Faculty of Pharmacy
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POTENTIAL OF AUTOMATIC SUBSTITUTION OF BIOLOGICS TO ENHANCE RATIONAL USE OF MEDICINES IN FINLAND

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DOCTORAL DISSERTATION

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ABSTRACT

Biological medicines (biologics) have revolutionised the treatment of many chronic and severe conditions. However, they are generally expensive, and their increased use causes a continuous growth in drug costs. Biosimilars, clinically equivalent copies of biological originator products, are expected to curb the costs of biologics. Given that the uptake of biosimilars has been modest or even slow, the automatic substitution of biologics has been suggested to increase the price competition and the use of lower-priced interchangeable biologics.

This doctoral dissertation examined the evolution of market shares and prices of original biologics and their biosimilars in outpatient care in Finland (Study I). The study also explored Finnish stakeholders' perceptions of the automatic substitution of biologics with special focus on medication safety aspects to be considered if the substitution of biologics will be implemented (Study II). Further, the study systematically reviewed international scientific evidence on the automatic substitution of biologics (Study III). Rational pharmacotherapy, covering quality, safety, effectiveness, cost-effectiveness, and equality of medicine use, was applied as a conceptual framework for the study.

In Study I, national community pharmacy wholesale data from January 2009 to August 2020 were analysed for outpatient care sales and prices of biosimilars and their reference products. The prices of the reference products mainly decreased after the first biosimilar entered the market. Biosimilar prices remained primarily stable or decreased, and the changes were not as remarkable as the changes in the reference product prices after the biosimilar market entry. The use of biosimilars of different active substances varied widely at the end of the observation period in August 2020.

Study II applied a qualitative interview method to explore perceptions of automatic substitution among a wide range of stakeholders involved in the pharmacotherapy process. The participants (n=62) of the interviews (n=32) reported main expected benefits of automatic substitution being 1) cost savings, 2) access to biological treatments for more patients, and 3) enhanced continuity of treatment. The participants identified six main potential risk categories in the implementation of biologics substitution: 1) the patient's medication is interrupted or complicated temporarily or permanently, 2) the patient may use two products with the same active substance (concomitant use), 3) the traceability of the product is compromised, 4) the patient cannot get into healthcare in case of problems, 5) the patient does not receive substitution-related advice from the community pharmacy and 6) the patient is distracted by the differences in support materials they receive. The most often mentioned risk mitigation measures were medication and device counselling by community pharmacists, longer substitution intervals

(compared to generic substitution) and better knowledge of biosimilars among healthcare professionals.

In Study III, a systematic review was performed to identify any interventions, pilots, or other studies, including experiences or perceptions of relevant stakeholders on the automatic substitution of biologics. Altogether, 27 studies were included in the quality assessment, of which 23 were surveys and four were semistructured interviews. Studies reported mainly on stakeholders' perceptions of automatic substitution, focusing on prescribers' views. The reported perceptions of substitution were primarily negative (18/27 studies). Studies evaluating risks, safety, or effectiveness, or documenting real-life experiences of biologic substitution were lacking except for one intervention and two prospective risk management studies. The overall quality of the studies was low to moderate, and the results were not generalisable due to convenience sampling not representing the populations of interest and low response rates.

In summary, the Finnish legislative framework has not so far supported genuine price competition between originator biologics and their biosimilars in Finland. The current scarce and not very high-quality international research evidence on the automatic substitution of biologics cannot be used to guide the creation of the Finnish substitution model for biologics. The safe and efficient implementation of automatic substitution requires well-designed practices with prospective risk management and evolving legislation. The substitution also introduces new tasks and communication needs to those involved in the pharmacotherapy process, particularly to community pharmacists who will be responsible for substitution and counselling the patients.

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Helsinki, January 2023

Hanna

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

I Luukkanen SV, **Tolonen HM**, Airaksinen M, Saarukka L. The Price and Market Share Evolution of the Original Biologics and Their Biosimilars in Finland. BioDrugs 36:537-547, 2022. DOI: https://doi.org/10.1007/s40259-022-00540-y (Open Access)

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III **Tolonen HM**, Falck J, Kurki P, Ruokoniemi P, Hämeen-Anttila K, Shermock KM, Airaksinen M. Is There Any Research Evidence Beyond Surveys and Opinion Polls on Automatic Substitution of Biological Medicines? A Systematic Review. BioDrugs 35:547–561, 2021. DOI: https://doi.org/10.1007/s40259-021-00493-8 (Open Access)

The publications are referred to in the text by their roman numerals.

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DEFINITIONS OF THE KEY CONCEPTS

Administration device
A medical device that is necessary for the administration of the medicinal product and supplied as an integral component of the medicinal product (e.g., prefilled syringes, auto-injectors, inhalers) or a co-packaged (e.g., pen-injectors), or independently marketed as compatible with the medicinal product [1]. The administration device can be used by a healthcare professional, lay caregiver, or patient.

Automatic substitution
Please see *substitution*.

Best-value biologic (BVB)
The competition induced by biosimilars may reduce the prices of reference products and competing products within the same or different therapeutic classes. Best-value biologic refers to the situation where, as a result of healthy competition between biological medicines, a medicine contributes to the sustainability of healthcare costs regardless of the authorisation framework of the biological medicine [2].

Bioequivalence
Two medicines with the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits [3]. These limits are set to ensure comparable *in vivo* performance, i.e., similarity in terms of safety and efficacy.

Biological medicinal product (biological product, biologic)
A medicine whose active substance is produced by or extracted from a biological source, i.e., a living organism [4].

Biosimilar
A biological medicinal product that is highly similar to its reference biological medicinal product on the basis of analytical, functional, and clinical comparability studies. The active substance in a biosimilar is the same as in the reference product but a different version [5].

Biosimilar Working Party (BMWP)
European Medicines Agency's (EMA) working party of European Union (EU) experts on biosimilar medicinal products [6].

Centralised procedure
The marketing approval process of medicines within the European Union (EU) which involves a single application, a single evaluation and, for approved applications, a single authorisation valid in all EU member states and European Economic Area (EEA) countries Iceland, Liechtenstein, and Norway. It is imperative for certain medicine types, including all medicines derived from biotechnology processes and medicines for specific conditions such as cancer, neurodegeneration, viral and autoimmune diseases. The other option for authorisation is a national procedure (i.e., the decentralised or mutual recognition procedure) [7].

Committee for Medicinal Products for Human Use (CHMP)
European Medicines Agency's (EMA) scientific committee formed by European Union (EU) experts who review and recommend marketing approval of human medicines by centralised procedure [6].

Community pharmacy
The legal and regulatory definition of community pharmacy varies by country. In Finland, a community pharmacy is a licensed healthcare unit responsible for the supply, distribution, and manufacture of medicines and ensuring their rational use and providing price information through patient counselling in outpatient care for the general public [8]. The general public sale of medicines is limited to community pharmacies in Finland (excluding nicotine replacement therapy products).

Comparability
Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function as well as safety and efficacy. This scientific principle is also routinely used when a change is introduced to the manufacturing process of any medicines made by biotechnology, to ensure that the change does not alter safety and efficacy [5,9,10].

Generic medicine
A medicine developed to be the same as already authorised medicine. Efficacy and safety data for its authorisation is based on studies from the authorised medicine. In the EU, generic medicines can be solely marketed after the patent and data protection of the original (reference) medicine has expired [11,12].

Generic substitution
Substitution of *generic medicine* in the community pharmacy. See also: *substitution*, *generic medicine*.

Glycosylation
Modification of a protein after its translation within a cell by the addition of carbohydrate (sugar) groups to the amino acid backbone. Depending on the amount and type of sugar groups added, the biological activity of the protein can change [13].

Inappropriate use of medicines (also: inappropriate pharmacotherapy)
If the use of medicines does not meet all the aspects of *rational pharmacotherapy*, it can be described as inappropriate use of medicines [14].

Interchangeability
In the EU, interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or *vice versa*) or replacing one biosimilar with another. Replacement can be done by *switching* or *substitution* [13].

Medication risk management
A strategy that aims to prevent or decrease risks associated with the use of medicines [15,16].

Medication safety
The freedom from accidental injury during the medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications [17–19].

Non-medical switch (NMS)
To change the patient's medication to an alternative medication that is expected to have similar effects, for reasons other than lack of clinical efficacy or response, adverse effects, or poor adherence [20].

Originator
Originator refers to a medicine that is licensed in the EU via a full marketing authorisation procedure, including the demonstration of clinical efficacy and safety versus a placebo, current therapeutic options, or the current standard of care in clinical trials [4,21]. The originator can be chosen as a reference medicine. Please also see *reference product*.

Pharmacovigilance
Activities to detect and assess adverse reactions and other effects of medicines in use. The science and activities relating to the detection, assessment, understanding and prevention of the adverse effects of pharmaceutical products [22,23].

Rational pharmacotherapy (also: rational use of medicines)
Pharmacotherapy, i.e., use of medicines, is rational when it is effective, safe, cost-effective, equitable, and of high quality [24]. Rational pharmacotherapy is realised when a patient receives medications appropriate to his or her clinical needs, in doses that meet his or her own individual requirements, for an adequate period of time, and at the lowest cost to the patient and his or her community [25].

Rational use of medicines
Please see *rational pharmacotherapy*.

Reference price system
If the substitutable and reimbursable medicine is included in the reference price system, the maximum reimbursement for the medicine is the confirmed reference price [26,27]. The aim of the reference price system is to increase price competition and price awareness among healthcare professionals and patients [28].

Reference product (reference medicine)
A *biological medicine* approved in the EU which is chosen by a company developing a *biosimilar* as a reference for the head-to-head comparison of quality, safety, and efficacy [5]. For *generic medicines*, a reference product is a product to which generic medicine is compared [11,12].

Responsible pharmacotherapy (responsible use of medicines)
Responsible pharmacotherapy supplements the definition of *rational pharmacotherapy* by implying that the activities, capabilities and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately and benefit from them [29].

Suboptimal use of medicines (suboptimal pharmacotherapy)
Suboptimal use of medicines or suboptimal pharmacotherapy is the opposite to the *responsible pharmacotherapy* [29].

Substitution
Substitution (automatic) is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy without consulting the prescriber [13]. In this thesis, the terms *substitution* and *automatic substitution* are used as synonyms.

Switching
Switching occurs when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent [13].

ABBREVIATIONS

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AIC	Akaike Information Criterion
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced therapy medicinal product
AUC	Area under the plasma concentration curve
BIC	Bayesian Information Criterion
BMWP	Biosimilar Medicinal Product Working Party
BVB	Best value biologic
BWP	Biologics Working Party
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CQA	Critical quality attribute
DDD	Defined daily dose
DNA	Deoxyribonucleic acid
DTCA	Direct-to-customer advertising
DUE	Drug utilisation evaluation
DUR	Drug utilisation review
EC	European Commission
ECHO	Economic, clinical, and humanistic outcomes
EEA	European Economic Area
EFTA	European Free Trade Association
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
FDA	Food and Drug Administration (in the U.S.)
Fimea	Finnish Medicines Agency Fimea
HCP	Healthcare professional
HRQoL	Health-related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAb	Monoclonal antibody
MUE	Medication use evaluation
NMS	Non-medical switch/switching
PASS	Post-authorisation safety study
PRAC	EMA's Pharmacovigilance and Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSUR	Periodic safety update report
R&D	Research and development
RCT	Randomised clinical trial

RMP	Risk management plan
SEB	Subsequent entry biologic (Canadian term for biosimilars until 2016)
SmPC	Summary of product characteristics (the EU prescribing information)
TNF-alpha	Tumour necrosis factor-alpha
U.S.	United States (of America)
VAT	Value added tax
VNR	Nordic Article Number
WHO	World Health Organization

e.g.	exempli gratia
i.e.	id est
n/a	not available

1 INTRODUCTION

Modern pharmacotherapy started to evolve in the late 19th century when the pharmaceutical industry was born as a segment of the chemical industry [30,31]. The pharmaceutical industry was able to produce large quantities of standardised pharmaceuticals. Increased research and medical knowledge led to the boom of new, synthetic medicines since World War II. In the 1980s, the introduction of biotechnological methods enabled the large-scale manufacturing of medicines that were previously out of reach of patient care or caused serious treatment complications [32]. For example, diabetes had been treated with insulin isolated from the animal pancreas since the 1920s [33]. Still, it was not until biotechnology enabled large-scale insulin production in cells with better purity and without the risks of animal-origin [33–35].

Today, it is evident that biotechnological medicines have revolutionised the treatment of many chronic diseases, such as various autoimmune diseases and cancer. Cancer has long been treated with cytotoxic agents that often target the dividing cells [36]. Because healthy, non-tumour cells also divide, chemotherapies have adverse drug reactions (ADRs) that limit their doses and frequency of dosing. As the knowledge of cancer biology was more advanced, it was possible to develop targeted biotechnological anticancer medicines with a more favourable safety profile. The potential of biologics in autoimmune diseases has also been remarkable. For example, inflammatory bowel diseases and rheumatic diseases can be treated today with highly effective biologics that improve function and quality of life [37,38]. In addition to the progress of pharmaceutical agents, the evolution of administration device technologies of biologics has been fast. In particular, insulin-treated diabetics, whose combination therapies have been difficult to manage, have benefited from the development of administration devices. Alongside multi-injection insulin therapy, insulin pumps have been developed to deliver short-acting insulin to the body [39]. When combining an insulin pump and continuous blood glucose measurement with a control algorithm, a therapy called artificial pancreas provides an effective and safe way to control blood sugar levels [40]. The development of multi-injection insulin therapy equipment has also been significant. In the past, insulin was administered using a syringe and needle. Now more and more patients benefit from continuous blood glucose measurement and injection pens with a memory function enabling advanced self-management of the treatment. Indeed, advanced medical therapies and self-injecting biologics have brought patients to the centre of disease management strategies [41].

Because of the significant advantages and positive outcomes of new therapies combined with the ageing population having a growing prevalence of chronic diseases, the use of biologics is increasing [42,43]. This challenges

healthcare budgets, as biologics are substantially more expensive than conventional small-molecule medicines on average [44,45]. The increasing use of biosimilars has been suggested as a strategy to control costs [13,46]. Biosimilars, developed as equally effective and safe as their reference products (original biologics), are believed to increase price competition and thus alleviate cost increases [13]. However, the introduction of biosimilars, especially those launched in the 2010s, has not been efficient enough to obtain their full potential in this respect [47–49]. The efficient biosimilar uptake has been limited by the reluctance of prescribers to initiate a patient's medication with a biosimilar or to switch a reference medicine to a biosimilar [50].

Automatic substitution is a practice of dispensing one medicine instead of another interchangeable and equivalent medicine at the pharmacy without consulting the prescriber [13]. With small-molecule generic medicines, automatic substitution in pharmacies has shown to result in remarkable cost savings to the public health systems and patients [51–53].

