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Modelling the cost-benefit impact of integrated product modularisation and postponement in the supply chain for pharmaceutical mass customisation

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ABSTRACT

Realisation of pharmaceutical product and production systems capable of delivering product customisation cost-effectively is essential for adding value to patients and society through improved tailoring of therapies to individuals relative to current mass-produced products. To address the continued lack of evidence-based system solutions, this study presents a holistic design framework and a novel computational platform for enabling design explorations of integrated pharmaceutical product and supply chain (SC) reconfiguration. The design and modelling framework developed herein takes an end-to-end SC perspective, adapts the mass customisation strategies of *product modularisation* and *postponement*, and demonstrates case study simulations based on real-life therapy and SC archetypes. The cost-effectiveness assessment with the derived integrated systems computational platform confirm that product modularisation drives patient benefit through variety provision and that postponement drives cost reduction in an end-to-end SC. A novel insight is therefore that both product modularisation and postponement, in an integrated manner, are required for maximising cost-effective customisation. Moreover, the computational simulations, founded and modelled on real-life scenarios, provide design requirements for reconfigurable product and SC systems in a pharmaceutical context. In all, these findings are imperative for providing guidance on integrated pharmaceutical product and production systems design and mass customisation/ mass personalisation/mass individualisation realisation.

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KEYWORDS
Design methodology; mass customisation; concurrent engineering; supply chain modelling; computational platform

1. Introduction

1.1. Background

Current pharmaceutical supply chains (SCs) and their associated products are not designed to enable the provision of enhanced variety for customisation. However, the diversity in

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patient populations, due to varying biological, behavioural, environmental, and preference-driven characteristics, necessitates a high variety of pharmaceutical products to enable tailoring to diverse patient needs and optimisation of health outcomes (Florence and Lee 2011; Govender et al. 2020c). Furthermore, the supply of such customised pharmaceutical products likely requires each product variant to be supplied at smaller volumes, corresponding to the smaller population subsets targeted during customisation. This required high variety – low volume provision of products is a major challenge for an industry whose manufacturing and supply chain is currently based on mass production (MP), that is, the use of economies of scale to supply high volumes of identical products (Govender et al. 2020c; O'Connor, Yu, and Lee 2016; Siiskonen, Folestad, and Malmqvist 2018; Srai et al. 2015; Wilson 2016). This challenge could make pharmaceutical product customisation in a typical MP paradigm too cost-intensive despite its potential value.

Mass customisation (MC) is an alternative production paradigm whose variety management strategies enable reconfiguration of products and SCs to promote variety provision in an affordable manner. MC's variety management strategies include product modularisation, process flexibility, and postponement (ElMaraghy et al. 2013, 2021; Hu 2013; Otto et al. 2016; Um et al. 2017). Product modularisation is a strategy by which both standardised modules and specialised module variants are produced to configure finished product variants (Bonvoisin et al. 2016; Gershenson, Prasad, and Zhang 2003; Hu 2013). Process flexibility involves increasing the flexibility in manufacturing or production to respond to the mix of product variants to be produced and provide a rapid response to uncertainties in demand (ElMaraghy 2005). Postponement is defined as a delayed point of product differentiation (variegation) in the SC (Hu 2013).

Govender et al. (2020c) define MC in a pharmaceutical product context as 'approaches and solutions for designing, manufacturing, and supplying pharmaceuticals ideal for affordable, customised therapy'. The first major challenge this leads to is that, despite the general adoption of MC and its variety management strategies outside of pharma, its adaption to pharma manufacturing and supply (i.e. production) is greatly unexplored (Govender et al. 2020c). The second major challenge is that, due to the complexity and criticality of pharmaceutical SCs, it is not possible to reconfigure SC designs or product designs by experimentation without posing a substantial risk to medicines access for patients and society. Yet, it is crucial to understand the cost–benefit trade-offs in adapting MC to pharma to determine if the theoretical benefits of MC could be feasible in practice. This makes modelling the cost–benefit impact of integrated product modularisation and postponement for pharmaceutical MC a key requirement for progressing towards the realisation of affordable customisation in pharma.

In response to the aforementioned challenges, this paper has two consecutive aims. First, it aims to propose a holistic design and modelling framework for integrating product and production system concepts for customised pharmaceutical products from an end-to-end SC perspective (i.e. considering a systems perspective for the integrated chain from drug substance materials through to the provision of the final dosage form to retailers and, ultimately, patients). Second, it aims to adapt the proposed framework into a computational platform to explore the impact of the degrees of product modularisation and postponement on pharmaceutical product customisation cost-effectiveness. Here cost-effectiveness denotes a favourable cost–benefit ratio. To perform the adaption of the framework into a computational model, case studies of two real-life therapy archetypes were selected.

To the best of the authors' knowledge, this will be the first cost model in a pharmaceutical MC context incorporating the SC from an end-to-end perspective, which integrates both pharmaceutical product modularisation and postponement into its estimates.

The remaining sections of the paper are structured as follows: related studies (Section 2), design and modelling framework (Section 3), computational adaptation of the framework and case study simulation results (Section 4), discussion (Section 5), and conclusions and recommended future research directions (Section 6).

1.2. Research scope

The MC variety management strategies, *product modularisation* and *postponement,* are in focus in this study, with *process flexibility* remaining out of scope. To enable high-level modelling and simulation of the impact of customisation on cost-effectiveness, a simplified pharmaceutical SC comprising the secondary manufacturer, wholesaler, pharmacy, and patient is considered. Pharmaceutical manufacturing, i.e. from raw materials until the point when the drug product has been produced (for example powders compressed into a tablet) and packaged, comprises both primary manufacturing and secondary manufacturing. Primary manufacturing generates the drug substance. During the secondary manufacturer's operations, this drug substance is then formulated with excipients to generate final dosage forms, for example, tablets. The primary manufacturer is beyond the scope of this study since modular product design involves a transformation in the design of the dosage form, not the drug substance, i.e. the secondary manufacturer's operations. In addition, alternative SC configurations with additional health system stakeholders, such as hospitals, nursing homes, regulators, and so forth, are excluded. Since this study is limited to the physical journey of the pharmaceutical product, as a finished dosage form, throughout the SC, the physician (who prescribes medicines that are not over-the-counter) is also not further addressed. The role of the distributor is not separately addressed in this paper. Pharmaceutical distributors currently serve as intermediaries that bridge the gap between manufacturers and end-users, ensuring that the integrity and availability of pharmaceutical products to retailers, providers, and ultimately patients, is secured. Their role embodies several functions, including but not limited to product sourcing, inventory management, logistics and transportation, regulatory compliance, and ensuring supply chain efficiency. Although the role of the distributor is important, it is currently evolving within an MP paradigm for pharmaceuticals (Roscoe and Blome 2016; Srai et al. 2016). Likewise, the role of the distributor in an MC context is expected to evolve (to potentially include final product assembly, for example), therefore, this future role, not yet defined, is beyond the scope of this paper.

Specific costs incurred in international SCs are also beyond the scope of this paper. In addition, production typically refers to both manufacturing and supply. Pharmaceutical manufacturing and supply can be for two purposes, commercial and clinical. This study concerns the manufacturing and supply of commercial pharmaceutical products. Finally, in a pharmaceutical context, product variety may arise from several sources, such as packaging and labelling, however, in this study, product variety refers only to the dosage form itself, exemplified by solid oral dosage forms (SODFs, see details in 2.2).

2. Related studies

This section describes the essential literature on which this study is founded and the concepts therein. Based on this body of literature, the key research gaps, which will be addressed in this study, are summarised.

2.1. Pharmaceutical MC

Within the field of personalised medicine, it is accepted that product customisation is necessary to improve the alignment of the pharmaceutical product offering to individual patient needs to achieve optimal health outcomes in terms of safety, effectiveness, and convenience for each patient (Ahmed et al. 2016; Crommelin, Storm, and Luijten 2011; Govender et al. 2020c). However, the extent of diversity in patient populations, originating from biological, behavioural, environmental, and preference-driven influences, means that current mass-produced pharmaceutical products are not available in sufficient variety to enable customisation of treatment to the needs of each patient (Govender et al. 2020c). Alternative production paradigms, like MC, offer opportunities to mitigate this challenge. Several variety management strategies, specifically product modularisation (Bonvoisin et al. 2016; Gershenson, Prasad, and Zhang 2003), process flexibility, and postponement (ElMaraghy et al. 2013, 2021; Pil and Holweg 2004; Scavarda et al. 2010), as defined in Section 1, are widely discussed as enablers for MC, which aims to provide individual customers with customised products at near MP efficiencies (Tseng and Jiao 2001). However, these strategies remain underexplored in pharma (Govender et al. 2020c; Siiskonen, Malmqvist, and Folestad 2021). Consequently, the requirement of affordable pharmaceutical product variety provision for optimising individual health outcomes remains largely unfulfilled.

2.2. Challenges faced by the current pharmaceutical production paradigm in providing product variety

The most frequently produced pharmaceutical products (dosage forms) are SODFs, for example, tablets and capsules (Nagashree 2015; Plumb 2005). Typically, the most common design of a SODF can be characterised as an integral product design, such as a tablet, with low flexibility for adaption to product design requirements complying with individual patient needs (Siiskonen, Malmqvist, and Folestad 2021).

