 Main industrial contribution

A contribution has been made to the product development process of pharmaceutical products, showing upon approaches to integrated product and production system design. The methodologies proposed contributes to the support for efficient product and production system development of pharmaceutical products. This support can be applied in the context of developing personalized medicines but also, in the current mass production-paradigm. Further, an approach to integrate a full sustainability perspective to assess pharmaceutical product designs contributes to the need for developing sustainable products. The increased knowledge of modularized tablet designs as enablers for personalized medicines suggests approaches to product customization that can individualize therapy and increase value and hence, perhaps the business of the pharmaceutical industry.

CHAPTER 6

Conclusions

Conclusions of the thesis are described by analyzing the fulfilment of the thesis goals posed in Chapter 1. Finally, suggestions for future research are proposed.

6.1 Conclusions

This thesis successfully proposes approaches to integrated product and production system design in the context of pharmaceutical product customization. This is conducted by proposing methodologies with which to establish integrated product and production system designs of pharmaceutical products. Further, these methodologies adapt platform-based design to product and production system design of pharmaceutical products. The adaptation of platform-based design is performed to support a mass customization-paradigm of pharmaceutical products.

Paper A suggests an approach to establish product platforms for pharmaceutical products to ensure flexible product designs that support customization. The CC method [Claesson, 2006] is applied to establish flexible product designs. Further, Paper A suggests an initial approach to integrate production considerations of flexible product designs by employing the complexity factor by [Pugh, 1990]. Paper B illustrates an integrated approach to assess the value of customized pharmaceutical product designs by integrating a full sustainability perspective as value indicator. A sustainability assessment is performed by employing the SLCA2.0 method [Villamil *et al.* 2018] to assess the sustainability of customized pharmaceutical product designs. Further, a consequence analysis of customized products for the pharmaceutical value chain is demonstrated. Paper C suggests an approach to integrated product and production system design by establishing product and production system architectures, employing the EF-M tree model [Schachinger and Johannesson, 2000]. The EF-M tree modelling approach supports the development of flexible product designs that support customization. Further, an approach to join these architectures is proposed by applying the *producibility model* by [Landahl *et al.* 2017]. This joint architecture is developed into an integrated product and production system platform

to enable the consequence assessment of product design for production system design.

This thesis demonstrates an adaption of SBCE principles in the context of pharmaceutical products successfully. The adaption of SBCE is illustrated in Paper A by suggesting an approach to generate product families, applying the CC method [Claesson, 2006], and assessing the performance of these product families by adopting the complexity factor by [Pugh, 1990]. The adaption of SBCE principles in Paper C is illustrated by a dynamic modelling approach of integrated product and production platforms, applying the EF-M tree modelling approach [Schachinger and Johannesson, 2000] and the *producibility model* [Landahl *et al.* 2017]. The update of the established integrated product and production system platform to enable response to changing customer needs is demonstrated, hence generating sets of product and production system platform variants. Paper C further suggests an approach to assess the performance of these variants by choosing criteria to indicate the success of a variant.

This thesis has contributed to the following knowledge regarding modularized tablet designs as enablers for personalized medicines:

- By introducing a few standardized modules of different sizes, for configurational means of a product, substantial flexibility on a product level can be achieved.
- A modularized tablet design can increase product value from a social and environmental sustainability perspective.
- A modularized tablet design can be an affordable design to support pharmaceutical product customization.

6.2 Future work

Thus far, research has assumed an exploratory nature. Various methodologies have been proposed to suggest approaches to an efficient pharmaceutical product and production development process of products supporting a mass customization-paradigm. This has been performed by proposing engineering-based approaches and methods to concurrently develop product and production system platforms for pharmaceutical products. These methodologies build on assumptions that working concepts applied in the manufacturing industry, such as platform-based development and SBCE principles, will work in the pharmaceutical context and are hence worth exploring. Further studies should be conducted to look into what type of information these methodologies should generate in order to be valid tools to implement into an industrial context.

Thus far, work has been focusing on setting up system-level models to integrated product and production system platforms. These platforms have been employed by studying the consequences of changing pharmaceutical product design from a traditional fully

integral to modularized product design. The production system of these product design has been assumed to reside in the current mass production paradigm. In the future, studies focusing on production systems shall be conducted to explore the existing opportunities of current production systems in industries beyond the pharmaceutical. Additionally, production systems for pharmaceutical products supporting mass customization will be studied to clarify the requirements on these in order to enable mass customization.

The system-level simulations regarding the modularized tablet designs have thus far mainly been considering dose and size flexibility as design parameters for customized product designs. The release rate of the drug substance is an important parameter to consider for customization. Models regarding release customization are essential to be incorporated to enable predictive modelling of product design. Hence, the release rate of drugs will be considered in future work.

The illustrative case studies have focused on oral dosage forms, more specifically tablets. Future studies should consider other pharmaceutical products to ensure the applicability of the methodologies beyond the oral dosage forms. Additionally, the illustrative case studies were mainly of a fictitious nature and thus, empirical information for establishing such modularized product designs need to be gathered to further develop the models and enable better predictive simulations of product and production system design.

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Paper A

Product Architecture Management of Medicinal Products:
An Integrated Function-Means Tree Approach to Customizing Oral Dosage Forms

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Paper B

Decision Support for Re-designed Medicinal Products:
Assessing consequences of customizable product design
on the value chain from a sustainability perspective

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S.

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Paper C

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