This study originated from authorities starting preparations for a possible implementation of automatic substitution of biological medicines in community pharmacies in Finland. The driving force for the preparations was the Government Programme 2015-2019, which required the promotion of rational pharmacotherapy as part of the ongoing social and health services reform [54]. Thus, the Ministry of Social Affairs and Health established a long-term Rational Pharmacotherapy Action Plan, one of its actions related to the enhanced use of biosimilars [24]. This literature review of this doctoral dissertation introduces the concepts of rational and responsible use of medicines, generic medicines and their substitution, and biological medicines and biosimilars. The empirical research focused on 1) the biosimilar market in Finland and the potential of biosimilars to promote price competition, 2) safety risks to consider if the automatic substitution was implemented in community pharmacies, and 3) systematically reviewing the international scientific research evidence on automatic substitution of biologics.

2 REVIEW OF THE LITERATURE

2.1 RATIONAL USE OF MEDICINES

Rational use of medicines (or rational pharmacotherapy) as a concept and a health policy goal has been on the stage as long as medicines have been available on a broader scale and used more commonly in patient care. The discussion has revolved around the efficacy, safety, and quality of medicines, and the effectiveness of pharmacotherapies. The costs of medication in relation to clinical, economic, and humanistic outcomes have been under continuous debate and evaluation. Chapter 2.1 reviews the main concepts of rational pharmacotherapy and the evolution of the definitions over time with a special focus on the Finnish context. The review covers the relevant national and international policy papers regarding the rational and responsible use of medicines, accompanied by a narrative selection of scientific literature.

2.1.1 WHAT IS RATIONAL AND RESPONSIBLE USE OF MEDICINES – DEFINITIONS OVER TIME

The World Health Organization (WHO) has been a key player in promoting rational use of medicines globally. The WHO has defined the rational use of medicines (rational pharmacotherapy) a few times in the past decades (Table 1, Figure 1). Pharmacotherapy should be considered inappropriate if it does not meet all the conditions for rationality [14].

Table 1. *Selected definitions of rational and responsible use of medicines by the World Health Organization* [14,25,29].

Year	Definition
1985	**Rational use of drugs** demands that the appropriate drug be prescribed, that it be available at the right time at a price people can afford, that it be dispensed correctly, and that it be taken in the right dose at the right intervals and for the right length of time. The appropriate drug must be effective, and of acceptable quality and safety [25].
2011	**Rational use of medicines** occurs when the patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community [14].
2012	**Responsible use of medicines** refers to the activities, capabilities and existing resources of health system stakeholders that are aligned to ensure patients receive the right medicines at the right time, use them appropriately and benefit from them [29].

The definition of rational use of medicines was supplemented with the term "responsible use of medicines" in 2012 (Table 1, Figure 1) [29]. The supplement was intended to emphasise the impact of healthcare functions, capabilities, and resources to ensure the rationality of patients' pharmacotherapy. The opposite of the responsible use of medicines is the suboptimal use [29]. In this thesis, the focus is on rational pharmacotherapy. However, where relevant, the term responsible use of medicines is mentioned, which is a more comprehensive concept than the rational use of medicines.

Recently it has been suggested to update the WHO definition of the rational use of medicines by incorporating the environmental effects of pharmacotherapy [55].

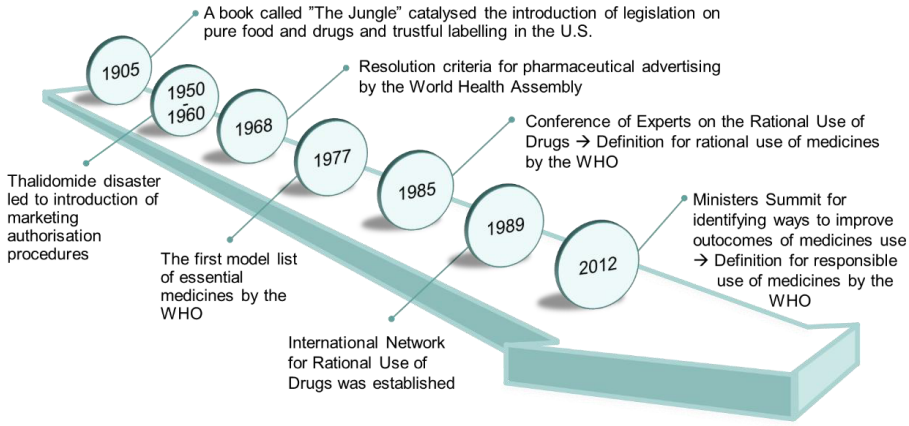

Figure 1. Selected milestones for initiatives to promote rational and responsible use of medicines [14,25,29,56–59].

2.1.2 EARLY-PHASE INITIATIVES TO PROMOTE RATIONAL AND RESPONSIBLE USE OF MEDICINES: SELECTED MILESTONES

In the 1900s, the reveal of severe medicine- and food-related disasters created a need to tighten pre- and post-marketing control over pharmaceutical products (Figure 1) [57–59]. In many countries, this led to the implementation of pre-marketing authorisation of pharmaceutical products [57]. Even though the increased number of pharmaceuticals on the market and evolved medication therapies improved health outcomes, they caused harmful adverse effects and increased costs related to treatments. The role and value of medicines in healthcare needed re-evaluation with a focus on the appropriateness of prescribing and medicine use [56]. Lack of balanced information on pharmaceuticals has been identified as one of the main

contributing factors to the irrational and suboptimal use of medicines [17,60,61]. Therefore, several initiatives have been introduced over time to improve access and quality of medicines information to healthcare professionals (HCPs) and consumers [18,60–62].

Despite several decades of work towards rational and responsible use of medicines, the inappropriate (incorrect, improper, irrational) and suboptimal (non-responsible) use of medicines is still a considerable challenge worldwide [29,60,63]. Inappropriate use of medicines can occur at any stage of the pharmacotherapy process leading to the lost value of medicines or even negative health outcomes (Figure 2) [24,29,64]. It is estimated that more than half of all medicines are prescribed, dispensed, or sold incorrectly [60,64]. Furthermore, only every other patient is estimated to use the medicines as intended, and HCPs are often unaware of how patients use their medicines [14,65–67]. According to a systematic review by Howard et al. in 2007, 33% of preventable medication-related admissions were related to medication nonadherence, 31% to prescription problems, and 22% to monitoring problems [68]. A recently published guideline estimates that the situation has remained the same [66,67].

2.1.3 FACTORS CONTRIBUTING TO INAPPROPRIATE AND SUBOPTIMAL PHARMACOTHERAPY

The inappropriate and suboptimal use of medicines is a multifactorial challenge concerning all stakeholders involved in the pharmacotherapy process [69,70]. Inappropriate and suboptimal pharmacotherapy may result from economic, systemic, scientific, competence and psychological factors (Figure 2, Table 2) that cross-interact in different ways [29,71,72].

Economic factors are important for both medicines access and prescribing behaviour perspectives (Figure 2, Table 2) [71]. Rational economic decisions may be influenced or even compromised by different, predictable behavioural models in different phases of the medicine use process, such as prescribing [2]. Out-of-pocket costs may limit patients' access to essential medicines [73–75]. Further, a lack of access to essential, good-quality medicines has long been a widespread problem in developing countries [76]. Also in high-income countries, attention has recently been drawn to the vulnerability of global pharmaceutical supply chains that may compromise the availability of even essential medicines [77–79].

Among economic factors influencing rational pharmacotherapy is the fact that pharmaceutical companies actively market medicines, particularly new medicines, to prescribers to promote their uptake and sales (Figure 2, Table 2) [72,80]. Marketing to prescribers, often disguised as education events, seems to be an effective strategy as pharmaceutical companies continue spending significant sums of money on it [72,80,81]. Studies indicate that physicians are vulnerable to interactions with pharmaceutical companies and drug

representatives, which influences their clinical decision-making, leading to increased prescribing and therapeutically suboptimal prescribing, prescribing branded drugs instead of low-cost generic drugs and rising direct and indirect healthcare costs [80,82–84]. In the European Union (EU), the promotion of medicinal products to prescribers and pharmacists accompanied by gifts or benefits is banned unless the gift or benefit is inexpensive and relevant to the clinical practice [4].

The advertisement of prescription drugs to customers (direct-to-consumer advertising, DTCA) is allowed in the United States and New Zealand [85,86]. In the EU, the DTCA is seen to increase unnecessary use of medicines, and it is prohibited for prescription drugs [4,87,88]. The national authorities and international collaboration have sought other strategies to increase patients' access to high-quality and balanced medicines information [61,62].

Even though economic factors may affect systemic factors contributing to rational pharmacotherapy (e.g., austerity in healthcare, resources), inappropriate and suboptimal medicines use is also contributed by the way the healthcare is organised, especially how the organisation's internal medication management practices are organised (Figure 2, Table 2) [61,89]. However, ensuring rational pharmacotherapy is not only an organisational issue but a regional and national issue, as coordination of medication management and information transfer processes are essential for the rational and responsible use of medicines [29,60,61]. Unsafe practices and errors in medication management processes are leading causes of injuries and avoidable harm, and they cause high costs for healthcare [90]. Especially polypharmacy, high-risk situations and transitions of care are found to compromise the safe use of medicines and result in inappropriate and suboptimal use [29,90]. In primary care, severe patient harm incidents are most commonly related to deviations in diagnostics, prescribing, or medication follow-up [91].

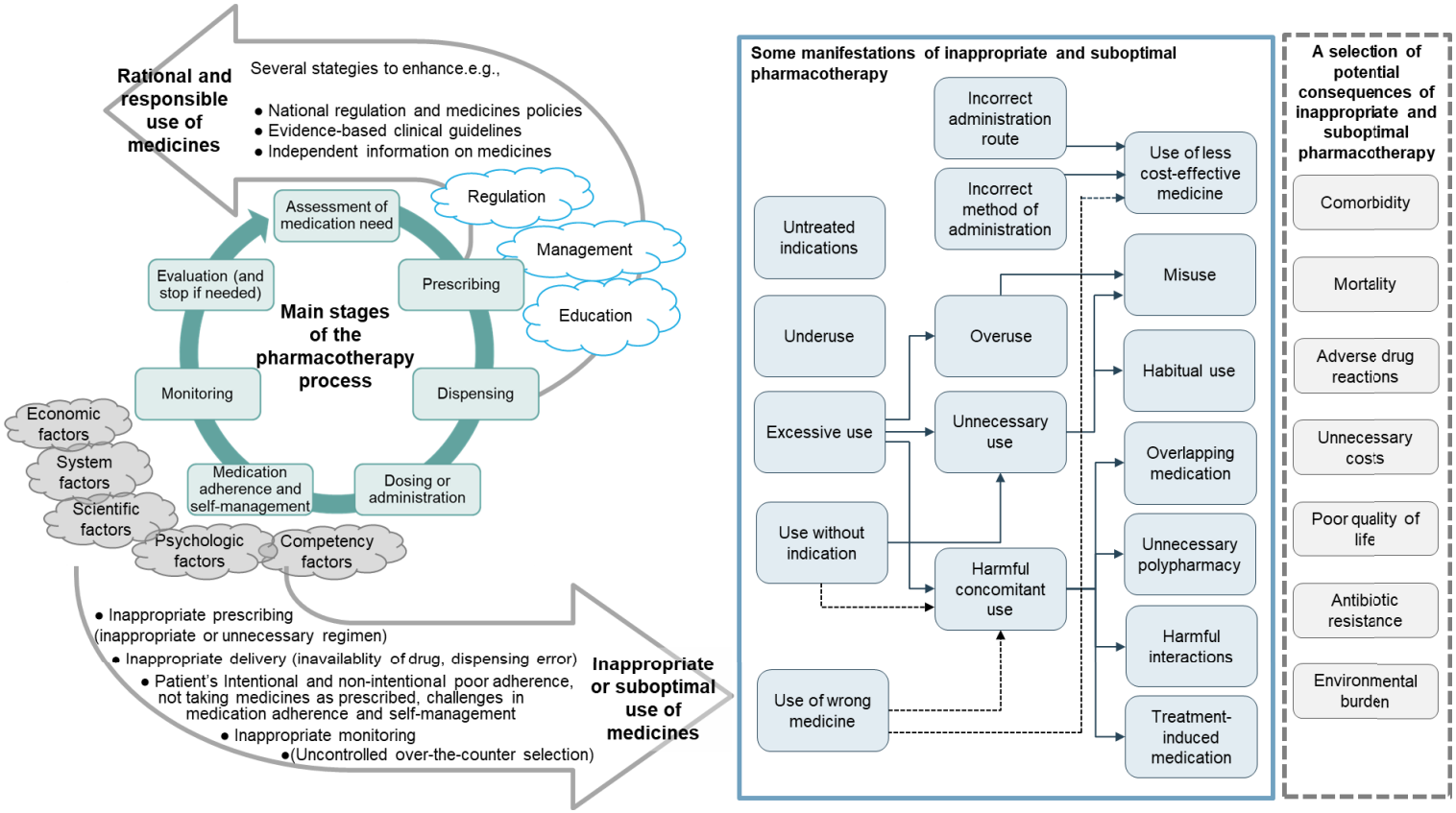

Figure 2. Main stages of the pharmacotherapy process and factors compromising rational and responsible use of medicines leading to inappropriate and suboptimal use and its consequences [24,55,61,64,71,72,89,92–94].

Table 2. *A selection of factors that can contribute to inappropriate and suboptimal use of medicines and some examples of the manifestation of these factors. Modified from* [2,60,61,71,72,89,95].

Factor	Examples
Economic	• Lack of money to purchase medicines (patient or health system) • Business-oriented market area selection of pharmaceutical companies • Marketing by pharmaceutical companies • Cognitive biases in economic decisions
Systemic	• Unsafe medication management processes • Unclear responsibilities, lack of interdisciplinary cooperation • Lack of resources • Lack of coordination of medication management processes • Lack of patient-centred approach • Lack of balanced medicines information to consumers and HCPs • Lack of prospective risk management and quality improvement
Scientific	• Patients are treated differently at different times as scientific knowledge evolves over time • Lack of evidence-based practices (e.g., current care guidelines)
Competency	• Deficiencies in education /knowledge of HCPs • Lack of patient counselling and communication skills • Lack of knowledge and skills in applied pharmacotherapy
Psychologic	• Power and human relationships • Nocebo and placebo effects • Patient does not have symptoms • Suspicious /over-eager attitude (patient or HPC)

HCP = healthcare professional

Scientific, competency and psychological factors to compromise rational pharmacotherapy are also interrelated. All HCPs should be educated to deliver patient-centred care as members of an interprofessional team, emphasising evidence-based practice, safety and quality improvement approaches, and informatics [95–97]. Current scientific knowledge influences patient care and requires evolving competencies of HCPs (Figure 2, Table 2). Evidence-based practices, such as clinical guidelines and medicines information, are vital from scientific, competency and clinical practice perspectives, and their lack contributes to inappropriate medicine use [60]. Guidelines and information should cover the dissemination of knowledge to patients, as patients' poor understanding of their illness and treatment may result in poor adherence [60,98].