Modular products, for example, pellets, minitablets, multilayer tablets, and other compartmentalised product designs, exist in pharma (Aleksovski et al. 2015; Demiri et al. 2018; Goh, Heng, and Liew 2017; Melocchi et al. 2020; Rahmani et al. 2013; Wang et al. 2020). However, such modular pharmaceutical products are primarily designed for the purpose of increasing processing flexibility, not for enhancing product variety. Product modularisation applied to enhance product variety has been explored only in a few recent academic publications, which also consider cost-effectiveness (Govender et al. 2020b, 2020c; Siiskonen, Folestad, and Malmqvist 2018; Siiskonen, Malmqvist, and Folestad 2021). These studies integrated product design requirements, originating from individual patient needs, into modular product architectures. Furthermore, strategies to introduce flexibility into these product designs were proposed. Govender et al. (2020a) and Govender et al. (2020b) demonstrated

the manufacturing of components for pharmaceutical product modularisation with predictable performance of individual modules and a sufficient degree of modularity to allow a high variety of finished products to be generated from relatively few module variants. These experiments demonstrated the manufacturing of parts for dose strength variety and drug release variety.

Customised patient packs and pharmaceutical compounding represent two scenarios of postponement, which involve repackaging or physical manipulation, respectively, of mass-produced pharmaceuticals to achieve customisation to individual patient needs for limited numbers of patients (Govender et al. 2020c; Wilson 2016). Outside of these limited examples of postponement in practice, few academic studies on postponement as a strategy to decrease complexity in the pharma SC can be found. Ladsaongikar and Martinez (2016) applied postponement to reduce the increase in product variety that country-specific government regulations and language specifications induce on pharmaceutical product packaging. However, they do not consider the entire SC from an end-to-end perspective. Verhasselt and Friemann (2012) studied the applicability and profitability of postponement in the pharma industry, studying variants of packaging postponement. This study was also limited to the operation as traditionally performed by the secondary manufacturer and excluded the consideration of an end-to-end SC where the wholesaler, pharmacy, and patient are included. In contrast, Siiskonen et al. (2021) performed a qualitative assessment of end-to-end SC performance, presented reconfigured SC designs for cost-effective manufacturing and supply of customised pharmaceutical products, and concluded that postponement can increase the overall cost-effectiveness of the SC.

Within pharma, the current standard of production (including SODF production) is MP, which uses economies of scale to supply high volumes of product offerings characterised by low variety. This typically translates into the manufacturing and supply of four to six dose strengths in a single product offering and exceeding this number is deemed cost-ineffective (Wilson 2016). Whilst this challenge in providing enhanced variety is largely due to economies of scale, it is also due to other factors such as low equipment utilisation rates in secondary manufacturing, which specifically concerns the series of unit operations resulting in the dosage form, with change-over times typically 2–3 times the fabrication time of a product (Wilson 2016), meaning that equipment utilisation is about 25-33%. Effective equipment utilisation for batch production is defined by Vervaet and Remon (2005) as 30% for standard processes, 74% for good processes, and 92% for 'best-in-class' processes. These figures for equipment utilisation agree well with the generally low asset utilisation reported for pharmaceutical industries (Bai et al. 2022). Siiskonen, Malmqvist, and Folestad (2020) and Siiskonen et al. (2021) studied the manufacturing and supply of customised pharmaceutical products when operating the production platforms in their current MP paradigm and confirmed that these platforms cannot achieve cost-effectiveness in a customisation context, due to the high product variety – low volume challenge emerging as a consequence of customisation. Overall, the current pharmaceutical SC is not intended or designed for MC (Govender et al. 2020c; Srai et al. 2015; Wilson 2016).

2.3. Pharmaceutical SC design

Within the SC scope defined in Section 1.2., the main stakeholders for commercial supply of pharmaceutical products are typically the primary manufacturer, secondary manufacturer,

wholesaler, pharmacy (retailer), and patient (Aitken 2016; Olson n.d.; Shah 2004; Savage, Roberts, and Wang 2006). The main responsibility of the secondary manufacturer is to transform raw materials and/or intermediates into finished pharmaceutical products such as tablets, capsules, and so forth, which are packaged and supplied to the wholesaler in bulk (Savage, Roberts, and Wang 2006; Shah 2004). The wholesaler purchases packaged finished products in bulk, bundles them, and sells them to retailers, such as pharmacies, according to their orders (Derecque-Pois 2010; Shah 2004). The wholesaler function can be described as keeping inventory since the main activities are to store pharmaceutical products prior to further distribution (Derecque-Pois 2010). The pharmacy, as a retailer, either supplies finished pharmaceutical products or compounded pharmaceutical products to patients according to their prescriptions or over-the-counter (Aitken 2016; European Alliance for Access to Safe Medicines n.d.; Olson n.d.). Upon receipt of the finished pharmaceutical product, further manipulation of the product by the patient, e.g. splitting tablets, may occur prior to administration (Govender et al. 2020c; Verrue et al. 2011). These strictly defined scopes of responsibility of each stakeholder result in pharmaceutical SCs being designed as a linear series of interconnected entities for the flow of material and information from manufacturers to patients, with limited opportunities for interchangeable and/or expanded stakeholder roles within current SC designs.

2.4. MC for enhanced product variety in non-pharma SCs

Kim and Lee (2023) recently presented an elaborate literature review on MC research, which confirms the lack of MC research in a pharma context. Even outside of pharma, the MC literature is mainly focused on operations management and business and marketing strategies, scarcely addressing design aspects in MC. Another notable recent publication by Andersen, Ditlev Brunoe, and Nielsen (2023) presented a holistic systematic literature review of platform-based product development strategies to increase product variety in process industries, which verifies emerging research applying MC strategies such as product modularisation and postponement. They further confirm that such MC strategies still exist in an immature state, with a lack of industrial implementation and validation of successful business results. They importantly highlight that most attention has been directed toward the product and less so toward manufacturing and SC issues in production environments seeking increased product variety.

The value of MC in pharma is primarily to enhance value for patients and society at large, which could result in increased sales as a consequence. In contrast, in non-pharmaceutical manufacturing industries, increased product variety to enable customisation is primarily justified by increased sales opportunities. However, the impact of increased product variety on both manufacturing and SC cannot be ignored (Yang and Burns 2003). Not only should internal operations be responsive to product variety, but SC partners also need to be aligned to changes in product variety. In general, a trade-off exists between product variety and SC performance (Barroso and Giarratana 2013; Syam and Bhatnagar 2015; Thonemann and Bradley 2002). The SC performance suffers from the increased costs of production due to an increased production complexity arising from enhanced product variety (ElMaraghy et al. 2013, 2021; Lyons, Um, and Sharifi 2020; Randall and Ulrich 2001). Lyons, Um, and Sharifi (2020) state that a key consideration is the optimal level of product variety to offer, which requires an assessment of the relationship between the increased benefits and costs.

2.5. Modelling and simulation in pharma SC

The pharmaceutical SC modelling and simulation literature focuses on cost optimisation and matching demand with supply (Carlos and Edgar 2017). Fatemi et al. (2022) illustrated an approach to pharmaceutical SC modelling, which aimed to minimise total cost, unfulfilled demand, and congestion. Gargari et al. (2021) presented a multi-objective optimisation problem to select suppliers and distributors in a healthcare SC. Sarkis et al. (2021) discussed mathematical models to support decision-making in the development, manufacturing, and distribution of new product classes such as advanced therapeutics and new-generation manufacturing processes for viral vector-based and RNA-based vaccines. The study by Sarkis et al. (2021) displays a worthwhile example of how a systems approach to modelling can support the management of complex systems with often conflicting objectives such as growing demand, technology scalability, complexity in process and supply, and costs. Abbassi et al. (2021) presented a study for optimising the distribution cost and time in a healthcare SC by using techniques such as swarm optimisation and genetic algorithms. This study, however, did not consider pharmaceutical products but rather non-medical products. It should be noted that pharmaceutical SC modelling and simulation literature is predominantly presented in an MP context and a review by Settanni, Harrington, and Srai (2017) pointed out that, although the need for product customisation challenges traditional pharmaceutical SCs, existing approaches to pharmaceutical SC modelling do not address the challenges or implications of operating pharmaceutical SCs in a customisation context.

2.6. Cost models in pharma SCs

Cost models of pharma SCs do exist but, in most cases, these involve direct costing with already known or easily obtainable costs under an MP paradigm (Krautmann et al. 2020). In traditional pharma SCs, operating in an MP paradigm, the overall costs which contribute to current medicine pricing originate from SC stakeholders in the health system. Each of these costs contributes to final medicines pricing, with price components accumulating along the SC from manufacturers to end-users. These components include the manufacturer's selling and landed price, the wholesale selling price, the retail price, and the dispensed price (WHO 2008). These prices are due to costs incurred from insurance, freight, banking fees, inspection charges, local transport, overhead costs incurred during storage and handling, tax, customs, and port fees for international SCs, and mark-ups (WHO 2008).

2.7. Identified research gaps

The literature review confirms the continued major gap regarding the lack of product and production approaches for affordable pharma customisation, recently addressed by Govender et al. (2020c). As pharmaceutical product customisation induces an increase in the product variety to be designed, manufactured, and supplied, it is pivotal to devise cost-effective approaches to product and production design. The following specific gaps were identified as areas deserving special attention in our study:

- Approaches to **integrated design and modelling** of the pharmaceutical product and production system, from an end-to-end SC perspective, in a pharmaceutical customisation context;

- Suitable **cost models** describing the production cost of the pharmaceutical SC, which can enable the management of **increased product variety**;
- An assessment of the **total value of pharmaceutical MC** with an end-to-end SC perspective.

More specifically, in response to these gaps, this study advances existing knowledge by presenting an integrated design and modelling approach, which incorporates the mass customisation strategies of both product modularisation and postponement, in contrast with previous studies, which have instead addressed these strategies in isolation (Siiskonen et al. 2021; Siiskonen, Folestad, and Malmqvist 2018; Siiskonen, Malmqvist, and Folestad 2021). In addition, the cost modelling and subsequent value assessment of a pharmaceutical SC from an end-to-end perspective in an MC context, advances knowledge compared to previous studies, which have limited such cost modelling to the assembly process (Siiskonen, Malmqvist, and Folestad 2021), to a single operation in the manufacturing process (Siiskonen, Malmqvist, and Folestad 2020), or to solely consider the production system (Siiskonen et al. 2021).

3. A framework for design and modelling of integrated product and production system concepts

Figure 1 illustrates a novel framework, which was built to address the gap in approaches to the design and modelling of integrated product and productions systems from an end-to-end SC perspective in a pharmaceutical MC context (see Section 2.7). Figure 1 encompasses three system domains, in red boxes, (therapy domain, design domain, and evaluative domain) involved in product and production system design adaption into a pharmaceutical context. Each system domain contains activities, which generated intermediate outputs. These intermediate outputs, i.e. target values for patient benefit metrics, product portfolio

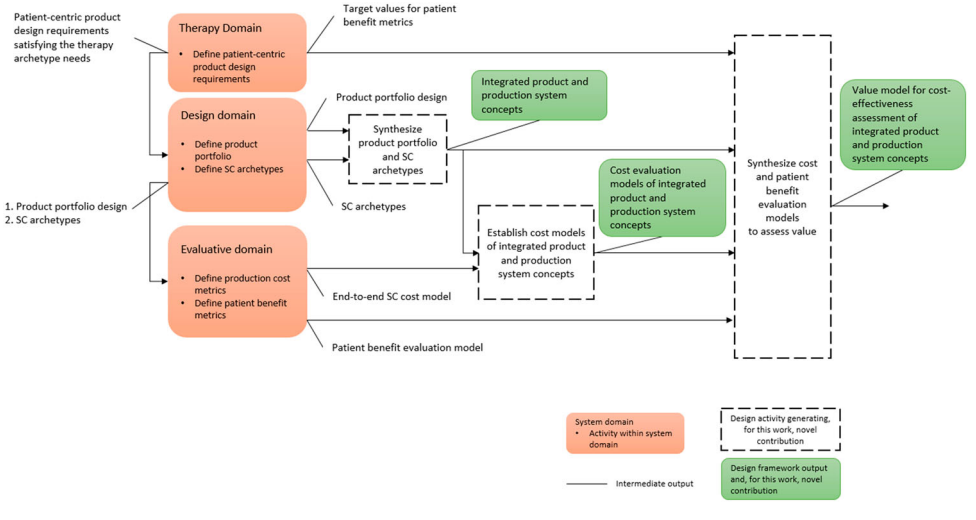


Figure 1. Framework for design and modelling of integrated pharmaceutical product and production system concepts for customisation.

design, SC archetypes, end-to-end SC model, and patient benefit evaluation model, served as inputs to subsequent design activities (depicted in the boxes with dashed frames), for further processing (synthesise product portfolio and SC archetypes, establish cost models of integrated product and production system concepts, and synthesise cost and patient benefit evaluation models to assess concept value). These design activities finally generated three outputs as novel contributions of this work (in green boxes), corresponding to the three major research gaps identified and described in Section 2.7, namely, integrated product and production system concepts, cost evaluation models for these integrated concepts, and finally, a value model for the concepts' cost-effectiveness assessment.

The following sections describe the activities within each system domain and their resulting intermediate outputs. The final outputs of this design framework (in green boxes) along with the activities generating these (boxes with dashed frames) are presented in Section 4.1.

3.1. Therapy domain

3.1.1. Define patient-centric product design requirements

The existing pharmaceutical therapy space is extensive, comprising a wide range of pharmacological agents (drugs or drug classes). These pharmacological agents can be delivered via various routes of administration to their target sites in the human body. Therapies delivered via the oral route of administration, as SODFs, represent a subset of this wider pharmaceutical therapy space and the scope of this work. Since this SODF therapy space encompasses innumerable real-world examples, we have designated therapy archetypes to represent and classify real-world examples within this continuous range. Although several discrete therapy archetypes can exist, two therapy archetypes were selected in this study at the extremes of the SODF therapy space to parameterise the SODF therapy space for modelling. The two therapy archetypes were based on whether the medication a patient takes during a treatment course remains unchanged or not with time (European Commission 2009; U.S. Food and Drug Administration 2010), which has differing implications for the required product variety and is therefore denoted fixed therapy (archetype 1) versus dynamic therapy (archetype 2). To execute the computational model, a specific example within each therapy archetype was selected and is further described in Section 4.2.

By representing patient needs for an increased number of product variants, the therapy archetypes have a dual purpose of defining the product portfolio with patient-centric product design requirements that satisfy the therapy archetype needs in the design domain and facilitating the cost-effectiveness assessment with target values for patient benefit metrics to assess value, see Figure 1.

3.2. Design domain

3.2.1. Define product portfolio

Defining the product portfolio included both the design of the customised pharmaceutical products as well as the conventional pharmaceutical product as a reference. For product design of the customised pharmaceutical products, the previously proposed patient-centric design requirements for individualised therapy, such as a scalable dose strength and flexible target release profile were selected (Govender et al. 2020c). Achieving such product

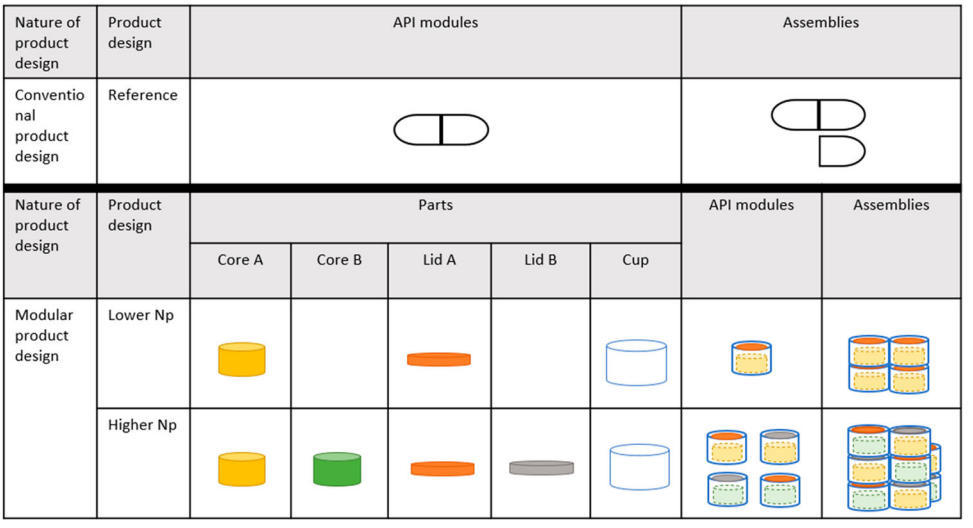


Figure 2. Parts, API modules and assemblies illustrated for reference design (conventional product design) as well as lower Np and higher Np designs (modular product designs).

designs, product modularisation was adopted as a design strategy to enable reconfiguration of these design requirements and was introduced in our earlier work (Govender et al. 2020c; Siiskonen, Malmqvist, and Folestad 2021). This study adopts the modular product designs by Govender et al. (2020b) and Siiskonen, Malmqvist, and Folestad (2021), which were based on three types of parts: API (active pharmaceutical ingredient)-containing cores, lids, and cups (Figure 2). These parts were designed to deliver the product design requirements, i.e. the API core delivers the dose strength and the lids and cups provide the target release profiles.

Figure 2 illustrates the components (i.e. parts, API modules, and assemblies) for both the conventional, and modular product designs with two degrees of modularisation, lower and higher Np (number of parts). The degree of modularisation refers to the number of API modules in the finished product configuration (assemblies), not the number of parts in the API module. The conventional (reference) product design is produced as an integral product categorised here as an API module, more specifically a tablet from which finished products (assemblies) are configured, for example, by combining whole and half tablets into the desired dose strengths.

Modular product design was adopted as a design strategy for the cost-efficient configuration of product variants by introducing reusable standardised components for the product variants throughout the portfolio in combination with reusable variant components for the creation of product variants through reconfiguration. For example, as seen in Figure 2, two variant parts delivering the dose of the product, i.e. the cores, have been introduced for portfolio design. By scalability of the number of cores as well as by different configurations of these two core variants, derivative product variants with respect to dose, although two reusable variant parts are used, can be established. For a more comprehensive discussion on using product modularisation as a strategy for pharmaceutical product design the reader is referred to our earlier work (Siiskonen, Folestad, and Malmqvist 2018;

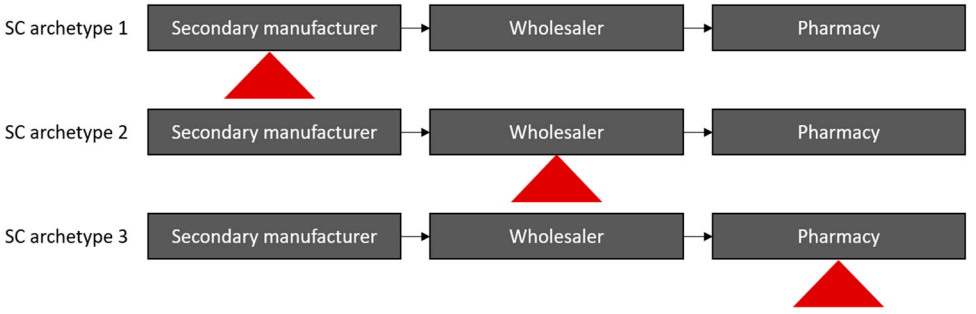


Figure 3. SC archetypes posing different levels of postponement. The red triangle marks the position for the point of variegation.

Siiskonen, Malmqvist, and Folestad 2021). Furthermore, previous studies have shown that independent control over two product features, dose strength and drug release kinetics, can be achieved by discrete parts, i.e. cores and lids, respectively, that can be flexibly reconfigured (Govender et al. 2020b, 2020c), justifying the selection of these discrete parts for product variant configuration.