2.1.4 OUTCOMES OF INAPPROPRIATE AND SUBOPTIMAL PHARMACOTHERAPY

The value and effectiveness of healthcare interventions such as medicines use can be evaluated with the ECHO (Economic, Clinical, and Humanistic Outcome) model [99]. Economic outcomes indicate direct, indirect, and intangible costs associated with treatment. Clinical outcomes are medical events that result from the treatment of the disease. In turn, humanistic outcomes are related to the impact of the treatment (i.e., intervention) on functional status, quality of life, or satisfaction with care. The idea of the ECHO model is to optimise the balance between different kinds of outcomes to show the effectiveness or even cost-effectiveness of the treatment intervention. The model can be utilised in evaluating whether the intervention improves clinical outcomes and quality of life while also saving money, a combination which can be regarded as the most optimal outcome.

Inappropriate and suboptimal use of medicines as a medical intervention influences economic, clinical, and humanistic treatment outcomes leading to a loss of optimum value of these interventions (Figure 2) [29,60]. This loss of optimum value could be at least partly prevented by optimising structures and processes in healthcare [100]. This also applies to pharmacotherapies and their rational and responsible use [61,101]. Increased healthcare costs constitute a significant threat challenging the sustainability of health systems (Figure 2) [29]. Suboptimal medicine use and the use of expensive brands instead of less expensive alternatives are among the factors increasing the economic burden on healthcare [102]. Delayed implementation of affordable medicines risks healthcare systems in many countries when expenditures increase uncontrolled, fuelled by new premium-priced technologies such as biologics [103,104]. Further, high public costs and growing out-of-pocket costs may hinder patients' access to medicines amplifying the loss of value of medical treatments.

Negative clinical outcomes of medical intervention can show, at their worst, increased comorbidity and mortality regardless of the treatment (Figure 2) [60]. This highlights the importance of appropriate prescribing and the need to monitor treatment outcomes [105]. In addition to the worst-case scenarios of poor clinical outcomes, several important negative humanistic outcomes, such as dissatisfaction, discomfort, and disability, may reduce a patient's quality of life [106]. These negative humanistic factors can lead to the discontinuation of medical treatments, especially for long-term illnesses.

Irrational and suboptimal use of medicines can also lead to unwanted results other than on the individual level. For example, the overuse of certain medicines, such as antibiotics, has received global attention [107,108]. Inappropriate use of antibiotics increases the risk of antibiotic resistance, leading to the ineffectiveness of many life-saving drugs [108]. Furthermore, excessive prescribing, dispensing and use of any medicines create

overproduction and pharmaceutical waste and release drug residues into the environment, compromising environmental sustainability (Figure 2) [55].

2.1.5 METHODS TO EVALUATE AND MONITOR RATIONAL PHARMACOTHERAPY ON THE SYSTEM LEVEL

Research evidence on rational pharmacotherapy is needed for scientific purposes and for informing decision-making nationally, regionally, and locally in healthcare organisations [60,89,101]. Especially research on structures and operating conditions enabling rational pharmacotherapy, research on the implementation of processes enhancing medication safety in various social and healthcare settings, and research on the effectiveness and cost-effectiveness of medicines and medical treatments are needed [101].

The state of rational pharmacotherapy can be assessed at different levels (i.e., national, regional, organisational, and individual) by various well-established methods and measures [14,60,101]. On a system level, it is recommended to have a multimethodological, stepwise approach, paying attention that not all the methods are suitable for all settings and all aspects to be evaluated under the concept of rational pharmacotherapy [60]. Pharmacoepidemiologic methods, indicator studies, surveys, observational methods, qualitative methods, and pharmacoeconomic methods are commonly used for identifying and/or managing inappropriate prescribing and use of medicines on organisational, regional, and national levels [101,109]. Health technology assessments (HTAs), systematic reviews and meta-analyses, among other HTA methods, provide information about the effectiveness of therapeutic interventions [110,111].

Medication safety research aiming at prospective risk management in medication use processes in various social and healthcare settings can apply a wide range of different methods and data [112,113]. Patient-reported outcomes and secondary use of health registers (real-world data) are exciting new opportunities to obtain data for prospective evaluation of rational pharmacotherapy and safe medication practices [97,114,115].

Pharmacoepidemiologic methods are suitable for studying medicines' use and value and estimating the probability of their beneficial and harmful effects in large populations or population groups of interest [116,117]. Pharmacoepidemiologic methods are applied in pharmacovigilance to evaluate the safety of authorised medicines and in medication use evaluations [116]. Applying more simplified methods to analyse aggregate medicine consumption data can be used to identify expensive, less effective drugs or to compare actual consumption with expected consumption (e.g., from disease data). Drug consumption at different levels (institutional, regional, national, or international levels) can be compared and monitored using the methodology of Anatomical Therapeutic Chemical (ATC) classification /

Defined Daily Dose (DDD) [60,118]. As the classification of both measures is stable and robust, it allows comparing the use of medicines over time [118].

In hospitals and other healthcare environments, focused assessment for certain medicines can be employed [60]. Drug utilisation review (DUR) and drug utilisation evaluation (DUE) are procedures to ensure medicines' safe and appropriate use generally at the individual patient level [109]. The terms DUR and DUE are often used interchangeably [119]. In DUR/DUE, drug use is evaluated against predetermined criteria either in a prospective (i.e., a pharmacist reviews prescription or order before dispensing), concurrent (i.e., monitoring the patient during treatment) or retrospective manner (i.e., review of patient records) [119–121]. Medication use evaluation (MUE) is used, for example, to evaluate the effectiveness of medications, improve patient safety, reduce variation in processes, optimise drug therapy, improve quality to meet standards and regulatory requirements, and minimise costs [122]. As an ongoing tool, MUE entails a data collection and analysis phase and, based on acquired evidence, a phase of modification of process or previous choices.

Medication use indicators can be used to continuously monitor the performance of health facilities to identify the units that do not meet the specified standards [123]. Several quality or performance indicators for the rational and responsible use of medicines have been developed over time [123,124]. Fujita et al. conducted a systematic review of existing quality indicators for the responsible use of medicines [124]. They identified 2431 validated indicators and classified them by different frameworks. Most indicators were for process evaluation when classified by Donabedian's framework. If classified by the Anatomical Therapeutic Chemical (ATC) code, the most significant number of indicators were related to medicines for the nervous system, anti-infectives for systemic use and the cardiovascular system. Most indicators classified as causes of drug-related problems pertained to 'drug selection', followed by 'monitoring' and 'drug use process'. However, the authors noted that some indicators are sensitive to the local context, and the data collection may be more challenging for some indicators.

The grounds and motives behind inappropriate medicine use detected in practice or by other research methods (e.g., surveys) can be examined with qualitative methods (e.g., focus group discussion, in-depth interviews, and structured observation) [60,125]. Once a sufficient understanding of the topic has been acquired with a qualitative approach, the information can be supplemented or validated, for example, with structured surveys and other more quantitative methods. The obtained results can then be used to design appropriate measures and to measure the impact of these measures on the use of medicines.

2.1.6 STRATEGIES TO PROMOTE RATIONAL AND RESPONSIBLE USE OF MEDICINES

Rational and responsible pharmacotherapy is a multidimensional and complex concept which challenges its promotion (Figure 2). Therefore, various strategies and actions on different levels are needed. This chapter discusses some of the different types of strategies to promote the rational and responsible use of medicines.

Although the importance of rational pharmacotherapy has long been recognised, countries have significant differences in how they promote rational pharmacotherapy, for example, in supporting rational prescribing [70]. In 2002, the WHO published a list of core components to enhance rational use of medicines that can be divided into the following three main types: regulatory, managerial and educational approaches (Table 3) [60,126]. Most components also enhance the responsible use of medicines [29].

Table 3. *The core components of strategies to enhance rational and responsible pharmacotherapy and their identified aims. Adopted from* [29,60,126,127].

Core component to enhance rational and responsible use of medicines	Aim(s) of the component
Regulatory	
Appropriate and enforced regulation	• To ensure that only safe, efficacious, and good-quality medicines are on the market. • To limit certain medicines available prescription-only. • To monitor and regulate medicines promotional activities. • To licence medicines supply chains and HCPs and ensure they have appropriate competencies.
Sufficient government expenditure	• To ensure the availability of HCPs and medicines.
National policies for medicines use	• To have a mandated national multidisciplinary body to coordinate strategies and policies to improve rational medicines use. • To develop, implement and evaluate interventions to promote rational medicines use at the national level.
Managerial	
Essential medicines lists	• To ensure that national government medicine budgets are used rationally for cost-effective, safe, and effective medicines, considering their relevance to public health and the local prevalence of diseases. • To ease medicine management in all respects; procurement, storage, distribution, prescribing and dispensing.
Avoiding false financial incentives	• To discourage overprescribing of medicines by limiting the financial incentives for prescribers. • To enhance the use of essential/evidence-based medicines with the reimbursement system
Evidence-based clinical guidelines	• To assist prescribers in making decisions about appropriate treatments for specific clinical conditions.

Medicines and therapeutic committees	• To monitor medicine's safe and effective use in the districts and hospitals under their jurisdiction.
Supervision of pharmacotherapy practices	• To guide practitioners in rational prescribing by analysing prescriptions' appropriateness (audits, reviews), giving feedback and utilising peer review and group processes. • To ensure medication safety practices.
Educational	
Problem-based pharmacotherapy training in undergraduate curricula	• To ensure evidence-based and cost-effective prescribing • To increase multiprofessional collaboration to ensure rational and safe use of medicines.
Ongoing education as a condition for licensing HCPs	• To ensure that prescribers and other HCPs get independent, balanced, and up-to-date information on new treatments in an effective and easily accessible way.
Independent information on medicines	• To ensure that sufficient unbiased information on medicines (such as clinical guidelines, drug bulletins, and academic detailing) is available and accessible for all participants in the pharmacotherapy process.
Public education about medicines	• To empower patients to be active actors with their pharmacotherapies and increase awareness about the importance of adherence. • To reduce inappropriate self-medication and demand for medicines

The early recommendations by the WHO on measures to promote rational pharmacotherapy have been quite physician-oriented and focused on promoting prescribing behaviours [25,60]. However, effective enhancement of rational and responsible pharmacotherapy (Table 3) requires seamless cooperation between different HCPs, such as medical specialists, general practitioners, nurses and pharmacists, and medicine users. This collaborative approach has been emphasised more and more in the most recent strategies [24,90]. Among forerunners on the topic has been the United Kingdom, as their strategies have already emphasised a multiprofessional patient-centred approach for decades [128–130].

Similarly, in 1990, Hepler and Strand published their principles of ensuring rational pharmacotherapy and prospectively managing medication-related problems and risks [92]. They called their patient-centred philosophy of professional practice pharmaceutical care that urged pharmacists to expand their role from the drug dispenser and information provider to a more holistic patient care provider who identifies, prevents, and resolves drug-related problems in collaboration with other HCPs. Inspired by the pioneering thinking of Hepler and Strand [92], pharmacists in hospital and community pharmacy settings have shifted towards providing more patient-centred services, with a focus on clinical pharmacy services and pharmaceutical care in recent decades [131,132].

In future, new strategies and enhanced interprofessional cooperation will be needed for rational and responsible medicine use because of the increasing complexity of medication regimens, mainly due to the ageing population [43,133].

2.1.7 EVOLUTION AND STEERING OF RATIONAL PHARMACOTHERAPY IN FINLAND

2.1.7.1 Early-phase research and developments

Rational and responsible pharmacotherapy has been part of health policy goals also in Finland for a long time. The roots of research focusing on rational prescribing and medicine use were in the 1970s when public health and social pharmacy researchers started to evaluate medicine use in large-scale population studies investigating the aetiology and prevention of cardiovascular diseases in high-prevalence areas in Finland [134,135]. The first studies used large population surveys and national register data from the Social Insurance Institution Kela to investigate medicine use and its appropriateness in various patient groups, particularly among those with cardiovascular diseases. From the beginning, one of the salient research themes has been adherence to treatment (compliance approach at that time) [136–138]. These studies can be considered as a starting point of pharmacoepidemiologic research in Finland, from which it has methodologically developed over time, following the international evolution [134].

Other important early-phase research areas in Finland to promote rational pharmacotherapy have focused on access to balanced medicines information for medicines users and HCPs [61,139]. The research extended to evaluate how health services and pharmacy services support rational medicine use and what is the availability and importance of medicines information and counselling in this respect. These developments also led to medicine policy changes that mandated community pharmacists' involvement in medication counselling in the early 1980s. The research further extended to prescribing practices and influencing factors, such as marketing. Based on the research, better access to balanced medicines information and restrictions on marketing by the pharmaceutical companies and their participation in continuing education for prescribers and other HCPs, were demanded. In hospitals, drug formularies were introduced, and medicines information centres started to be established in university hospitals.

2.1.7.2 From ROHTO Programme to ROHTO Centre

In primary healthcare, attention was paid to prescribing medications to outpatients and promoting adherence to treatment and self-care, especially for patients with long-term medication. In 1993, the Finnish Medical Society Duodecim introduced a project called "Good clinician practice" (in Finnish "Hyvä lääkärin työ") that aimed to identify definitions and indicators for good

treatment practices [140]. However, the inventory of the treatment guidelines revealed that the quality of the guidelines was variable, and a lot of duplicated work was done. As a result of the project, the national treatment guideline library, Current Care Guidelines (in Finnish "Käypä hoito"), was introduced in 1997 to unify treatment practices [141,142].

At about the same time with Duodecim's project, the medicines reimbursement working group, nominated by the Ministry of Social Affairs and Health, recommended several actions to improve the effectiveness of pharmacotherapy and control over increasing drug costs [143,144]. The growing medicine expenditures were proposed to be tackled by increasing price awareness of prescribers, creating a prescribing feedback practice, and providing balanced information about medicines [143]. One of the suggested interventions was the concept of local experiments and workshops to increase the rational use of medicines [143]. Eventually, in 1997, another working group set up by the Ministry of Social Affairs and Health suggested launching a large-scale national project for enhancing the more appropriate prescribing of medicines [145]. The established project was called the ROHTO Programme, and it was operated under the Ministry of Social Affairs and Health [143].

The ROHTO Programme, active from 1998 to 2001, focused on general practitioners and improving rational prescribing in primary care [143]. The goal was to change prescribing practices to follow evidence-based treatment guidelines (e.g., Current Care Guidelines) and, thus, promote their implementation [143,146]. One of the programme's practical aims was to ensure the availability of independent and unbiased information on medicines. The ROHTO Programme involved seven relevant stakeholders: the Finnish Medical Society Duodecim, the Finnish Medical Association, the Ministry of Social Affairs and Health, the National Agency for Medicines, the Social Insurance Institution Kela, the Ministry of Education and the Association of Finnish Local and Regional Authorities.