The different cores and lids have different properties, i.e. dose strength and release properties, respectively. The assemblies illustrated in Figure 2 are not an exhaustive set. Numerous configurations are theoretically possible. Based on the design strategy used in this study, a product portfolio is defined as a set of product variants generated from predetermined parts. The reference design, the lower Np design, and the higher Np design each generate one portfolio. These product portfolios serve as an input into the synthesise product portfolio and SC archetypes activity in Figure 1.

3.2.2. Define SC archetypes

This section considers the SC archetype design using postponement as a strategy. Siiskonen et al. (2021) developed reconfigured pharmaceutical SC designs applying the MC principle of *postponement* to support cost-effective manufacturing and supply of customised pharmaceutical products. Postponing the *point of variegation*, i.e. the position of final assembly in the SC, where product parts become dedicated to a specific product variant, was intended to decrease the product portfolio complexity to be managed throughout the SC. This formed the basis for the three SC archetypes exemplified in this work, presented in Figure 3. The *point of variegation* was placed at the secondary manufacturer, wholesaler, and pharmacy for SC archetypes 1, 2, and 3, respectively, representing various degrees of postponement. Similar to the product portfolio input, these SC archetypes served as intermediate inputs into the synthesise product portfolio and SC archetypes activities in Figure 1.

3.3. Evaluative domain

3.3.1. Define production cost metrics

In this study, the production cost was divided into two categories: the cost of the product variety managed throughout the SC and the final assembly cost, i.e. the cost of assembling

the finished product variant. The production cost was therefore assessed for each SC stakeholder. To assess the final assembly cost of the reference design, the same model for final assembly cost was used as for modular product designs, even though the technical process of assembly may differ. These metrics established models to assess the cost of end-to-end SCs, see Figure 1.

The production time by the secondary manufacturer was used to describe the production cost of the secondary manufacturer. According to Wilson (2016), the production time for the secondary manufacturer is two- or three-fold the fabrication time of the product itself, due to changeovers. Thus, the findings from Wilson (2016) was adapted as a proxy for the production cost of the secondary manufacturer, $C_{Sec,PD}$, in Equation 1. Equation 1 comprises two terms to represent both the fabrication time and change-over time. In Equation 1, $Nt_{comp,PD}$ is the number of components, *comp*, produced for the product design, *PD*, and serves as a proxy for the fabrication time. For modular product designs, the number of components produced corresponds to parts whereas for the conventional product design the number of components produced corresponds to API modules, see Figure 2.

$$C_{Sec,PD} \sim Nt_{comp,PD} + 3 \times Nt_{comp,PD} \tag{1}$$

The wholesaler operation can be associated with keeping inventory. Benjaafar, Joon-Seok, and Vishwanadham (2004) showed that a linear relationship is expected between the inventory cost and the number of product variants, thus, this relationship was adopted in this study to describe the production cost of the wholesaler, *WS*. The pharmacy is an example of a retailer, *Ret*, and Thonemann and Bradley (2002) describe retailer cost as being concavely increasing at a rate that is asymptotically linear rather than increasing proportionally to the square root of product variety, which is more common in risk-pooling literature for perfectly flexible manufacturing processes. In this study, for simplicity, the relationship between production cost and product variety for the pharmacy was assumed to be linear, similar to the wholesaler cost. This linear relationship is a conservative estimate, which compared to using the square root will over-estimate the production cost. Hence, the costs of product variety management for the wholesaler, $C_{WS_{mod,PD}}$, and the pharmacy, $C_{Ret_{mod,PD}}$, were estimated through Equation 2.

$$C_{WS_{mod,PD}} = C_{Ret_{mod,PD}} \sim Nt_{mod,PD} \tag{2}$$

In Equation 2, $Nt_{mod,PD}$ is the number of API modules, *mod*, managed by the stakeholder. If the product has been assembled, $Nt_{mod,PD}$ is replaced by $Nt_{assm,PD}$ in Equation 2 giving Equation 3. Equation 3 is thus used as a proxy for product variety management cost of the assemblies, *assm*, managed by the SC stakeholders in their operation.

$$C_{WS_{assm,PD}} = C_{Ret_{assm,PD}} \sim Nt_{assm,PD} \tag{3}$$

The two types of assembly considered in this study were pre-assembly and final assembly. Models suggested in previous work by Siiskonen, Malmqvist, and Folestad (2021) were applied in this study to evaluate the cost of assembling modular product designs based on the complexity factor by Pugh (1990). The pre-assembly, *pre*, cost, $Ca_{pre,PD}$, or final assembly, *fin*, cost, $Ca_{fin,PD}$, were estimated through Equations 4 and 5, respectively.

$$Ca_{pre,PD} \sim \sqrt[3]{Np_{parts,PD} Ni_{parts,PD} Nt_{parts,PD}} \tag{4}$$

$$Ca_{fin,PD} \sim \sqrt[3]{Np_{mod,PD} Ni_{mod,PD} Nt_{mod,PD}} \tag{5}$$

In Equations 4 and 5, $Np_{parts,PD}$ is the number of parts, *parts*, in a module for pre-assembly costs and $Np_{mod,PD}$ is the number of modules in an assembly for final assembly costs. Furthermore, $Ni_{parts,PD}$ and $Ni_{mod,PD}$ are the number of interfaces between the parts in a module or modules in an assembly, respectively, and $Nt_{parts,PD}$ and $Nt_{mod,PD}$ are the number of types of parts in the module or the number of types of modules in an assembly, respectively. Since each product portfolio generates a set of finished product variants, $Ca_{fin,PD}$ is given as a weighted average of each product variant within a product portfolio generated by the product design *PD*.

A comprehensive explanation of the selection of the assembly cost model, the simplifications made, and the calculations of the weighted averages are provided by Siiskonen, Malmqvist, and Folestad (2021).

3.3.2. Define patient benefit metrics

In this activity, a model to assess patient benefit was established to serve as an intermediate input to the activity synthesise cost and patient benefit evaluation models to assess value, see Figure 1. Siiskonen, Malmqvist, and Folestad (2021) proposed metrics to assess the patient benefit of pharmaceutical product designs in a customisation context and these metrics were, in this study, applied for dose strength scalability and target release profile flexibility.

The model in Equation 6 assesses the benefit, $B_{dose,PD}$, from scaling the dose strength (*dose*) for a product portfolio. This equation was adopted from previous work by Siiskonen, Malmqvist, and Folestad (2021) and estimates how closely matched the product variant available to a patient is to their required dose.

$$B_{dose,PD} = \frac{1}{Population} \sum_{m=1}^{n} \frac{|Dose_{rec,m,PD} - Dose_{optimal,m}|}{Dose_{optimal,m}} \tag{6}$$

In Equation 6, $Dose_{rec,m,PD}$, is the dose received, *rec*, by the patient, *m,* and is dependent on the product portfolio that the product design *PD* can generate. $Dose_{optimal,m}$ is the optimal dose, *optimal*, for the patient and *Population* is the size of the patient population.

Product variety is commonly used as a proxy for the level of customisation achievable (Um et al. 2017). Previous work by Siiskonen, Malmqvist, and Folestad (2021) used this approach by Um et al. (2017) to model target release profile (*release)* flexibility, where the benefit of a treatment, $B_{release,PD}$, was given by the number of release profiles a patient can select from, given a fixed dose strength. In this study, to assess target release profile flexibility, the model by Siiskonen, Malmqvist, and Folestad (2021) has been adopted in this study, Equation 7.

$$B_{release,PD} = \sum_{segment=1}^{k} x_{segment} \times ReleaseVariants_{segment,PD} \tag{7}$$

In Equation 7, $ReleaseVariants_{segment,PD}$ is the number of release variants a patient can choose from given a fixed dose strength, which is dependent on the product design *PD* (i.e. the number of product variants per dose strength that a product portfolio can offer)

and $x_{segment}$ describes the ratio of the patients requiring that dose strength. A weighted average value for $B_{release,PD}$ for each product design, *PD*, was established.

For further descriptions of the benefit metrics and the approach to patient segmentation, the reader is referred to Siiskonen, Malmqvist, and Folestad (2021).

4. Results

In this section, the design outputs from Figure 1 are presented, together with the case study designed to facilitate computational modelling and subsequent simulation results.

4.1. Design output

4.1.1. Integrated product and production system concepts

Figures 4 and 5 together display nine designs of integrated product and production system concepts. R-SC1, R-SC2, and R-SC3 are reference designs for the conventional pharmaceutical product at three degrees of postponement. L-SC1, L-SC2, and L-SC3 and H-SC1, H-SC2, and H-SC3 are customised pharmaceutical product designs with lower (L) and higher (H) degrees of modularity, respectively, at three degrees of postponement. The management of increased product variety, to create the customised product portfolio, commences at whichever stakeholder performs the final assembly step and continues downstream in the SC. For simplicity, Figure 4 shows the evolution of the product variety achievable for the reference product design when starting with a single dose strength. In reality, several dose strengths of a therapy would be produced. For the reference design, API modules (tablets) are transformed into assembled (finished) product variants in the final assembly process, which involves, for example, splitting tablets or combining whole tablets and/or split tablets into dose variants. The term *API module* was introduced in Figure 2 since these are transformed in the final assembly process to the customised finished product variants.

Figure 5 illustrates that, for the modular product designs, parts are transformed into API modules in a pre-assembly process. API modules are then transformed into assembled (finished) product variants in the final assembly process. Pre-assembly and final assembly can be performed by the same stakeholder, e.g. the secondary manufacturer in L-SC1 and H-SC1 or by different stakeholders (see L-SC2, L-SC3, H-SC2, and H-SC3). The rationale for separating the stakeholders performing the pre-assembly and final assembly is the decreased number of variants to be managed by downstream stakeholders after pre-assembly. For example, for lower Np designs, i.e. L-SC2 and L-SC3, the product variety to be managed downstream from the secondary manufacturer up to the point of final assembly was a single API module instead of three parts, which would have been the case if the pre-assembly was not performed by the secondary manufacturer.

4.1.2. Cost evaluation models of integrated product and production system concepts

The end-to-end SC cost models synthesised with the integrated product and production system concepts generated cost evaluation models for each SC archetype, i.e. SC1, SC2, and SC3. These models are displayed in Table 1.

The cost of the secondary manufacturer, $C_{Sec,PD}$, as well as the pre-assembly, $Ca_{Pre,PD}$, and final assembly costs, $Ca_{final,PD}$, were assumed to be unaffected by the SC archetype or the

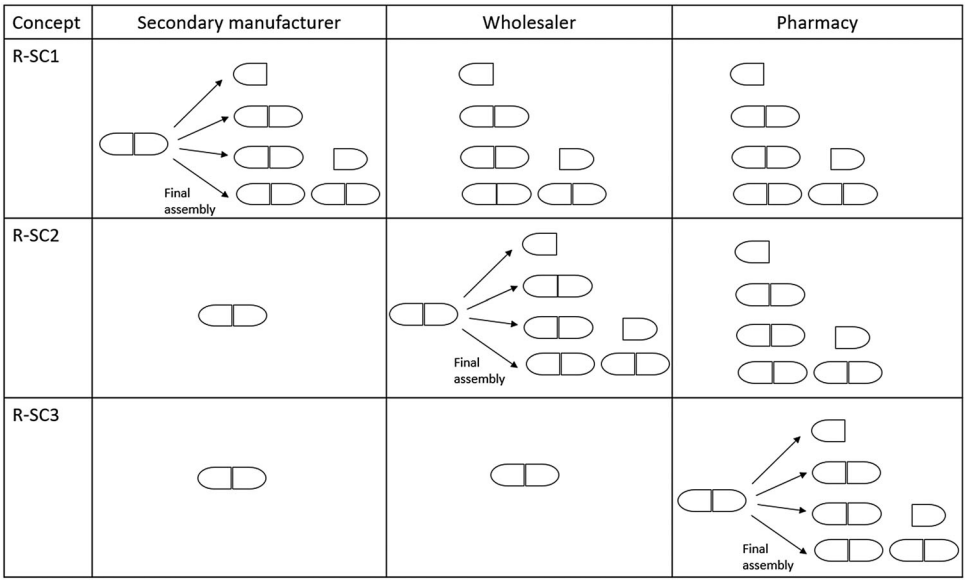


Figure 4. Conceptual illustration of the product variety for reference case for each SC stakeholder for each SC archetype.

Figure 5. The nature of product variety conceptually illustrated for modular product designs for each SC stakeholder for SC archetype.

position of the assembly. The *point of variegation* within each SC archetype is illustrated in Figures 4 and 5.

The product variety management cost of the wholesaler and pharmacy depends on the *point of variegation* as this denotes if the stakeholder is managing modules or assemblies.

Table 1. Cost models of SC stakeholders for respective SC archetype.

SC arch.	Sec. manufacturer	Wholesaler	Pharmacy	Pre assembly	Final assembly
SC1	$C_{sec,PD}$	$C_{WS_{assm}PD}$	$C_{Ret_{assm}PD}$	$Ca_{pre,PD}$	$Ca_{fin,PD}$
SC2	$C_{sec,PD}$	$\frac{C_{WS_{mod}PD} + C_{WS_{assm}PD}}{2}$	$C_{Ret_{assm}PD}$	$Ca_{pre,PD}$	$Ca_{fin,PD}$
SC3	$C_{sec,PD}$	$C_{WS_{mod}PD}$	$\frac{C_{Ret_{mod}PD} + C_{Ret_{assm}PD}}{2}$	$Ca_{pre,PD}$	$Ca_{fin,PD}$

The stakeholder cost for SC2 and SC3 was calculated as an average of the cost of managing modules and the cost of managing assemblies. The incorporation of both types of product variety when estimating the stakeholders' production costs was suggested to clarify that the stakeholder performing the assembly process needs to manage both modules and assemblies, pre- and post-final assembly.

4.1.3. Value model for cost-effectiveness assessment of integrated product and production system concepts

Siiskonen, Malmqvist, and Folestad (2021) presented a first adaption of the concept scoring approach by Ulrich et al. (2020) for value modelling in a pharma context, using weighted sums of the cost and benefit metrics, which was then implemented here. Equation 8 presents the calculation of value, V, from two terms: the benefit metrics (first term) and cost metrics (second term).

The therapy domain provided the target values for patient benefit metrics, namely the dose strength need of each patient. The integrated product and production system concepts provided product portfolio definitions, i.e. the dose strength and the number of variants of each dose strength that the product portfolio could generate. These inputs were needed to assess $B_{dose,PD}$ (Equation 6) and $B_{release,PD}$ (Equation 7), which were required to calculate the benefit term in Equation 8.

$$V = w_{benefit}\frac{\sum norm.benefit}{i} + w_{cost}\frac{\sum norm.cost}{j} \tag{8}$$

The cost term of the value model was based on the cost evaluation models for integrated product and production system concepts, Table 1. The number of variants of each dose strength that the product portfolio can generate was also required as this defines the components (parts, API modules, and assemblies) that need to be manufactured and supplied throughout the SC.

The cost and benefit metrics were, however, in their respective units, which are not directly comparable. Consequently, each metric was normalised through their respective scale to generate scores from 1 to 5. These scales have been built based on the resulting performance of each integrated product and production system concept on the respective cost model and benefit metric. The scales were created based on the best and worst performing concepts and, in between, a linear relationship has been created from 1 to 5, where the concept performing the worst was scored 1 and the concept performing the best was scored 5. This linearity of the scales was selected due to the linear relationship of the cost models of product variety management, Equations 2 and 3. The remaining concepts were

assigned scores according to the scale depending on their performance on the respective benefit metric and cost model.

The benefit term of Equation 8 consists of the sum of the normalised scores for the benefit-metrics, $\sum norm.benefit$, averaged by the number of benefit metrics, i, and multiplied by a weight factor, $w_{benefit}$. Similarly, the second term consists of the averaged normalised scores for production cost, $\sum norm.cost$, multiplied by a weight factor, w_{cost}. In this study, the benefit and cost terms were, for brevity, weighted equally and, therefore, assigned the value 0.5. This limitation to a single weight factor in simulations was deemed sufficient to reveal whether the proposed integrated product and production system concepts can provide enhanced value even when cost and benefit are weighted equally. Since customised pharmaceutical products are expected to provide value to the health system and society at large through optimising health outcomes, another scenario could be to emphasise the benefit metrics over cost, which could translate to a higher accepted cost. Notably, a scenario weighting cost and benefit equally will under-estimate value compared to a scenario emphasising benefit over cost. If this study indicates that enhanced value can be obtained through equal weighting, this implies that this value will be further enhanced in benefit-prioritised scenarios.

4.2. Case study design

As mentioned in Section 3.1, two therapy examples were selected to represent fixed therapy (archetype 1) and dynamic therapy (archetype 2). For **therapy archetype 1**, maintenance antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) was selected for the case study. The dose strength window (i.e. the range within which each patient's required dose lies) was chosen as an exemplification of one part of a treatment regimen where enhanced variety is needed for customisation. The most common dose in this example is 50 mg but the prescribed dose strength can reach 200 mg (NHS 2018). The common approach to treatment is to begin at a dose of 25 mg. To model the patient population, a *dose strength window* of 25 mg to 200 mg was used as an execution bandwidth and, for this window, the patient population needs are fixed for the entire treatment period. Any titrations to the dose were disregarded.

For **therapy archetype 2**, a so-called titration regimen typical of an induction phase of treatment is exemplified by an antiepileptic drug whose dose is incrementally increased during a fixed treatment period. This example was chosen because many product variants thereof are currently available on the market, more than the usual number of product variants available under an MP paradigm. The patient population modelled for this therapy archetype follows the titration scheme presented in the prescribing information by the U.S. Food and Drug Administration (2009). An approach to treatment is to increase the dose by 25 mg every other day for two weeks. Thereafter, the dose is increased by 25 mg every 1–2 weeks until a maintenance dose of 100–200 mg daily is reached. To describe this dynamic treatment procedure, patient population needs were modelled for a ten-week period with a varying dose strength window throughout, starting with two weeks with the dose strength need normally distributed over the dose strength window 7.5 mg to 42.5 mg with a median of 25 mg. Every two weeks, an incremental increase to the dose window was made, finishing with a maintenance dose range of 100–200 mg, which was obtained during weeks 9 and 10.

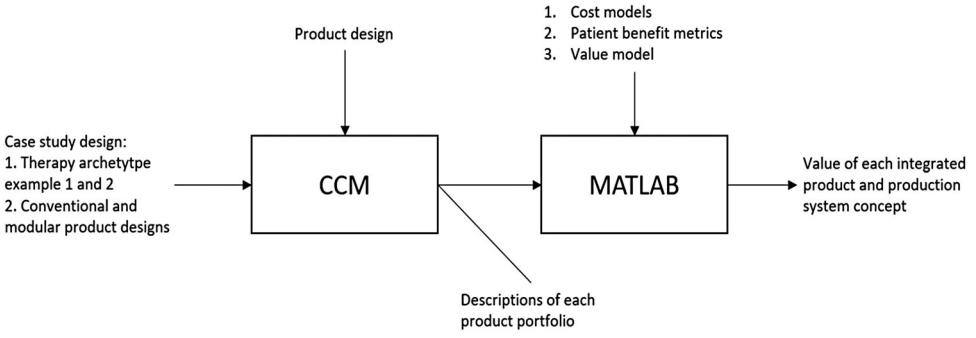


Figure 6. An overview of the software used for computational model implementation along with the main inputs and outputs of each software.

4.2.1. Integrated product and production system concepts for case study

The realised designs of the integrated product and production system concepts of this study are those illustrated in Figures 4 and 5, for both therapy archetypes 1 and 2, respectively.