Although the programme's resources were scarce, ROHTO's activities were well-known, and it also covered, to some extent, other HCPs than physicians, although its focus remained on primary care physicians. Local workshops were a primary method in ROHTO and were successful [143]. ROHTO workshops, as they were called, addressed topical issues with high impacts, such as the treatment of type 2 diabetes and the use of analgesics in musculoskeletal disorders. Each workshop covered the chosen topic from pharmacological, clinical, drug use and utilisation perspectives.

In the external evaluation of the ROHTO Programme, it was considered essential to continue its successful work [146]. The National Centre for Pharmacotherapy Development ROHTO was established to continue the ROHTO Programme [147,148]. It became an essential national focal point for promoting rational pharmacotherapy [149]. The ROHTO Centre continued to support regional and local education networks targeted mainly at physicians in primary care, although it extended actions towards other HCPs, also

community pharmacists [150]. As within the ROHTO Programme, ROHTO Centre's strategy to enhance rational and responsible pharmacotherapy was based on increasing knowledge. Local workshops on rational pharmacotherapy were popular, covering almost 15 000 participants in 900 workshops during 2005-2008 [151]. The other main tasks of the ROHTO Centre were evaluating and disseminating evidence-based information on medicines and monitoring and studying medicines use and medication practices [147,150].

When systems-based patient safety work was initiated in Finland in the mid-2000s according to Council of Europe recommendations [18], the ROHTO Centre established a multiprofessional working group to prepare actions to be taken in medication safety. This working group prepared a glossary of the key concepts of patient and medication safety that was based on the extensive glossary published by the Council of Europe as part of its recommendations for building up safe medication practices in the member countries [17,94,152]. The glossary is still widely used, and it aims to provide a shared understanding of the key concepts in patient and medication safety to all healthcare workers.

The ROHTO Centre also assisted working groups at the Ministry of Social Affairs and Health that focused on preparing recommendations to improve medication safety. Among the most important were the working groups that 1) prepared the first national guidelines on building up safe medication practices in healthcare organisations [153] and 2) prepared actions to be taken to improve the safety of geriatric pharmacotherapy [154].

2.1.7.3 Continuation of ROHTO's work at Fimea

The successful work of the ROHTO Centre was merged into the Finnish Medicines Agency Fimea, which was established in 2009 [155,156]. Fimea continued to focus on local actions to enhance rational pharmacotherapy by establishing a national program that promoted local interprofessional collaboration in medicines optimisation for older adults during 2012-2016 [157–160]. In 2012, Fimea also established the first national medicines information strategy in Finland, aiming at improving access and quality of medicines information to consumers and health professionals [61,161,162]. The strategy was updated in 2021 [163]. These long-term national programs have produced several recommendations and resources to enhance rational pharmacotherapy in real-life clinical practice. The programs have also produced rich research data, which was used in the implementation of the programs, the development of medical treatment implementation practices, and the undergraduate training and continuing education of HCPs. Furthermore, these programs have been an important basis for establishing the government program-based Rational Pharmacotherapy Action Plan in 2016-2017 which has laid the foundation for the ongoing development of

rational pharmacotherapy as part of the social and health services reform [24,164,165].

2.1.7.4 Definitions of rational pharmacotherapy in Finland

The definition of rational pharmacotherapy has evolved over the last twenty years in Finland (Table 4). In 2002, the government's proposal for establishing the National Centre for Pharmacotherapy Development Rohto used the WHO's definition of rational pharmacotherapy as effective, safe, economical, and appropriate for patients [147]. The same definition was used in the Medicines Policy 2020 document in 2011 [166].

There was a thorough discussion on the concept of rational pharmacotherapy while processing the Rational Pharmacotherapy Action Plan [24]. It resulted in five core attributes instead of four. The newly added attribute was equitability, which reflects recent societal changes towards increased inequity that can also be seen in medicine use. The definition of "efficient" ("tehokas") attribute was changed towards "effectiveness" ("vaikuttava"), meaning outcomes of the treatment in real-life clinical practice. Furthermore, the previous component, "purposeful," was included in the new "high quality" component.

Table 4. *Attributes of the concept of rational pharmacotherapy in the definitions used in the key official governmental documents in Finland since the year 2000* [24,147,166]

Year	Definition in English	Definition in Finnish	Source
2002	• Efficient • Safe • Cost-effective • Appropriate for patient	• Tehokas • Turvallinen • Taloudellinen • Potilaan kannalta tarkoituksenmukainen	Government's proposal* [147]
2011	• Efficient • Safe • Cost-effective • Purposeful	• Tehokas • Turvallinen • Taloudellinen • Tarkoituksenmukainen	Medicines Policy 2020 [166]
2018	• Effective • Safe • Cost-effective • Equitable • High-quality	• Vaikuttava • Turvallinen • Taloudellinen • Yhdenvertainen • Laadukas	Rational Pharmacotherapy Action Plan [24]

* Only the Finnish version is officially available. Translation to English by the author.

2.1.7.5 National policies and action plans for rational pharmacotherapy

In 2003, the Ministry of Social Affairs and Health published the document Pharmaceutical Policy 2010, which defined the main targets for national medicines policy until 2010 [149]. One of the targets in the policy was to ensure the promotion of rational prescribing and use of medicines.

The following national medicines policy document was published in 2011, and it was extended by the year 2020 [166]. It was jointly developed with a wide range of key stakeholders in the pharmaceutical sector, the work being coordinated by the Ministry of Social Affairs and Health. The document outlined the following five joint objectives for the healthcare authorities and stakeholders to address rational pharmacotherapy:

- Pharmaceutical service is a part of the social and health service system.
- Pharmaceutical service is of high quality, efficient and cost-effective.
- Rational pharmacotherapy and medication safety enhance the population's wellbeing, improve public health, and decrease healthcare expenditures.
- Clinical drug trials enhance health, wellbeing, and employment.
- Veterinary medicine safeguards public health and promotes the wellbeing of people and animals.

Based on the policy document, the Rational Pharmacotherapy Action Plan 2018-2022 was compiled in 2018 as a part of Prime Minister Sipilä's Government Programme [24]. The Action Plan introduced five attributes to define rational pharmacotherapy: effective, safe, cost-effective, equitable, and high quality (Table 4, Figure 3). The Action Plan emphasised the measures that promote rational pharmacotherapy concept in the overall management of pharmacotherapies, including electronic patient-specific medication information management, which has been prioritised in the ongoing implementation [164,167]. Patient partnership in the medication management process is highlighted in the Action Plan [24]. The partnership requires that patients have enough information to participate in the planning and using their medication. In addition, they should receive support from HCPs to self-manage their medication. Coordination of the pharmacotherapy and pharmaceutical services and knowledge-based pharmacotherapy management is essential to promote rational medicine use. The Action Plan set objectives for different levels of national implementation.

To ensure the long-term work for the Rational Pharmacotherapy Action Plan, the Ministry of Social Affairs and Health published a roadmap for implementation. The implementation program (roadmap) covers several governmental terms and includes a broad range of fundamental reforms such as funding, data management and guidance at the different levels [24,168].

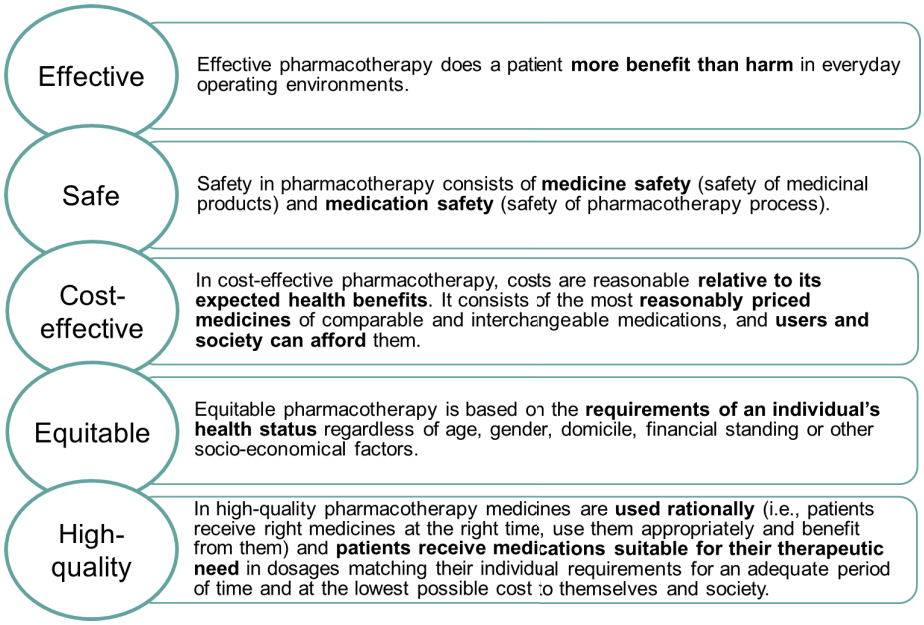

Figure 3. The definitions of the attributes of the concept of rational pharmacotherapy as described in the Rational Pharmacotherapy Action Plan 2018-2022 [24].

2.1.7.6 Authorities and other stakeholders involved in guiding and supervising rational pharmacotherapy in Finland

The Ministry of Social Affairs and Health is the regulatory authority responsible for planning, guiding, and implementing health and social policy in Finland according to the government programme (Figure 4) [169]. This also applies to the regulation and guiding rational pharmacotherapy. The Ministry of Social Affairs and Health works in close cooperation particularly with the Finnish Medicines Agency Fimea, which operates under the Ministry of Social Affairs and Health.

The Finnish Medicines Agency Fimea is a mandated authority for pharmaceutical affairs (Figure 4) [155]. Besides regulation and supervision duties, Fimea is appointed to, e.g., develop and study the sector of pharmaceuticals, provide medicines information for public and HCPs, conduct health technology assessments (HTA) and collaborate on European and international levels. Fimea coordinates the Research Network for Rational Pharmacotherapy (RATTI) that aims to, among other goals, increase multiprofessional collaboration, information sharing, and research and development activities in social and healthcare in Finland [101,170].

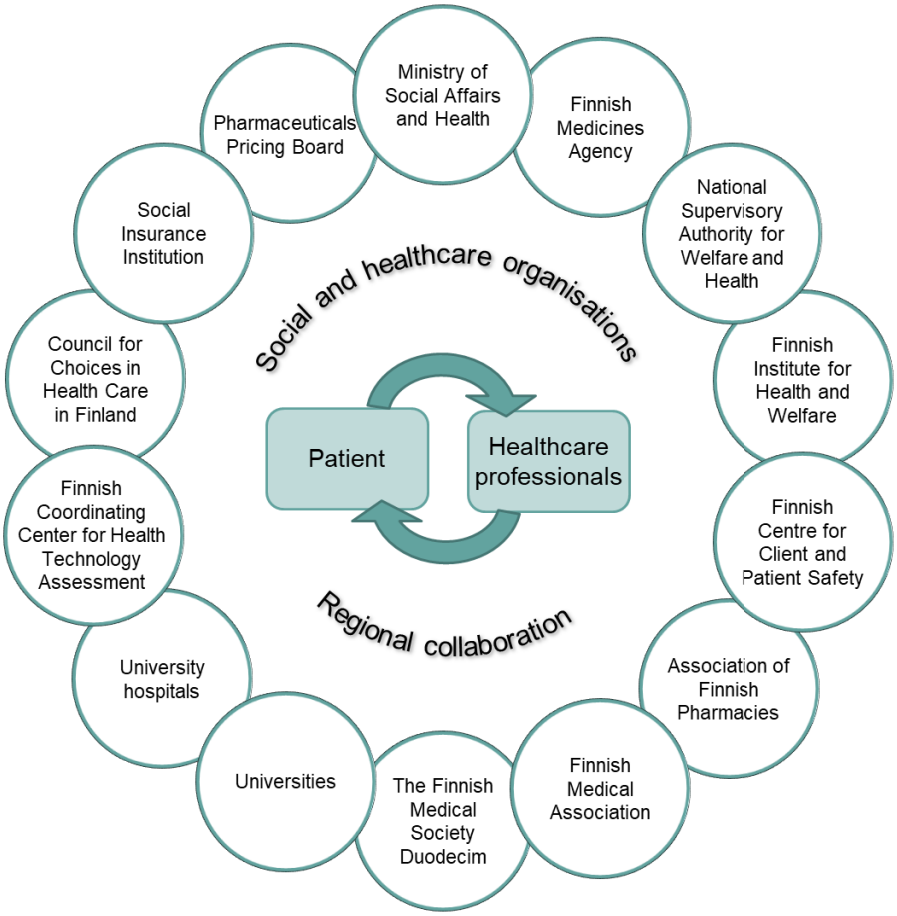

Figure 4. Key authorities and other stakeholders involved in enhancing rational pharmacotherapy in Finland (the outer circle: national level actors). Social and healthcare organisations, including community pharmacies, play an essential role in forming local collaborative networks for patient care (the inner circle).

The Ministry of Social Affairs and Health cooperates closely with the Social Insurance Institution Kela and the Pharmaceuticals Pricing Board in drug prices and reimbursement (Figure 4) [26,171]. Pharmaceuticals Pricing Board is responsible for evaluating the reasonable prices of medicines accepted for the reimbursement system [26]. Social Insurance Institution, an independent institution under public law, executes the implementation of medicine reimbursements according to public health insurance by being the main third-party payor of medicine reimbursements in Finland [171]. Social Insurance Institution also has a research unit that monitors the use of reimbursed drugs and drug costs paid from public funds and prepares proposals for changes to the reimbursement system to keep public drug costs under control.

The Council for Choices in Health Care (COHERE) in Finland monitors and evaluates the publicly funded healthcare service selection [172]. However,

COHERE Finland does not evaluate medicines for outpatient settings [173]. HTA work is nationally coordinated by Finnish Coordinating Center for Health Technology Assessment (FinCCHTA) in close collaboration with Fimea's HTA unit and COHERE Finland [174,175]. Further, FinCCHTA collaborates closely with university hospitals and HUS Pharmacy, which is responsible for price negotiations of certain expensive hospital medicines nationally [176].

The Finnish Institute for Health and Welfare was founded in 2009 when the National Public Health Institute, the National Research and Development Centre for Welfare and Health STAKES and the Rohto workshops were merged [156,177]. The Institute produces a wealth of statistical information on the population's health and health promotion to support decision-making [178]. Institute conducts population surveys that include the use of medicines.

The National Supervisory Authority for Welfare and Health provides licensing for social and healthcare professionals and supervises their activities in social and healthcare in cooperation with regional supervisory authorities [179]. In addition, the authority investigates severe patient safety incidents, including those related to medicines [180,181].