Conventional product design. The product design realisation for the conventional product imitates the therapy archetypes selected. For therapy archetype 1, the selected SSRI treatment is currently offered as scored tablets of two dose strengths, 50 and 100 mg. Split tablets are allowed, generating API modules of doses 25, 50, and 100 mg from which required doses can be configured. For therapy archetype 2, the selected antiepileptic drug is produced as scored tablets of four dose strengths, 25, 100, 150, and 200 mg. Tablet splitting is also allowed, generating API modules of doses 12.5, 25, 50, 75, 100, 150, and 200 mg from which required doses can be configured, defining the product portfolio of the reference design of therapy archetype 2.

Modular product design. For the modular product designs, the contents of core A and core B were selected as 5 and 2.5 mg, respectively. Core A was based on a justification presented in Siiskonen, Malmqvist, and Folestad (2021), where the core should be smaller in dose content than the commercially produced tablet to create dose scalability. The physical properties of the lids or cups and the resulting release profiles are not further discussed in this study, however, the lids A and B provide different types of target release profiles. For more details about the parts and their designs, the reader is referred to Govender et al. (2020b) and Siiskonen, Malmqvist, and Folestad (2021).

4.3. Computational platform development and simulation

The framework was adapted through the case study into a computational platform for enabling integrated product and production modelling and simulation. The purpose of the computational platform is to evaluate the consequences of the design strategies, product modularisation and postponement, for a set of alternative integrated product and production system concepts from a patient benefit and production cost perspective. An overview of the computational implementation and the constituent software modules is described in Figure 6, together with the main inputs and outputs of each software.

The software CCM (Claesson 2006) and MATLAB were used here for the case study simulations. CCM is a research tool for platform modelling, which allows the graphical modelling of product modules and their interactions with each other and, by model execution, configures product portfolios based on the defined modules. This tool was, therefore, used to model alternative product designs, i.e. the conventional and modular product designs, for therapy archetypes 1 and 2. Executing the product models in CCM-generated portfolios of product variants that each product design can configure for each therapy archetype. To be able to perform cost-effectiveness simulations, a script was written in MATLAB consisting of the patient benefit and production cost models. Furthermore, the scales to normalise the patient benefit and production cost metrics were scripted in MATLAB. Simulations in MATLAB generated a readout on the performance with respect to the *cost-effectiveness* of each integrated product and production system concept.

4.4. Case study simulations

Through design work, i.e. following each design activity in the design framework presented in Figure 1, integrated product and production system concepts as well as models to assess the cost-effectiveness of such concepts were established. The computational platform was used as a complementary tool to enable the prediction of total value of each integrated product and production system concept through simulation. In this section, the simulation results for therapy archetype 1 and 2, respectively are presented. The performance on *production cost* and *patient benefit* is displayed as well as *value*, which serves as a proxy for cost-effectiveness. *Cost-effectiveness* of a modular product design (lower Np or higher Np) occurs when the final *value* exceeds that of the reference product design.

4.4.1. Benefit performance for therapy archetypes 1 and 2

In Figure 7, the patient benefit scores for the concepts presented in Figures 4 and 5, are displayed separately for therapy archetype 1 and 2. This benefit score of each concept is an average of normalised scores of the performances on the benefit metrics, $B_{dose,PD}$ and $B_{release,PD}$. It should be noted that the performance with respect to benefit is, in this study, solely dependent on the product design and independent of the SC design. The results indicate that an increased patient benefit can be achieved by increasing the degree of modularisation of the product design. The results further suggest that a similar trend in patient benefit can be expected regardless of the treatment regimen, i.e. fixed (therapy archetype 1) or dynamic (therapy archetype 2). Observe that the numbers in Figures 7(a,b) are not directly comparable.

4.4.2. Production cost

In Figure 8, the production cost scores for each concept from Figures 4 and 5 are presented separately for therapy archetype 1 and 2. These scores are displayed as an inverse of the average of normalised scores of the performances on the production cost metrics, i.e. those displayed in Table 1. The inverse of the cost performance scores provides a more intuitive readout from Figure 8 since a lower production cost implies a higher cost performance. The results indicate that an increased degree of modularisation increases the production cost and that a decrease in production cost can be achieved by an increased degree of postponement. Thus, in general, when fixing the product design, for example, high Np design (H), the

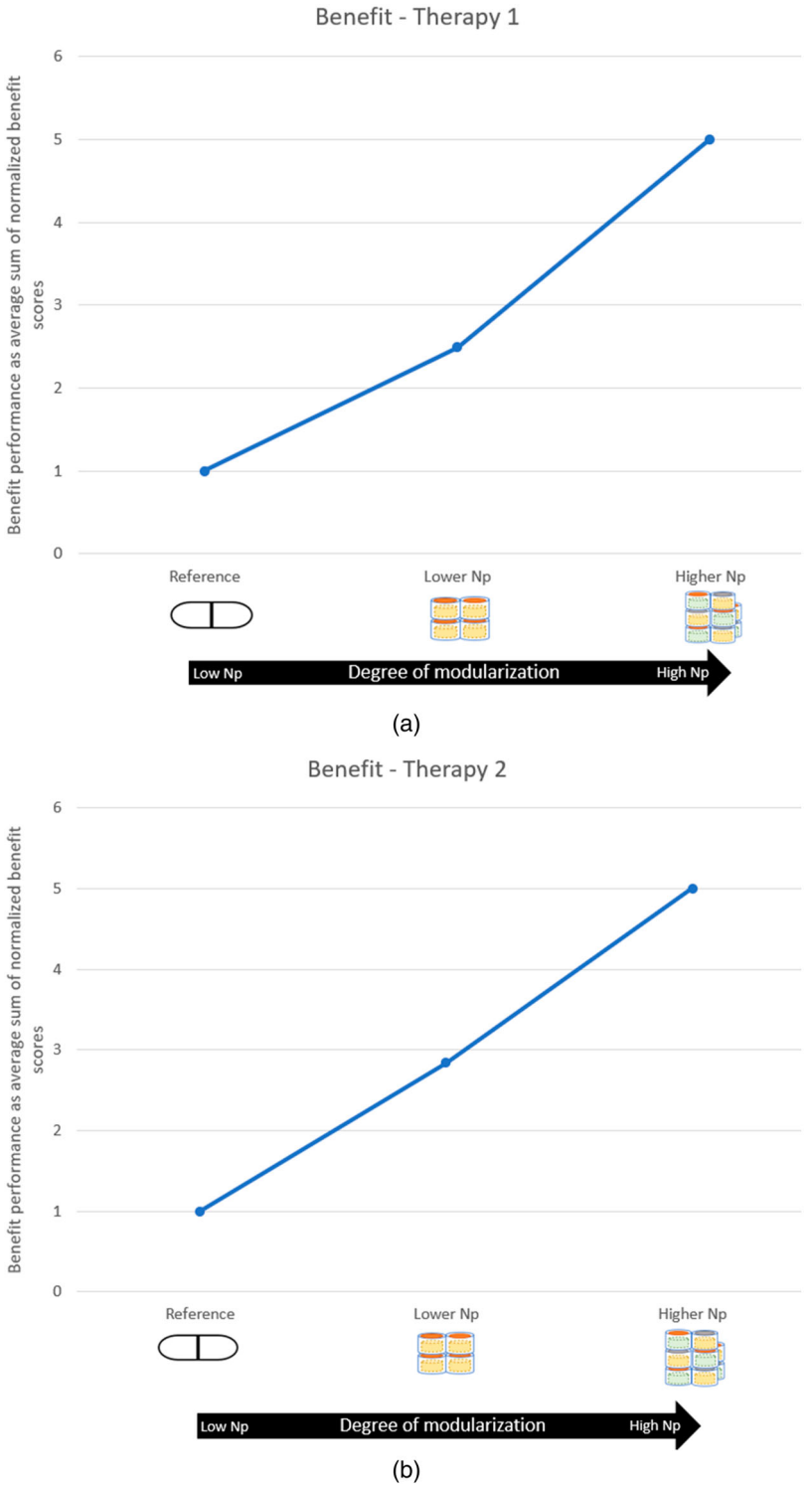


Figure 7. The normalised score for the average performance of therapy archetypes (a) 1 and (b) 2 on patient benefit.

final value is improved by postponement, i.e. the final value increases in the order H-SC1, H-SC2, and H-SC3. Similar to the results obtained for patient benefit, these results suggest that similar trends can be expected regardless of the treatment regimen, i.e. fixed (therapy archetype 1) or dynamic (therapy archetype 2). Observe that the numbers in Figure 8(a,b) are not directly comparable.