The recently established focal point for patient and client safety, Finnish Centre for Client and Patient Safety, is funded by the Ministry of Social Affairs and Health [182]. It coordinates the development and planning of customer and patient safety nationally and the implementation of the Client and Patient Safety Strategy and Action Plan 2022-2026, including medication safety [183].

With its publishing company, the Finnish Medical Society Duodecim has a vital role in the practical implementation of rational pharmacotherapy in Finland. Duodecim produces national Current Care Guidelines and Smart to Avoid Recommendations for prescribers and other HCPs [184]. Evidence-based and independent clinical practice guidelines are developed in collaboration with Duodecim and relevant medical societies. As a basis for treatment decisions, the guidelines aim to decrease inconsistency in treatment practices and thus improve the quality of care. The Finnish Health Portal, Terveysportti, contains versatile electronic databases for risk management of medical treatments in clinical practice and is available throughout social and healthcare, also in community pharmacies. For patients, Duodecim provides patient-targeted versions of Current Care Guidelines, and the Health Library are freely available online [185,186]. Another comprehensive database for patients is the Health Village, which is produced in collaboration with university hospitals [187].

In addition to providing training for undergraduates and ongoing education for HCPs, the universities produce plenty of research on rational pharmacotherapy and its implications [101,134].

Professional and advocacy associations for healthcare professionals, such as the Finnish Medical Association and the Association of Finnish Pharmacies, work broadly to develop the health sector and promote professional competencies [188,189].

2.2 GENERIC MEDICINES AND GENERIC SUBSTITUTION

2.2.1 CONCEPT OF GENERIC MEDICINES

After the patent and data exclusivity of a chemically synthesised small-molecule brand medicine expires, its generic options can become available in the market [190]. The availability and use of unbranded versions of the medicine usually increase competition, leading to lower prices and reduced medicinal expenditures [191]. These copies, i.e., generic medicines or generics, are identical to the original product and have the same clinical performance (Table 5). However, the term "generic product" has slightly different meanings in different jurisdictions lacking globally harmonised terminology and regulation [192–195].

Table 5. *The definition of generic medicine by the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and the World Health Organization (WHO).*

	Definition	Reference
EMA	A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine. A company can only market a generic medicine once the 10-year exclusivity period for the original medicine has expired.	(European Medicines Agency, 2022) [11]
FDA	A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.	(U.S. Food and Drug Administration, 2022) [196]
WHO	The term 'generic product' means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights.	(World Health Organization, 2005) [195]

The definitions of generics by competent authorities in the EU and the U.S. are formulated to be understood by the public and are somewhat similar to each other (Table 5). Since the WHO does not represent any particular jurisdiction, its definition is more general.

When considering the legislative wording on generics in the EU, Directive 2004/27/EC gives the meaning of generic medicines as follows:

> *"- a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form*

as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy." [190].

Thus, the directive defines the concept of bioequivalence that is fundamental for generic medicines. The bioequivalence of two medicines with the same active substance can be demonstrated by appropriate bioavailability studies [3]. The similarity of the bioavailability of immediate-release formulations for systemic use means proving that generic medicine's rate and extent of absorption are comparable with reference medicine within predetermined limits. It is generally studied with healthy volunteers by assaying the plasma concentration-time curve after a single dose [3]. The extent of the exposure and the absorption rate are assessed by determining the area under the plasma concentration curve (AUC), the maximum plasma concentration, and its timing.

European legislation and the marketing authorisation approval process enable the approval of so-called hybrid medicines, i.e., medicines that do not entirely fulfil the definition of generic medicine but are based on a reference medicine [11,190]. For example, a hybrid medicine can have different strength, route of administration or indication compared to the reference medicine. In these cases, the marketing authorisation applicant must provide additional data from trials carried out in human volunteers.

2.2.2 GENERIC SUBSTITUTION

Substitution is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [13]. As with the concept of generic medicines, the definition, conditions, and implementation of generic substitution vary across the world [192,197]. In the EU, the generic substitution is subject to national regulation [11]. Generic substitution is one of the strategies to increase competition within pharmaceuticals [191,198].

When reviewing the scientific literature on generic substitution since 2000, the geographic focus of substitution-related economic evaluations, studies on the views and opinions of different stakeholders, and narrative reviews on the topic have shifted. In the early 2000s, the increased availability of generics and the introduction of generic substitution in several Western jurisdictions may have stimulated research interest, particularly in Europe and North America [199,200]. In recent years, the increased research interest, especially in stakeholders' perceptions of generic substitution, has expanded to developing and emerging countries (e.g., [201,202]).

Straka et al. reviewed peer-reviewed articles published between January 2003 and March 2013 to summarise the potential negative clinical and economic consequences of generic substitution [199]. Based on the included articles (n=30), they categorised the possible negative outcomes of the generic substitution into three groups: 1) patient attitude and adherence, 2) clinical and safety outcomes and 3) cost and resource utilisation. Most of the included articles focused on medicines for central nervous system diseases, as drugs with narrow therapeutic indexes are often used for these conditions. As the study design of the review was set to identify negative outcomes of generic substitution, the conclusion was that mandatory generic substitution might lead to unintended consequences such as decreased adherence, poorer clinical outcomes, increased adverse events, and increased total costs [199]. They further highlighted the need for retaining patients' and prescribers' rights to request the branded product and the need for patient education on generics.

In a systematic review, Gothe et al. studied potential differences between generics and original products and the economic outcomes of generic substitution [200]. They identified 40 studies with 119 outcome comparisons published between 2000-2012. Two-thirds of the included clinical outcome comparisons (n=97) gave similar clinical outcomes between generic and original drugs. Two-thirds of the included economic outcome comparisons (n=22) suggested generic substitution to increase costs. The authors suggested that differences in clinical outcomes and negative economic outcomes were potentially due to studies conducted among drugs of narrow therapeutic indexes. The authors noted that studies on generic substitution in pharmacologically less demanding therapeutic areas were needed.

In Finland, the content of generic substitution-related patient counselling was studied in 2018 in community pharmacies [203]. The survey with 498 respondents resulted that patient counselling covered a wide range of topics and that community pharmacists should increase the price counselling when dispensing interchangeable medicines. Further, some Finnish studies regarding generic substitution (with or without reference price system) have focused on its economic aspects, such as the impact of substitution on the price and sales evolution of medicines [204–207]. Studies on stakeholders' perceptions of generic substitution are reviewed in Chapter 2.2.2.3.

2.2.2.1 Drug cost containment by generic substitution - an international perspective

In Europe, generic substitution has been implemented in most countries in the European Free Trade Association (EFTA; EU countries and Iceland, Liechtenstein, Norway, and Switzerland) either on a mandatory or voluntary basis [197,208]. Implementation of substitution and the uptake of generics vary between European countries as the regulatory landscape, and healthcare systems are diverse. Further, most European countries have a reference

pricing system that limits how much insurers reimburse for the medicines included in the reference pricing system. In 2015, IMS Institute for Healthcare Informatics (currently known as IQVIA) estimated that European health systems were able to save up to 100 billion euros in 2014 due to expired patents of original branded medicines [209]. However, the report did not specify the means for the uptake of generic medicines (substitution or prescriber-led practices). More recent estimations from Europe on savings triggered by generics are lacking.

Launching generic medicines to the market has been possible in the U.S. since 1984 when the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) was introduced [210]. In the U.S., FDA does not regulate generic substitution, and there are different strategies to encourage the use of generics that vary between states [211,212]. In some states, generic substitution can be mandatory, although prescribers can limit it with "a dispense as written" designation, whereas some states define it as a voluntary practice [197]. A study on angiotensin-converting enzyme inhibitors and angiotensin-II-receptor blockers, common cardiovascular drug groups, estimated that public expenditures of these medicines could have been reduced by almost 90% in 2016 and 2017 in the U.S. with maximised use of generic and therapeutic substitution [52]. Therapeutic substitution (therapeutic interchange) refers to the practice of dispensing a medicine of different active substance but the same expected therapeutic effect [211]. In 2020, FDA estimated that generic drugs had saved 2.2 trillion dollars in ten years in U.S. healthcare [213].

2.2.2.2 Generic substitution and reference price system in Finland

In Finland, a pursuit was made to increase the use of generic drugs in the early 2000s by enabling prescribers to issue generic prescriptions [214]. However, the use of generic prescriptions remained low, and the attempts to encourage physicians to prescribe lower-priced generics instead of expensive brand drugs did not produce the desired result [215]. In the government's proposal in 2002, which justified the law enabling generic substitution, it was stated that medicine's price is not that important in guiding its use in case the medicine is highly reimbursed [215].

The generic substitution was introduced in Finland in 2003 to increase the cost-effectiveness of pharmacotherapies [215]. The amended relevant laws on medicines (395/1987) and health insurance (364/1963) mandated community pharmacies to substitute a drug prescribed by a physician for a more affordable product containing the same active substance unless the prescriber or the purchaser of the drug prohibits the substitution [215].

Generic substitution has reduced costs by substituting the medicine with a lower-priced alternative at the community pharmacy and triggering price competition between interchangeable medicines [204]. However, as observed

by Aalto-Setälä (2008), the price development of drugs varied from substantial price reductions to increased prices [204]. The higher prices were assumed to be a consequence of purchasers' denied substitution. Although the annual savings obtained from generic substitution were from 25,7 to 36,2 million euros in the years 2004-2007, the public spending on medicines continued to rise due to the more extensive use of medicines or the use of more expensive medicines or both [28]. Further, prohibiting substitution by purchasers, especially for drugs with a higher reimbursement category, decreased savings from substitution. In 2009, the generic substitution was supplemented with a reference price system to control drug costs increase [28,216,217].

The generic substitution with the reference price system is still in use for paying pharmaceutical reimbursements in Finland [8,26]. The system aims to induce price competition between pharmaceutical products and increase price awareness among prescribers and patients [48]. Indeed, it is estimated that more than a billion euros have been saved since introducing generic substitution in 2003 [218]. Interestingly, sales of drugs within the reference price system were one-third of all reimbursed drug sales in 2019 [48].

The list of interchangeable medicinal products is approved by the Finnish Medicines Agency Fimea quarterly [8]. Prerequisites for interchangeability are that the medicines contain the same amount of the same active substance, have the same pharmaceutical formulation (e.g., tablets and capsules can be equated in certain situations) and are bioequivalent [219]. Medicines with a particularly narrow therapeutic window or other pharmacological or clinical reasons are not defined as interchangeable. Therefore, e.g., warfarin, antiepileptics and most antiarrhythmics have been non-interchangeable, except for parallel import and parallel distribution products.

Based on the list of interchangeable medicines, Pharmaceuticals Pricing Board defines medicine groups to be subjected to pricing announcements [26,220]. Once the pharmaceutical companies have set the prices for their medicines, the Pharmaceuticals Pricing Board confirms reference price groups, the reference price for each group, and the products to be included in each group. The confirmed reference prices are valid for three months. If the purchaser (patient or someone on behalf) chooses the medicine within the reference price at the pharmacy, the medicine will be reimbursed based on the reference price. The purchaser will have to pay the difference if choosing a more expensive medicine [27]. If there is a more affordable alternative for medicine, community pharmacists must inform the purchaser of the prices.

Not all reimbursable medicines are in the reference price system in Finland [26,220]. For example, medicines with valid patents or data exclusivities are not included in the generic substitution and reference price system. Still, their reasonable wholesale prices are confirmed by the Pharmaceuticals Pricing Board to gain reimbursable status.

2.2.2.3 Stakeholders' perceptions on generic substitution

Generic substitution is controversial in scientific discussion [193,199]. In general, HCPs' overall attitude toward generic substitution is positive [221]. Increased use of generic medicines has led to substantial savings [222]. On the other hand, drugs with a narrow therapeutic index are considered unsuitable for generic substitution [199]. Also, vulnerable patient groups, such as older adults, frail, or patients with multimorbidity and polypharmacy, cognitive impairment or mental health disorders, are considered cautiously suitable for generic substitution [221].

Pharmacists are more positive towards generic substitution than physicians and the general public [223]. This might be due to pharmacists' better understanding of the generic substitution practice and the concept of bioequivalence [224]. However, the perceptions of generic substitution may reflect the overall suspicious attitude towards generic medicines, as one-third of HCPs (physicians and pharmacists) have concerns about generic medicines, and their perceptions may impact patients' views if patient counselling conveys HCPs' cautious attitude towards generic medicines and their substitution [223].

In Finland, perceptions of generic substitution have been studied at the University of Eastern Finland. The views of pharmaceutical companies and wholesalers on generic substitution were studied in the doctoral dissertation applying methods of quantitative content analysis of statements and mass communication, postal surveys and thematic interviews [225]. The data for the dissertation was collected before the reference price system was implemented in Finland. The perceptions of pharmaceutical companies and wholesalers were negative due to decreased sales margins and increased workload.

The perceptions of the Finnish general public have been studied through surveys in pharmacies and by post [226–229]. The pharmacy surveys were conducted three to seven months after the implementation of generic substitution [229]. The respondents were positive about generic substitution and considered it to save money. The postal survey was conducted in 2008, that is, before the implementation of the reference price system [226–228]. The three reports from the survey concluded that the respondents (n=1844) considered generic substitution as good practice that saves money [227]. The main factors influencing the product choice were price, availability, familiarity and, for refusals, satisfaction with the medicine in use [226,228]. Similar results were obtained from the survey among pharmacy customers (n=1043) in 2018 [230].

One year after the implementation of generic substitution, physicians' perceptions were studied through interviews in Finland [229]. The perceptions of participants (n=49) were positive towards generic substitution, although some participants had doubts about the efficacy and safety of generics.

2.3 BIOLOGICAL MEDICINAL PRODUCTS AND THEIR BIOSIMILARS

2.3.1 CATEGORISATION OF BIOLOGICAL MEDICINAL PRODUCTS (BIOLOGICS)

Biological medicinal products (biologics, biologicals, or biopharmaceuticals) are a heterogeneous group of medicines produced by or extracted from living cells or organisms [4,231]. Biologics can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances, or they can be living entities such as cells and tissues [232,233]. The complexity and the size of different biologics vary. Biologics can be divided into three groups: 1) traditional biological products, 2) biotechnological products, and 3) advanced therapy medicinal products (Figure 5). The first group (traditional biological products) includes traditional vaccines, plasma-derived drugs, allergens, and proteins and carbohydrates isolated from animal-origin tissues or secretions. The second group of biotechnological products consists of medicines produced by recombinant DNA technology, a sophisticated technology by which deoxyribonucleic acid (DNA) from different species can be combined [32,234]. The third group is advanced therapy medicinal products (ATMP), including gene and cell therapy and tissue-engineered products.