4.4.3. Value

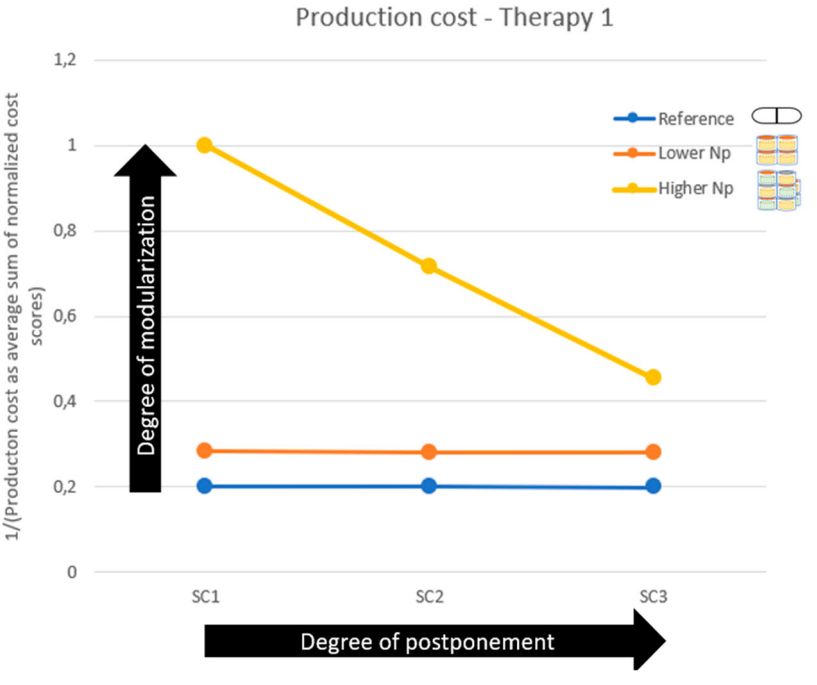
In Figure 9, the final value score, calculated through Equation 8, is displayed. The results indicate that cost-effectiveness is maximised by an integrated pharmaceutical product modularisation and postponement strategy. This holds regardless of the therapy archetype (i.e. fixed or dynamic treatment regimen), with the highest final values obtained for the concepts with a higher degree of modularity and the highest degree of postponement, i.e. H-SC3. It should, however, be emphasised that postponement is enabled by product modularisation. An interesting result for therapy archetype 2 is observed for SC1, where both lower Np and higher Np designs perform better than the reference. The reason is that therapy archetype 2 already has a product portfolio with many product variants in its conventional design, therefore any degree of modularisation allows a fewer number of components to be produced and managed in the SC, thereby providing cost-saving opportunities.

5. Discussion

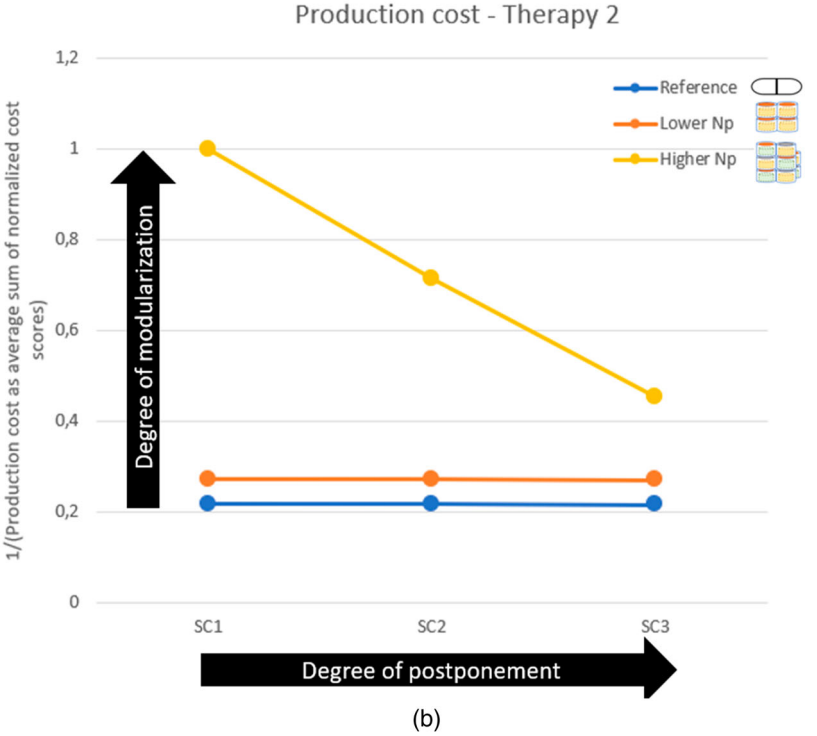
5.1. Utility of the cost model for pharmaceutical MC

The anticipated production costs for reconfigurable modular pharmaceutical products consist of both product variety management costs incurred throughout the SC and assembly costs that arise from generating the finished product variants through combining module variants. To the best of our knowledge, no prominent models providing such metrics exist to facilitate pharma SC systems modelling. Although the cost models adapted and developed in this study were based on the product variety produced and managed throughout the SC and corresponded to the number of product components and assembled product variants, they are not intended nor validated for absolute estimations, only relative comparisons between various integrated product and production system concepts. The estimation of absolute cost requires the elicitation of actual material, processing, labour, logistics, and administrative costs for the production of an increased product variety for customisation. Whilst models that incorporate these costs do exist for pharma SC, they exclusively address an MP not an MC context (nor the reconfigurable modular products that MC produces to enhance variety) (Basu et al. 2008; Hill, Barber, and Gotham 2018). In addition, the cost comparison has been performed for each stakeholder in the SC in isolation. In reality, absolute costs could accumulate along the SC, therefore, the output from these simulations could over- or under-estimate cumulative SC costs.

When developing the model, 'assembly' was conceptualised for the reference design as a process to accumulate and/or split tablets to provide 'customised' treatments to the patient. In contrast, reconfigurable modular products for MC would require an assembly technology to finish the product variants, for example, gluing module variants together (Demiri et al. 2018), filling module variants in capsules, and so forth. Whilst the technical



(a)



(b)

Figure 8. The inverse of the normalised score for the average performance of therapy archetypes (a) 1 and (b) 2 on production cost metrics.

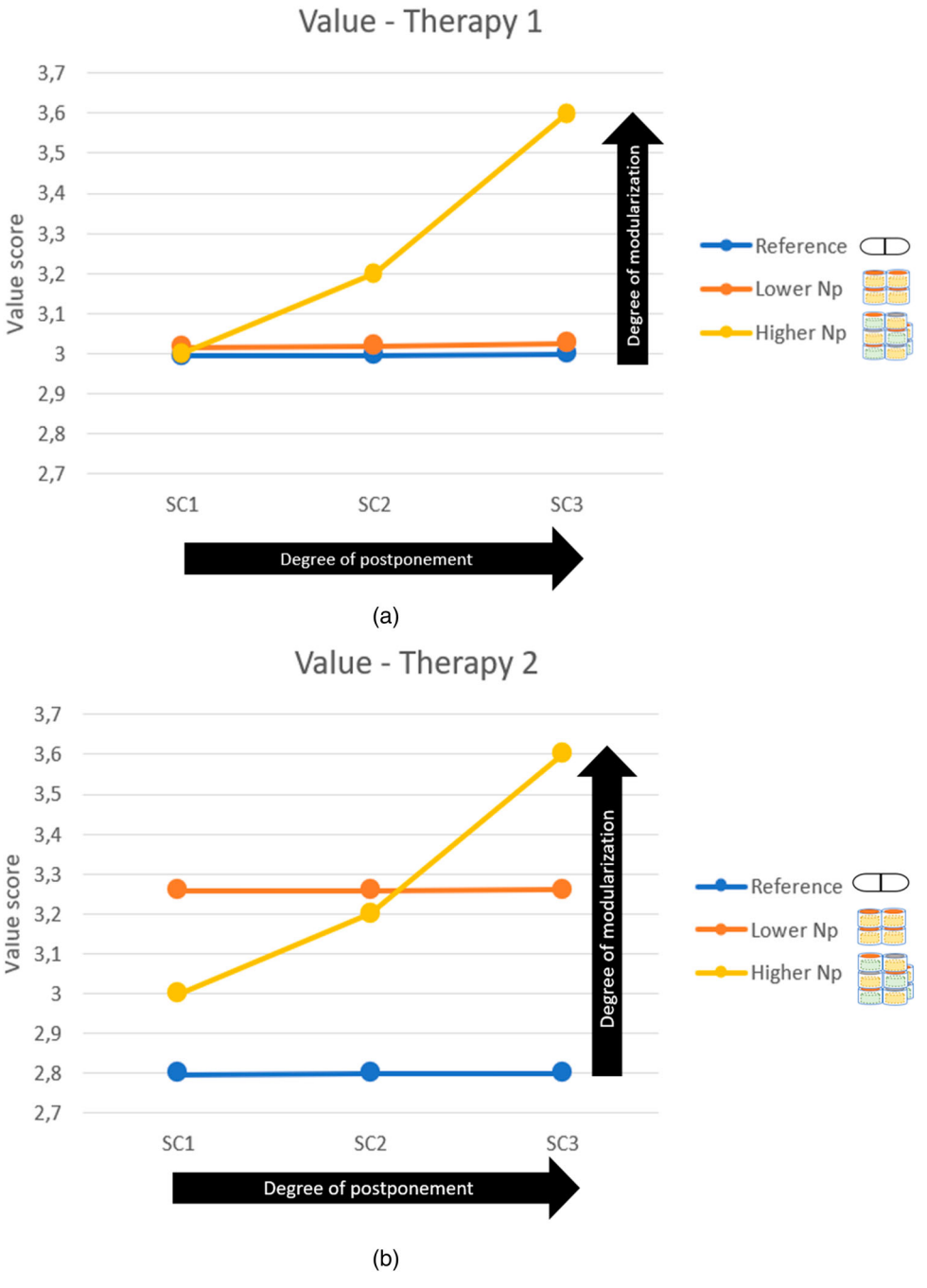


Figure 9. Final value scores for therapy (a) 1 and (b) 2 of each integrated product and production system design.

process of assembling reconfigurable modular products for MC has not been established in pharma, this assembly process is expected to be cost-inducing. To what extent this cost compares to the cost of redesigning and redeveloping each product variant in a typical MP paradigm depends on the specific assembly technology and remains an important factor when designing production. This study has adapted the cost of assembly from the complexity factor by Pugh (1990), based on the number of components, the types of components, and the interfaces between components, which are assembled into finished product variants. Once the specific assembling technology is defined, the production cost can be addressed in more elaborate terms. For example, the model by Swift and Booker (2003) accounts for the type of assembly process, i.e. how the components are joined as well as how the components are handled. In addition, Moussa and ElMaraghy (2022) presented an interesting cost optimisation approach to redesign product platforms for customisation by additive and/or subtractive manufacturing in the context of a gear shaft family. Their model is a holistic cost model, in a non-pharmaceutical context, that includes the cost of inventory, MP, as well as the cost of customisation through additive and/or subtractive manufacturing, i.e. demonstrating variety-generating processes beyond assembly. Their study also addressed a way to combat the need for low and changing production volumes by carrying over unused product components as inventory into the next production period. To build on the contribution of our study, realising individualised/customised/personalised therapies and pharmaceutical MC could benefit from adapting and integrating further volume-variety management strategies already demonstrated in other manufacturing industries. In cases where product modularisation drives costs upwards compared to non-modular reference designs (e.g. when coupled to an assembly process with high cost), this study has demonstrated that the incorporation of postponement into SC design becomes a critical factor responsible for decreasing the cost of production.