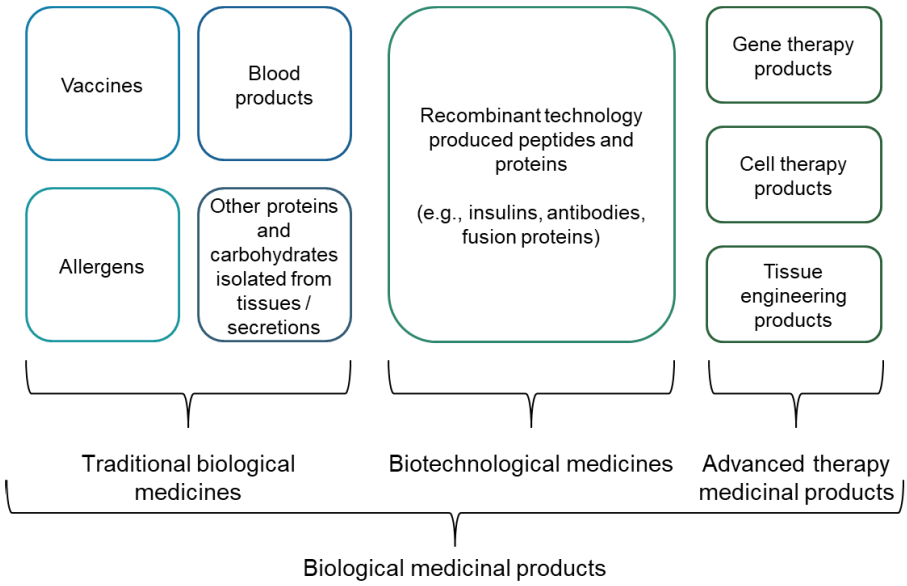

Figure 5. Categorisation of biological medicinal products and examples of groups of medicines under each category. Adopted from [232,233].

Although the first vaccines were developed more than a century ago [235], the development of biotechnology, followed by the launch of biotechnology products to the market in the 1980s, introduced their novel applications for many chronic difficult-to-treat conditions. Indeed, therapeutic proteins produced by biotechnological methods have revolutionised the treatment of chronic conditions such as cancer, rheumatic diseases, inflammatory bowel diseases, asthma, infertility, and diabetes [13]. In addition, biologics have recently been introduced to hyperlipidaemia, migraine, and various orphan diseases [236]. Moreover, the importance of biologics is expected to continue to grow in healthcare, as more than half of the new medicines are biologics, and the majority of current drug candidates in the research and development (R&D) pipeline come from biopharmaceutical companies [237,238].

2.3.1.1 Centralised authorisation procedure within the EU

All biotechnological and advanced therapy medicinal products in the EU are authorised via the centralised authorisation procedure [239]. This harmonised EU-wide procedure involves a single marketing authorisation application, a single evaluation and a single authorisation covering all EEA countries (i.e., EU member states and Iceland, Liechtenstein, and Norway) [13]. For biotechnological medicines, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) carries out the scientific evaluation of products' safety, efficacy, quality, and benefit-risk balance based on the marketing authorisation application [7]. The evaluation is carried out by the members of the relevant Committee (the rapporteur and the co-rapporteur) with their assessment teams from the national agency [240,241]. Fimea has had an active role in rapporteurships with a particular interest in biologics, generics, and new chemical entities. The CHMP's multidisciplinary expert working parties, such as the Biologics Working Party (BWP) and Biosimilar Medicinal Products Working Party (BMWP), and other EMA scientific committees, contribute to evaluating the marketing authorisation application [6,7]. If the product's benefits outweigh its risks, the CHMP may issue a favourable opinion [7]. Based on that evidence-informed opinion, the European Commission (EC) makes a legally binding decision on the marketing authorisation. However, other biologics (e.g., naturally derived biologics such as low-molecular-weight heparins) may be nationally authorised in the individual member states.

2.3.1.2 Production of biotechnological medicines and the batch variation

The active substances of biotechnological medicines are produced with cutting-edge technology in large and sophisticated cultures of cells modified by recombinant DNA technology [13]. Mammalian cells, such as Chinese hamster ovary (CHO) cells and bacteria or fungi, are used as a platform for producing biologics [242,243]. CHO cells are typically used to produce therapeutic proteins, as CHO cells can produce glycosylated proteins, and they can be optimised for high protein yield of good quality in a reasonable time [242,244]. Bacteria and fungi produce smaller biological molecules [243]. For example, the bacterium Escherichia coli is a host cell line in insulin production.

Because biologics' production takes place in living cells, it creates some minor variation (i.e., microheterogeneity) in the desired substance. Changes in cell culture conditions may substantially impact the biological substance's properties [13,242]. Thus, variation between batches of the same biological product is possible. The variation does not occur in the protein's amino acid sequence but most typically after protein synthesis in post-translational modifications such as glycosylation (Figure 6). Glycosylation refers to the enzymatic attachment of sugar molecules to a protein, which is vital for the functionality of certain biologics. This intermolecular variation typical for any biologics is called inherent microheterogeneity [13].

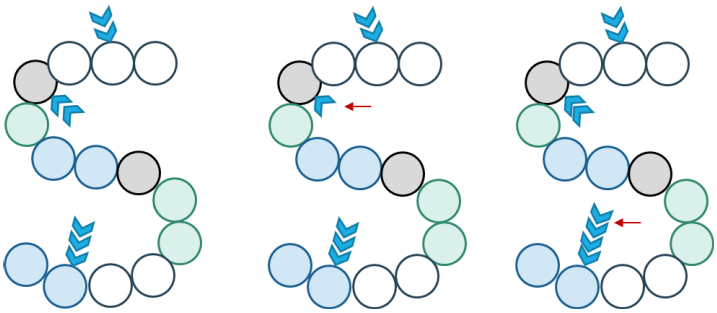

Figure 6. Batch variation of biological medicines. The primary amino acid structure, as well as the folding of the protein, are the same, but variation between batches may occur with, e.g., glycosylation. Adopted from [13].

The variation between production batches is particularly evident in connection with changes in the production process [10,13]. When the manufacturing process is changed, the manufacturer must demonstrate that the change does not alter the biological product's clinical performance (e.g., quality, safety, and efficacy) [10]. These comparability studies are performed several times during the biological product's life cycle due to, for example, process improvements, production relocation, or scale changes. For example, the production of

therapeutic monoclonal antibodies (MAbs) is subjected to changes demanding comparability studies an average of 1.8 times per year [245]. The scope of comparability studies depends on the extent of the change in the production process. International Conference on Harmonisation (ICH) guideline (Topic Q5E) has been issued for comparability studies [10].

The CHMP's multidisciplinary expert working parties, such as the BWP and BMWP, and other EMA scientific committees, contribute to the development of guidelines for the evaluation and development of biologics, including biosimilars [6,232].

2.3.1.3 Safety of biotechnological medicines in terms of adverse drug reactions (ADRs)

The most severe adverse drug reactions (ADRs) of biologics are related to an augmentation of their known pharmacological action, such as immunosuppression, cytokine release, or tumour lysis [246,247]. The known target of biologics enables a precise effect in the body, reducing the risk of ADRs. The most common ADRs related to administrating biologics are common infusion reactions and hypersensitivity reactions, which often appear as irritation at the administration site or systemic reactions such as fever, chills, nausea, and vomiting [248]. However, severe ADRs, such as an anaphylactic reaction, can also occur [249]. A specific unwanted reaction of biologics is an immune reaction, where the antibodies produced in the body bind to the biological molecule [34]. If these anti-drug antibodies (ADAs) neutralise the biological medicine, it will result in reduced or lost efficacy of the medication [34,248]. The solution in these situations can be increasing a dose or switching to another active substance to improve clinical outcomes.

2.3.1.4 Costs of biologics and potential factors contributing to their high prices

Biologics are expensive and involve high and ever-increasing costs to society, challenging the sustainability of healthcare [13,44,46,49]. In Europe, biologics caused 30% of total pharmaceutical expenditures in 2018 [250]. In the same year, eight biologics were among the top ten best-selling drugs globally [251]. Adalimumab has been the best-selling biologic for many years. In 2021 vaccines against the pandemic virus SARS-CoV-2, being biological products as well, stirred the statistics of top-selling drugs [252].

The production method and expensive production materials explain a small part of the high prices of biologics [242,253]. The impact of production costs on the prices of biologics has diminished as the size of production facilities has enlarged, and processes' productivity has been maximised by

optimising process steps to improve yield [242]. Product and process development, the need to cover the costs of failed R&D projects, and costly clinical trials have been communicated as major reasons for the high prices of biologics, although explicit evidence of the magnitude of these costs is lacking. However, it has been estimated that there is a 5-10-fold profit compared to production costs [238]. It is likely that the lack of proper price competition among biologics, even after the patent and data exclusivity, is the most important single factor contributing to their high prices [254].

2.3.2 SIMILAR BIOLOGICAL MEDICINAL PRODUCTS (BIOSIMILARS)

To curb increasing costs associated with biological treatments, new versions of biological medicine can be introduced to the market after the patent and data exclusivity of the original biological medicine have expired [13]. Biosimilar is a copy of an original biological medicine with an identical amino acid sequence and similar three-dimensional structure [5,13]. However, due to the heterogeneity induced by the biotechnological production process, different versions of the originator product, including its biosimilar copies, cannot be entirely identical. Thus, the "generic approach", i.e., demonstrating bioequivalence, is insufficient for biosimilar development, regulatory assessment, and authorisation [255].

New versions of already-known biological medicines can be developed in different parts of the world following very different standards [255]. Thus, the term "biosimilar" can have slightly different meanings in different jurisdictions. According to the WHO, only products developed according to its guideline or corresponding local guidelines (such as those in the EU or the U.S.) can be called biosimilars [256]. However, other copies of the originator products in low or middle-income countries are also called biosimilars [257].

2.3.2.1 Definitions of biosimilars and their legislative frameworks in the EU and the U.S.

In the EU, a similar biological medicinal product (biosimilar) is "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established" [5].

The EU became the pioneer of biosimilar legislation worldwide when it introduced an abbreviated pathway for assessing and approving biosimilars in the early 2000s (Figure 7) [13]. The amendments to the Medicines Directive (2001/83/EC) in 2004 made it possible to license biosimilars in the EU [231].

Since the EU legislative framework was enacted, the EMA has issued several general and drug group-specific guidelines for the development and assessment of biosimilars (Figure 7). Over the years, it has been possible to simplify guidelines as the knowledge and experience of biosimilars have accumulated among the regulators and developers, and the analytical methods have improved.

The marketing authorisation applications of biosimilars often contain reports of switching studies. These studies are evaluated during the evaluation of marketing authorisation application, and the scientific opinion is expressed in the European Public Assessment Report (EPAR) [258]. Nevertheless, the EU does not formally address the interchangeability of biosimilars during the centralised marketing authorisation procedure [13]. The policy is based on the principle of subsidiarity defined in Article 5(3) of the Treaty on European Union [259]. It aims to ensure that decisions are taken at the closest possible level to the citizen unless the specific area is not within the exclusive competence of the EU [260]. In general, the protection and improvement of health are within the competence of EU member states. However, it is not always feasible to perform all health-related tasks separately in all member states, and high-level health protection may require collaboration measures on issues that are relevant for all member states, such as improving public health, preventing illness and diseases, and obviating sources of danger to human health [261]. Currently, the EU sets standard criteria for regulating medicines, including manufacturing, safety, efficacy, and post-marketing surveillance [4]. In addition, the regulation and licensing of innovative medicines are performed mainly by the EU. Instead, the supervision and guidance of the use of medicines remain within the competence of member states [262]. This also covers the practices of switching and substitution [13].

This division of duties regarding interchangeability has faced criticism as it has led to heterogeneous interpretations of the interchangeability of biosimilars across Europe, thus confusing both patients and HCPs [263]. In the autumn of 2022, EMA and the Heads of Medicines Agencies (HMA) published a joint statement on interchangeability to harmonise the European approach [264]. The statement confirmed that EU-approved biosimilars are interchangeable with a reference medicine or with other biosimilars of the same reference product.

The evaluation of the U.S. biosimilars is carried out by the Food and Drug Administration (FDA). The licensure of biosimilars was enabled by Biologics Price Competition and Innovation Act (BPCI Act), approved in 2009 (Figure 7). Since BPCI Act was enacted, the FDA has published several guidance documents for the industry on biosimilars and interchangeable products [265].

In the U.S., there are two levels of biosimilarity [266,267]. First, the biosimilar can be licensed via an abbreviated licensure pathway [196]. That refers to the potential to utilise data obtained from the reference product, aiming at a shorter and less costly process in biosimilar development. Further,

the biosimilar product can be designated interchangeable if it meets additional requirements. These specific clinical studies are intended to demonstrate that an interchangeable product is expected to produce the same clinical outcome as its reference product in any given patient, and the switches do not generate any risks to the safety or efficacy of the treatment [266,268]. Interchangeability is a U.S.-only designation, meaning a pharmacist may substitute a biosimilar product for the reference product without the prescriber's intervention [266,267]. Although a biosimilar product has the interchangeability designation, the final decision on its substitution status remains at the state level [267]. By the end of July 2022, three biosimilar brands had obtained interchangeability status in the U.S. [269].

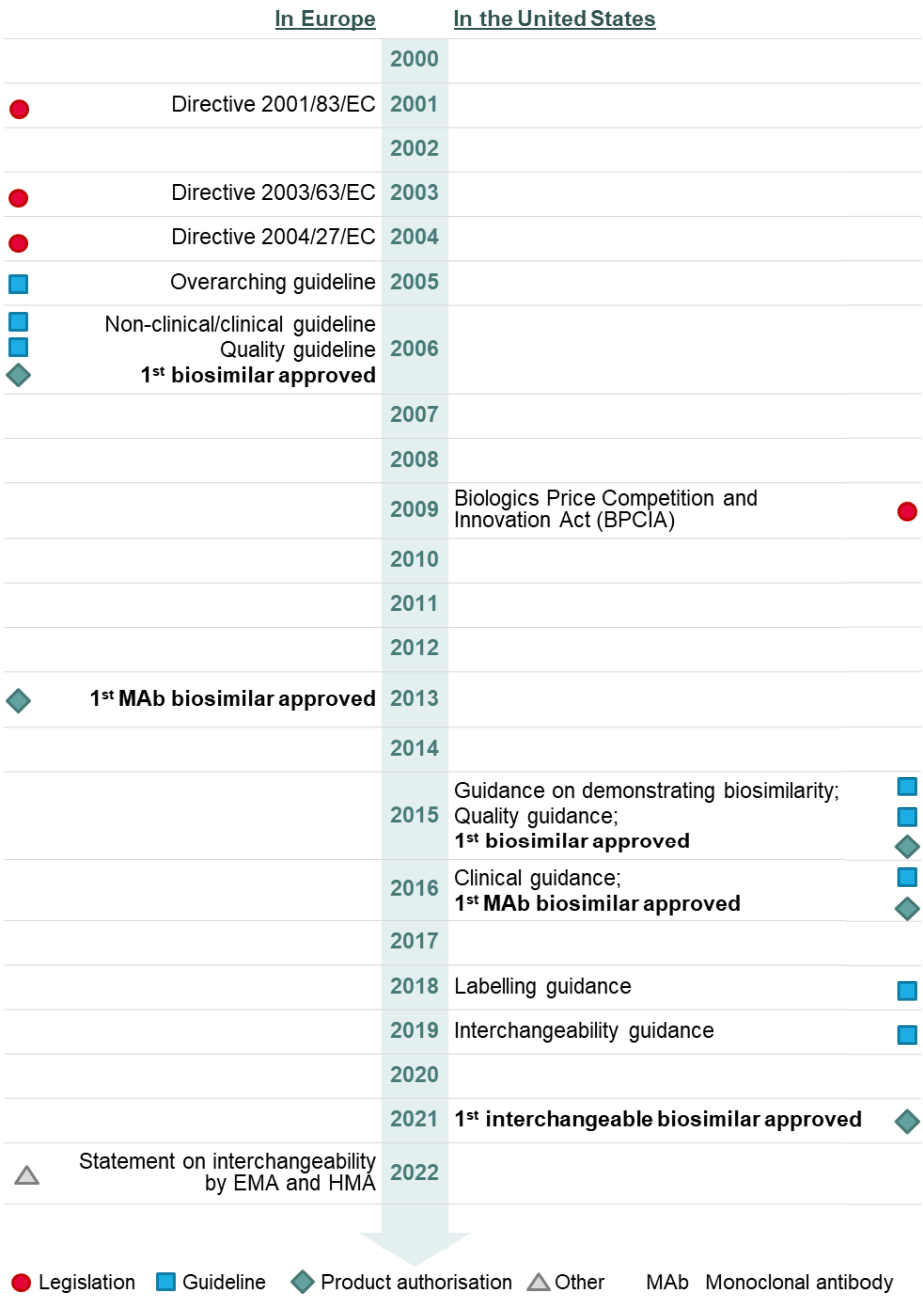

Figure 7. Selected regulatory milestones regarding biosimilars in the EU and the U.S [4,5,190,231,236,264–266,269–273].

2.3.2.2 Biosimilar development in the European biosimilar framework

The safety and efficacy of the active substance of the original biological product are studied and demonstrated by comprehensive and sound non-clinical and clinical studies (Figure 8) [4,232]. In contrast, the goal of biosimilar development is to demonstrate the similarity of the product to the reference product by extensive comparability studies using state-of-the-art analytical tests and suitable in vitro non-clinical and clinical studies [5]. After analytical and functional studies, clinical data are employed to confirm the biosimilarity (Figure 8).

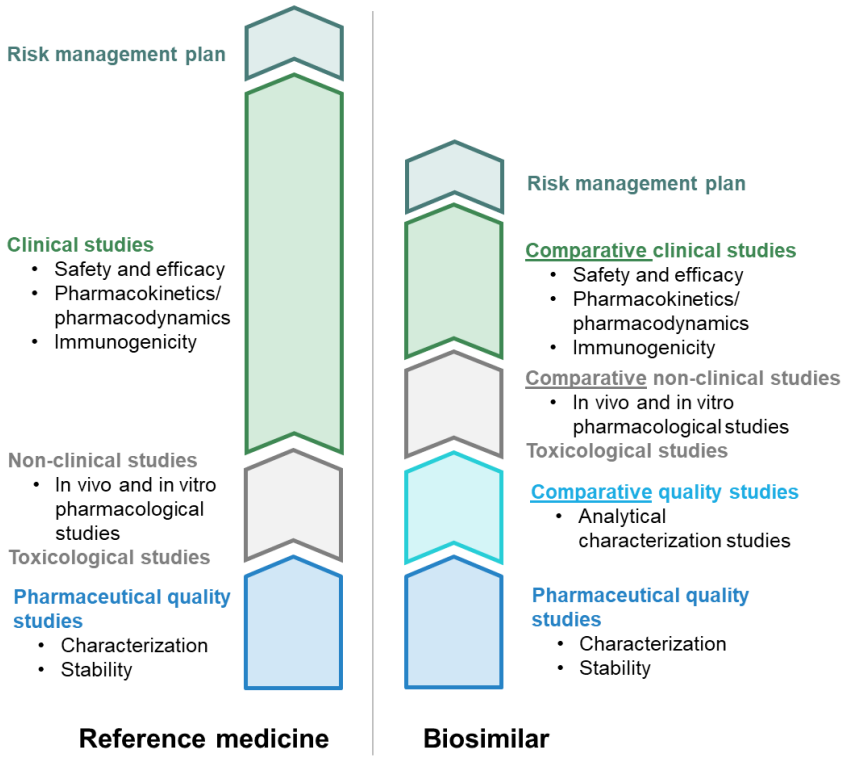

Figure 8. Comparison of the documentation required for the marketing authorisation application of a reference biological medicine and its biosimilar. Adapted from [13,190,244,274,275].

To overcome this comparison challenge, a company developing a biosimilar product needs to make a comprehensive investigation of the features called critical quality attributes (CQAs) of the reference product [244,274,276]. These CQAs have a direct impact on the safety and efficacy of the product. The understanding of variation in batches of reference product gives the limits for

acceptable variation of the biosimilar. Developing a biosimilar product with better clinical features than a reference product should not be an intended goal. If a biosimilar product is intended for self-administration, its administration device should be tested for usability in the marketing authorisation process [16].

Like all biologics, biosimilars may present differences because of post-translational modifications (such as glycosylation and phosphorylation) and different manufacturing processes [13]. Thus, comparability exercises are needed routinely in later phases of the biosimilar lifecycle. However, the demonstration of the biosimilarity to the reference product does not have to be repeated after the biosimilar product has been authorised [274].

2.3.2.3 Pharmacovigilance and post-marketing surveillance in the EU

With the marketing authorisation application, the applicant must submit a risk management plan (RMP) for each new medicine (Figure 8) [13,22,277]. The product-specific RMP includes a pharmacovigilance plan and a plan for managing possible product-related risks. The biosimilar RMP lean on the knowledge and experience obtained with the reference product [13]. Patient registers, additional educational materials and patient alert cards are examples of measures to detect and minimise risks related to a new product or a product with limited experience [277]. One of the mandatory risk minimisation measures is to display a black inverted triangle in the summary of the product characteristics (SmPC) and the package leaflets. The black inverted triangle is a designation for additional monitoring, a signal for HCPs and patients to report any suspected adverse drug reactions (ADRs) at a low threshold [22,278].

After the marketing authorisation is granted, the marketing authorisation holder must continuously monitor the safety of any biological medicines (Directive 2010/84/EU, 2010). For some pharmaceutical products, conducting a post-authorisation safety study (PASS) is also mandatory. The need to conduct the PASS is set by the predetermined criteria [22,279]. For biosimilars, it is required if it is required for their reference product [13].

Companies that are marketing biosimilars (or any biological medicine) must collect spontaneous reports on suspected ADRs [22,280]. In periodic safety update reports (PSURs), companies must summarise the ADRs and other relevant data concerning possible adverse events for regulators. If any safety signals are suspected, EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) evaluates the data and determines further actions [6].

Considering batch variation is an inherent characteristic of all biological medicines, it is essential that an HCP or a patient provide both the trade name and the batch number when reporting suspected ADR of biological medicine [13]. The identifiability of the biological product (trade name), including biosimilars, has been high in reports. Still, the batch numbers have been

lacking in the reports regardless the reported product has been an originator or a biosimilar [281].

According to the safety data obtained so far, the ADR profiles of EU-approved biosimilars are the same as those of their reference products [258]. No new ADRs have been added to the SmPCs, and no biosimilar products have been withdrawn from the market due to safety reasons.

2.3.2.4 *Tricky jungle of terminology on switching and substituting biologics*

According to European regulators, interchangeability refers to "the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect" [13,264]. Interchangeable biological medicines can be switched by the prescriber or substituted at the pharmacy [13]. Different terms can be used when a patient's biological treatment is changed from one product to another (Figure 9).

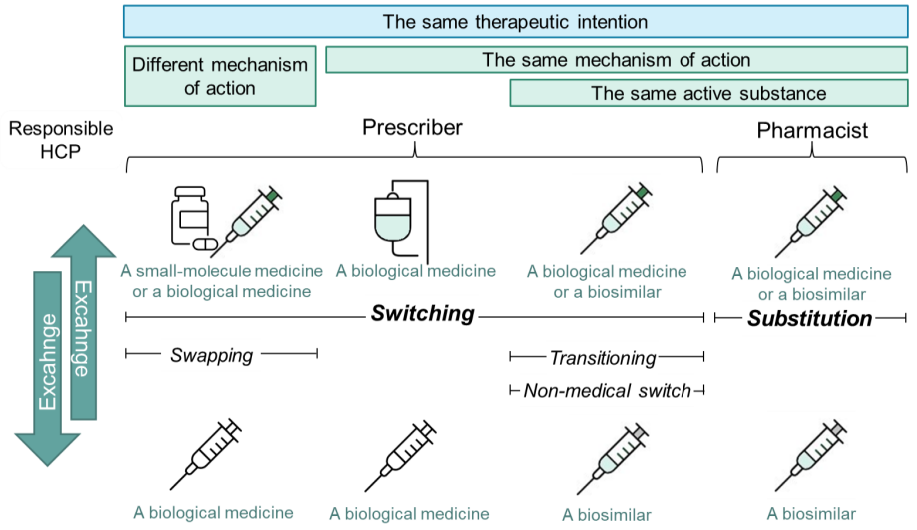

Figure 9. Key terminology on the exchange between biological medicines including biosimilars [13,282–284].

Switching can be carried out in various ways (Figure 9). It can mean an exchange made by a prescriber between two medicinal products intended for the same therapeutic purpose [13]. This may mean changing the active substance to another active substance (for example, continuing infliximab treatment with adalimumab) or between two interchangeable products.

Switching of two interchangeable products refers to an exchange made by a prescriber between two different products with the same active substances, as happens if a prescriber changes the original biological product used in the patient's treatment to a biosimilar. The latter has also been called **non-medical switching** (NMS) in the literature when it has been wanted to emphasise the financial motive for switching, usually mandated by national guidelines [20,285]. Further, it has been suggested that switching between products with the same active substance should be called **transitioning** [284]. If a prescriber changes a medicine to another medicine that belongs to a different product class (i.e., medicine with another mechanism of action), the action is called **swapping** [282,283]. For example, changing the patient's medication from adalimumab to vedolizumab can be considered swapping. All the terms mentioned earlier refer to situations involving the prescriber. If the change is made without the presence of a prescriber in the dispensing phase, it is called (automatic) **substitution** of biologics, and it is conducted by a pharmacist (Figure 9) [13].

2.3.2.5 Safety, efficacy, and quality of biosimilars

Biosimilars' safety, efficacy, and quality are studied and evaluated in the marketing authorisation process [13]. In fact, an analysis of FDA-approved biosimilar documentation showed that biosimilars are often evaluated in longer and larger trials than new medical agents [286]. Despite the comprehensive evaluation of the totality of the evidence in the marketing authorisation process, doubts about biosimilars' safety, efficacy, and quality have been cast over time [255,287,288].

When the experience of biosimilar use increased, the debate shifted to the safety of switching. For example, in 2017, a global organisation representing the innovative pharmaceutical industry warned in its position paper about the switching-related risk for immunogenicity [289]. Immunogenicity, an inherent feature of biologics, leads to the formation of anti-drug antibodies (ADAs) that rarely can result in clinically meaningful effects, such as safety issues or loss of efficacy to the certain biological treatment [34]. One of the turning points in the scientific discussion was the NOR-SWITCH study (and its extensions), a randomised, double-blinded study on infliximab treatment with a reference product or a biosimilar in Norway [290–292]. No differences in safety or efficacy attributes were detected in the trials. Two Danish nationwide register studies on infliximab and etanercept had similar results: no clinically significant changes in patient care were observed [293,294].

Several systematic reviews on interchangeability, and/or safety, efficacy and/or immunogenicity of switching have been published over time (e.g., [285,295,296]). Interestingly, the authors of two different systematic reviews conducted with almost the same inclusion criteria came up with similar results but different conclusions [285,295]. Cohen et al., sponsored by the biosimilar

industry, viewed that the switching is not related to safety or inefficacy issues, whereas McKinnon et al., sponsored by a manufacturer of originator (reference) products, concluded that there were still gaps in the evidence of the safety of switching [285,295]. The differences in the interpretation of the results in these studies might be related to the heterogeneity of study designs but also the authors' affiliations or financial commitments [285,295,296].

A recent systematic review on switching from a reference product to a biosimilar or *vice versa* collected the literature up to June 2018 [296]. Based on the identified 178 studies, the authors concluded that no evidence was found that replacing a reference product with its biosimilar or *vice versa* would generate any major safety, efficacy, or immunogenicity issues. However, the authors noted that in several studies, discontinuation of the treatment after switching may be related to the nocebo effect. Within the nocebo effect, patients' negative beliefs, potentially amplified by negative perceptions of an HCP, can induce subjective adverse events or other unwanted treatment outcomes that may lead to stopping the medicine taking [297]. Further, the limited evidence on multiple switches and switches from a biosimilar to another biosimilar was prominent in the literature published before June 2018 [296].

In 2022, Cohen et al. published an article summarising the scientific evidence on switches between biosimilars for the same reference product [298]. Of 23 studies that covered more than 3500 patients, the authors did not detect reduced efficacy or increased frequency of adverse events (such as ADRs or hospitalisation). In another recent systematic review, the re-transitioning rate (switching back to the reference product) of patients with TNF-alpha inhibitor treatment was 7.6% [299]. Based on their results, Meijboom et al. (2022) concluded that retransition risk might be reduced if transitioned patients are with stable disease, extra laboratory monitoring is implemented, and the possibility of retransitions is not actively offered to patients [299].

The short- and long-term safety and interchangeability of monoclonal antibody (MAb) and fusion protein biosimilars were analysed from European Public Assessment Reports (EPARs) and EMA's post-marketing safety surveillance reports [258]. The analysis did not reveal any safety concerns related to switching. The safety and immunogenicity profiles of MAbs and fusion proteins remained similar upon switching.

2.3.2.6 Savings generated by biosimilar uptake

The development of biosimilars is attractive to many pharmaceutical companies [275]. This is because the development of biosimilars may gain potential savings in R&D costs compared to the reference products. It is estimated that developing a biosimilar product takes a minimum of four years less than developing an originator product [47,275]. Furthermore, no similar extensive clinical trials are needed to demonstrate the safety and efficacy of

the active substance as with the originator [270,274]. Thus, biosimilars can be sold at a lower price than the originator product. Having biosimilars on the market can lead to price competition between products leading to cost savings provided that biosimilars are utilised.