Beyond product modularisation in product design and postponement in SC design, process flexibility in manufacturing system design is another MC strategy (ElMaraghy et al. 2013; Hu 2013; Um et al. 2017). Whilst beyond the scope of this study, process flexibility has previously been discussed for MC realisation in pharma (Siiskonen, Malmqvist, and Folestad 2020). There, it was concluded that the current process flexibility in pharma MP is insufficient on its own to support the cost-effective production of customised pharmaceutical products. Therefore, expansion of the design and modelling framework to include process flexibility and its implications for manufacturing system design should be considered in future pharma MC research. Such adaptions could consider continuous manufacturing (CM) and additive manufacturing (AM) as these are examples of processing technologies on the rise (Aulakh, Settanni, and Srai 2022; Awad et al. 2023). This would enable a systematic assessment of alternative CM and AM based manufacturing system designs for realising MC.

5.2. Total value of pharmaceutical MC from an end-to-End SC perspective

Performing simulations on the computational platform established in this study enabled the identification of MC benefits, realisation opportunities, and challenges. Figure 10 illustrates the cost-efficiency gains obtained through combined product modularisation and postponement for the provision of enhanced product variety. Although founded on the case study simulation results (Figures 9(a,b)), the MC curve shapes are intended for conceptual illustration and are not fitted to a mathematical formula. The MP curve is based upon

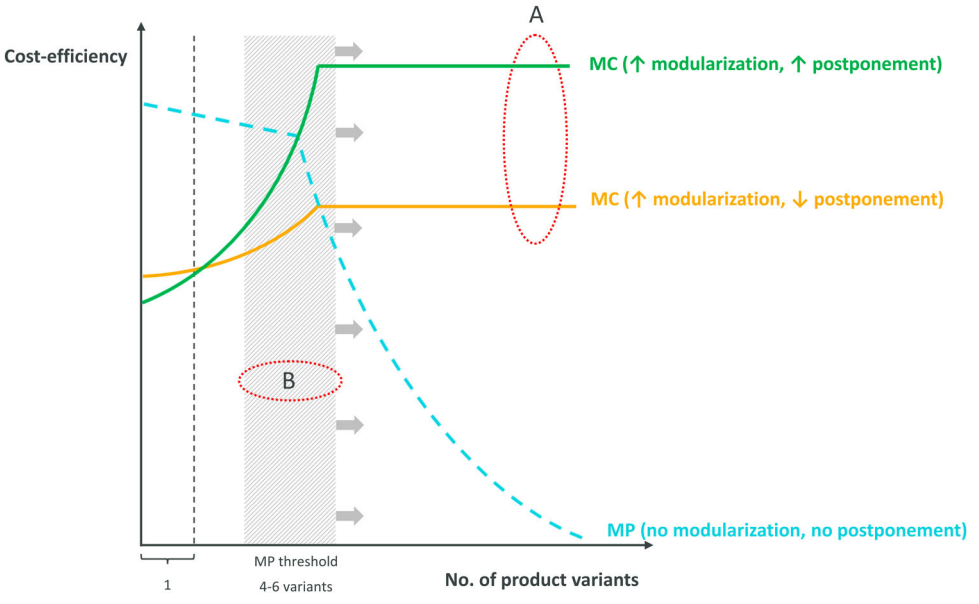


Figure 10. Cost-efficiency gains obtained through combined product modularisation and postponement for the provision of enhanced product variety.

the current performance of this production paradigm in low product variety contexts and the projected performance, limited by economies of scale, in high product variety contexts (Govender et al. 2020c; Siiskonen, Malmqvist, and Folestad 2021; Srai et al. 2015).

The region marked A in Figure 10 denotes the major MC opportunity identified in this study. Whenever the demand for product variety is higher than the number of product variants that can be produced by MP, a rapid decay in the cost-efficiency of MP is expected, due to the loss of economies of scale. This loss is a key consideration during customisation – a consequence of producing products in higher variety and lower volumes per product variant compared to MP (Govender et al. 2020c; Siiskonen, Malmqvist, and Folestad 2021; Srai et al. 2015). Beyond the MP threshold (grey zone in Figure 10), employing product modularisation (yellow line) and/or combined product modularisation and postponement (green line) offer considerable cost-efficiency gains compared to comparable non-modular MP products. These cost-efficiency gains increase further as the requirement for more product variants increases further. Modular product reconfigurability is, therefore, a crucial product design characteristic when cost-effective customisation is the goal since this allows enhanced product variety without a proportional increase in cost, thereby preventing the decay in cost-efficiency depicted for the MP paradigm. Product modularisation can therefore be viewed as an enabler of reconfiguration. The optimal degree of product modularity, i.e. the degree of modularity that results in a favourable cost–benefit ratio, is one where a minimum number of product parts (e.g. cores, cups, lids) can be reconfigured to provide a maximum number of assembled (finished) product variants (Govender et al. 2020a, 2020b; Siiskonen, Folestad, and Malmqvist 2018; Siiskonen, Malmqvist, and Folestad 2021). The gain in product variety is therefore enabled by reconfiguration, not by the number of fabricated parts. The number of fabricated parts should still be low enough to produce at a

relatively low cost via economies of scale (via MP). However, even with an optimal degree of modularity, product design alone is limited in its capacity to maximise cost-efficiency during customisation. Figure 10 emphasises the importance of a unified product and production approach to customisation since the combined modularisation and postponement approach (green line) provides the greatest cost-efficiency gains. Product modularisation is a prerequisite to maximise the potential of postponement, since a unified approach allows the production and management of a few fabricated parts throughout the SC and closer to the patients where the final product portfolio is created, supporting cost-efficiency. Notably, prior to the establishment of the design framework presented in this study, approaches that simultaneously and holistically tackle both product and SC design for customisation have not been comprehensively addressed for pharmaceutical applications (Govender et al. 2020a, 2020b, 2021; Siiskonen et al. 2021; Siiskonen, Folestad, and Malmqvist 2018; Siiskonen, Malmqvist, and Folestad 2020, 2021), therefore, this opportunity could not be revealed previously. The framework provided key design characteristics of both product and SC that, when integrated, enables exploration of opportunities for cost-effective pharmaceutical MC. In addition, although the SODF was used as the product example in this work, a feature of the presented framework is that the design approach is generalisable and adaptable to a wide range of medicinal product types, including other dosage forms, medical devices, and so forth.

A major MC challenge is exemplified in the region marked B in Figure 10, i.e. the transition zone between low and high product variety. This transition zone encompasses the economies of scale limit (Wilson 2016) beyond which it is no longer feasible to mass-produce product variants at low cost. Whilst region A highlights the benefit of moving towards MC, the current as-is production paradigm in pharma is still MP. The transition zone (region B) is where the relative performance of each of these two production paradigms starts to change, emphasising the need for a paradigm shift in pharmaceutical production to facilitate the provision of a high variety of products for customisation. A key consideration is the potential change in cost-efficiency during this transition from MP to MC across the grey zone in Figure 10. When the demand for variety is high, economic advantages through decreased product variety management costs may be gained through product modularisation and its associated decrease in product portfolio complexity (by requiring fewer modules to be manufactured and managed throughout the SC than MP finished product variants), however, product modularisation requires an alternative manufacturing approach that is designed and tailored to support both manufacturing and cost-efficiency. CM and AM based manufacturing platforms may offer opportunities here, however, there is still a need to validate cost-efficiency specifically in the context of end-to-end systems. Moreover, SC for AM based MC scenarios has so far only been suggested in terms of plausible layout sketches (Beer et al. 2021; Jørgensen et al. 2021). The design framework and computational platform presented in this study thus offer a means for more systematic evaluation of product and production systems design.

6. Conclusions and future work

The current value chain for product development, manufacturing, and supply is, in practice, highly complex, which makes empirical-based ways for re-engineering it, in part or in its entirety, often seen as a nearly impossible task. This study has demonstrated novel

results that cost-effective customisation in pharma is realisable. The systematic and semi-quantitative nature of this work forms the basis for translation to real products and the rational selection or design of manufacturing processes, assembly processes, and supply, based on product and production design requirements that facilitate MC. The conceptual framework for design and modelling and subsequent simulation work performed in this study has shed light on major opportunities and major challenges for pharma MC. The computational platform and case study model developed and presented here can be regarded as a first-generation means for the realisation of MC in pharma. The development of the mathematical model into a computational tool permits simulating the effect of product and/or SC design choices on the production system performance and vice versa, opening up new opportunities for the design and optimisation of integrated product and production system concepts. To build on the contribution of our study, we propose future research directions specifically regarding

(1) Further advancing unified product-process-production modelling by expanding the model established herein to, for example, accommodate manufacturing system engineering design explorations;
(2) Validation of cost models with real-world data to accelerate the realisation of MC/mass personalisation/mass individualisation.

Navigating the transition towards establishing these capabilities can rely upon using this work as a tactical guide to realising affordable pharmaceutical customisation. In all, these findings are imperative for providing academic and industry guidance on integrated pharmaceutical product and production systems engineering design and MC realisation.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Johan Malmqvist (johan.malmqvist@chalmers.se), upon request.

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