It is challenging to make reliable comparisons between countries on cost savings gained by using biosimilars because of the differences in health systems and legislative frameworks. The health insurance and drug reimbursement systems, tendering, and positions of key opinion leaders and stakeholders are factors that may, among other factors, influence biosimilar use and savings [300]. Positive or negative experiences from other countries can influence interest in introducing and promoting biosimilar use. For example, Norway reported almost 80% savings in direct drug costs with the infliximab biosimilar in 2014 [301]. On the other hand, doubts that biosimilar use will increase healthcare visits and other costs have been raised, resulting in a reduction of potential savings [302]. However, nationwide register studies in Denmark have shown that mandatory switching from a reference product to its biosimilar did not increase costs or healthcare use among patients within etanercept or infliximab treatment [303,304].

In a Finnish study, patients were switched from the originator infliximab to biosimilar, and their health-related quality of life (HRQoL), evaluation of disease activity with disease-specific measures and healthcare costs were studied [305]. A one-year follow-up did not show differences in HRQoL or disease activity. Still, direct infliximab costs were 35% lower with a biosimilar product than the originator product.

2.3.2.7 Me-too products and biobetters

A biological product that is not the first-in-class can enter the market either by a biosimilar procedure, resulting in practically a copy of the reference product or with a complete marketing authorisation procedure [255]. Latter is called a me-too product. These me-too medicines are stand-alone products that are not compared in the marketing authorisation process with any biological products of the same category [255,306]. Tinzaparin-containing Innohep® and insulin lispro product Liprolog® are examples of biological me-too products [307,308]. Possible studies on switching between me-too and first-in-class products are usually conducted locally after the marketing authorisation approval [255].

The properties of the new product can also be improved compared to the first-in-class product [255]. For example, the new product can be formulated so that it can be administered less often or does not require intravenous dosing. Also, other pharmaceutical, pharmacologic, or therapeutic properties such as higher activity, enhanced stability, fewer side effects, or lower immunogenicity may be the target of product improvement [255,306,309,310]. These so-called biobetters or next-generation medicines

have been developed for many active substances. For instance, for trastuzumab used for breast and stomach cancer, Roche developed a product that can be administered subcutaneously, in which case no vascular connection is needed [310]. Further, pegfilgrastim is an improved form of filgrastim, as it can be administered less frequently [309].

Biobetters and me-too products need original R&D, increasing their development costs [255,306]. Despite their prices, the uptake of biobetters and me-too products is important in limiting the uptake of biosimilars and shortening their lifecycle [310]. If the patients' biological treatments are swapped to another drug class or non-interchangeable medicine, biosimilar-induced savings are not achieved.

However, a biobetter is optional also for biosimilars after granting the marketing authorisation. For example, Celltrion's biosimilar Remsima® has been granted marketing authorisation in the biosimilar framework. Remsima®'s reference product is Remicade®. After the marketing authorisation process, the life cycle of the biosimilar is independent, and changes made to the biosimilar product are no longer compared to the reference product but to the biosimilar itself. A biobetter has been developed for Remsima®, in which, unlike other infliximab preparations, Remsima® can be administered as a subcutaneous injection [236].

2.3.2.8 Automatic substitution of biologics – international legislation

Automatic substitution is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at a pharmacy without consulting the prescriber (Figure 9) [13]. With biological medicines, substitution can occur in theory from a reference medicine to its biosimilar or *vice versa* or between biosimilars of the same reference products. A study that collected global data on substitution policies of biologics in spring of 2017 summarised that in most countries, substitution was forbidden [311].

Australia was the first country to establish clear guidelines and enable substitution of biologics in pharmacies in 2015 [312]. If the biological medicine is deemed substitutable in Australia, a pharmacist can decide what product is dispensed to a patient if the prescriber has not ticked the "brand substitution is not permitted" box in the prescription [313].

France has been one of the few European countries with legislation on biologics substitution since 2014 [311]. However, the national regulation was not implemented into practice in the 2010s. The French legislation allowed substitution for treatment-naïve patients. Since Larkin et al. study, several European countries have introduced or plan to introduce the substitution of biological medicines [263].

2.3.3 HEALTHCARE PROFESSIONALS' AND PATIENTS' PERCEPTIONS OF BIOSIMILARS AND SOURCES OF INFORMATION

The perceptions of HCPs and patients of biosimilars have been studied over time in different settings. According to published studies, prescribers have variable perceptions of biosimilars [50]. This may be due to their knowledge of biologics in general and biosimilars in particular, which has been found to vary as well [50,314]. Prescribers gain biosimilar knowledge via scientific publications, professional societies, and pharmaceutical companies. Prescribers' most important source of biosimilar information has been found to be the originator industry [315]. This may explain their hesitancy towards biosimilars.

One of the challenges in the biosimilar concept for some prescribers is that they are used to reading reports on randomised clinical trials (RCTs) assessing the efficacy and safety of an active substance, whereas comparative clinical studies aiming to demonstrate similarity and not safety and efficacy *per se* are mainly conducted for biosimilars [13,190,274,275]. Therefore, the concept of biosimilars and their development process can be confusing and easily misunderstood [316]. The difference between efficacy studies conducted for medicines with new active substances and those with biosimilars is in the clinical endpoints; The former is based on "hard endpoints," such as time to tumour progression whereas disease-specific sensitive endpoints are preferred in studies aiming to demonstrate the similarity between the originator and its biosimilars [270].

The impact of pharmaceutical companies on providing information, in other words, marketing their products, is remarkable. Their information may bias prescribers' and other HCPs' knowledge and understanding of the therapeutic value of different treatment options [80,82–84,317]. In a Finnish study, the attitude of physicians was found to be primarily positive towards biosimilars, but their positive attitude did not reflect in the prescribing practices, even though most of the interviewed physicians considered biosimilars equal to their reference products [315]. The treatment naïve patients have been considered the most suitable for biosimilar prescribing, indicating a reluctance to switch patients from the originator product to a biosimilar [50,315].

The perceptions of other HCPs of biosimilars have been found to be in line with the perceptions of the prescribers [50,318]. A recent systematic review of pharmacists' perceptions of biosimilars summarised a wide variation in their attitudes and perceptions [319]. Altogether 22 studies from different jurisdictions were included, and the data of the studies were collected between 2012 and 2021. The systematic review found that pharmacists' knowledge of biosimilars was reported good, considerable, above average, or excellent for at least half of the respondents in seven out of 19 studies assessing pharmacists' knowledge, awareness, or familiarity with biosimilars. Pharmacists' primary

sources of information about biosimilars were scientific publications, pharmaceutical companies, colleagues, product information, regulatory authorities and commercial pharmaceutical or clinical databases [319].

Nurses' perceptions of biosimilars have been mainly studied in connection with other HCPs [318]. Due to limited evidence on nurses' insights, any conclusions on their perceptions of biosimilars should not be drawn. Despite the lack of studies on nurses' perceptions, several studies evaluate nurses' and patients' preferences for administration devices of biosimilars [320–323]. These usability studies are typically conducted by pharmaceutical companies, resulting in potential publication bias. It is possible that only favourable results for administration devices marketed by a company are published [317].

There is little research evidence on patient-reported switching experiences [324]. A recent study among Danish patients pointed out the need for patient-centred information on the safety, efficacy, and use of biosimilars [325]. Patients using reference products were more suspicious of biosimilars than patients already on a biosimilar treatment. A recent study conducted in Finland also reported a more positive attitude towards biosimilars among biosimilar users [326].

2.3.4 MEDICINES AUTHORITIES' POSITIONS TO BIOSIMILARS' INTERCHANGEABILITY IN EUROPE

Within the EU, EMA's first official position on the interchangeability of biosimilars was recently announced in a joint statement with HMA [264]. The statement concluded that biosimilars with EU approval are interchangeable from a scientific viewpoint, meaning that a biosimilar can be used instead of its reference product or another biosimilar of the same reference product or *vice versa*. Before declaring the position on interchangeability on the European level, there has been a need for EU member states to declare their positions and set the appropriate regulation.

Barbier et al. (2022) investigated national medicines agencies' regulatory information and position statements on biosimilars covering 31 European countries [263]. The study conducted in 2019 revealed the lack of national positions and information sharing regarding biosimilars. About two-thirds of the national medicine agencies provided information on biosimilars on their websites. Interestingly, the authors pointed out that the agencies that were actively involved in biosimilar issues on the EU level generally provided more detailed biosimilar information nationally. Further, the national medicines agency had taken a position on the interchangeability, switching, or substitution of biologics in 8, 12, and 10 countries, respectively. Endorsing interchangeability positions were reported in five out of eight countries: Croatia, Finland, France, Italy, and the Netherlands. Physician-led switches were advocated in Belgium, Denmark, Finland, Germany, Italy, Norway, Portugal, and the Netherlands. Ten national medicines agencies provided their

position regarding the automatic substitution of biologics. Most of the agencies did not allow or endorse automatic substitution.

In Finland, the Finnish Medicines Agency Fimea has already stated its position on biosimilars' interchangeability in 2015 [327]. According to Fimea's statement, biosimilars are interchangeable with their reference products under the supervision of an HCP. However, Fimea's statement does not address the substitution of biologics in community pharmacies, nor does the recent EMA's and HMA's joint statement [264,327].

2.3.5 BIOSIMILARS IN FINLAND

In Finland, biologics are dispensed and used both in hospitals and outpatient care. These two settings have separate funding mechanisms. Most of the administered biologics in hospitals are intravenous and/or monoclonal antibodies (MAbs) for anti-cancer treatments [328]. Most self-injectable biologics are reimbursed by public health insurance and dispensed from community pharmacies for outpatient care. The prices of reimbursable biologics are highly regulated. The Pharmaceuticals Pricing Board sets the maximum wholesale prices for reimbursable medicinal products in outpatient care [26,220,329]. The retail prices of reimbursable prescription medicines are based on maximum wholesale prices, whereas pharmaceutical companies can freely set the price of non-reimbursable medicines. Since 2017, each originator's first biosimilar product entering the market must be priced at a maximum of 70% of the reference product's price to gain reimbursable status. The Pharmaceuticals Pricing Board re-evaluates the reasonable wholesale price for the reference product after the biosimilar has entered the reimbursement system [26,220]. The prices of prescription medicines are the same in all Finnish community pharmacies.

As biologics, biosimilars are available in outpatient and inpatient settings in Finland. At the end of July 2022, of 70 biosimilars authorised in the EU, 56% (n=39) were on the market in Finland (Figure 10, Appendix 1). Further, two nationally authorised enoxaparin sodium biosimilars were on the market, resulting in a total of 41 biosimilars available at that time in Finland. Altogether 28 biosimilars of those authorised within the EU were never introduced in Finland, and three biosimilars (of the active substance being epoetin alfa, pegfilgrastim, and trastuzumab) had exited the Finnish market (not presented in Figure 10). It has been suggested that Finland is not an attractive market for biosimilar companies [330]. However, the difference may at least partly be explained by the delays in the market entry to the local market (Figure 11). The delays can be due to differences in the duration of patent and data protection [275,331]. Further, some pharmaceutical companies may submit duplicate marketing authorisation applications for their very same biosimilars to obtain different brand names for different

markets in Europe [274]. Therefore, not all these biosimilar brands are probably ever entering the Finnish market.

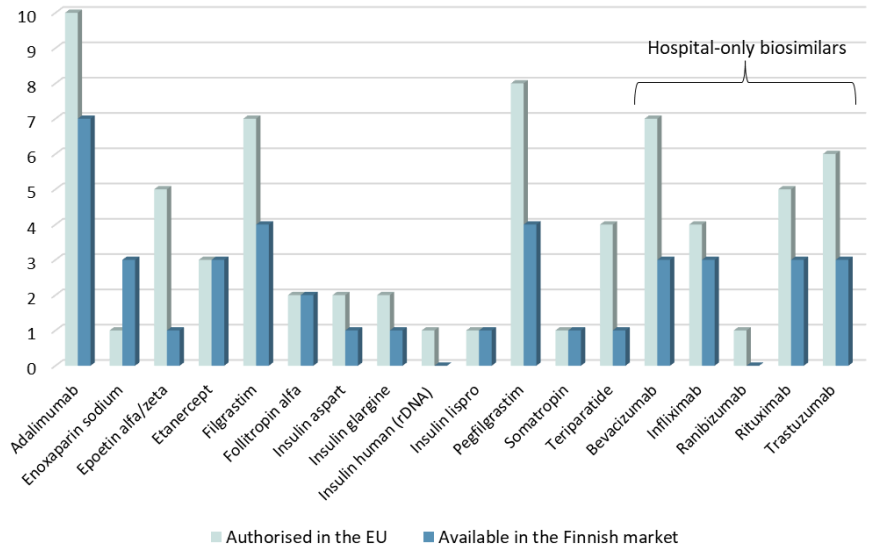

Figure 10. The number of centrally authorised biosimilars (n=70) in the EU and their availability in the Finnish market by active substance in July 2022. In addition, two enoxaparin sodium biosimilars with national authorisation are on the Finnish market giving three enoxaparin sodium biosimilars in total. For infliximab biosimilar, there is also a product that can be administered subcutaneously outside a hospital. Please see Appendix 1 for the data collection description.

In 2020, biological medicines with more than one product on the Finnish market (i.e., at least one biosimilar on the market) were reimbursed for about 225.000 patients [48]. The reimbursed costs were 174,4 million euros, and out-of-pocket costs were 15,4 million euros. Most of these patients on biological treatment were reimbursed for reference products as only epoetin, filgrastim, insulin lispro, and somatropin biosimilars were prescribed more frequently than their reference products. In addition to these biosimilars, treatment was initiated with a biosimilar for most patients prescribed etanercept and adalimumab.

Systematic switches are already carried out in Finnish hospitals directed by drug formularies [332]. The drug formulary is based on expert opinions and tendering and has brought remarkable savings in drug costs at the hospital level [332,333]. As described by Ahomäki et al. (2019), it is possible that, because of tendering, the reference product is lower-priced product and chosen for the hospital's formulary [332]. However, there are hospital-

administered biosimilars among authorised biosimilars that have not been brought to market in Finland (Figure 10). It should also be noted that the hospital's formulary does not directly control the use of medicines or their prices in outpatient care in Finland.

The price differences between biosimilars and their reference products are still remarkable. Searches from two Finnish databases in August 2022 revealed a two-fold price difference in wholesale prices of two adalimumab products (Table 6) [334,335]. Although the databases did not provide consumption data, based on the number of adalimumab reference product prescriptions in 2020 (Saastamoinen et al., 2021), one can assume that there is room for improvement in the cost-effectiveness of prescribing in Finland.

Table 6. *An example of two adalimumab products and their wholesale price, the price for the society (reimbursement) and the reimbursed price for a patient with a rheumatic disease (reimbursement code 313). The information is extracted from the Social Insurance Institution's medicine search and the reimbursement counter provided by the Association of Finnish Pharmacies on August 9, 2022* [334,335].

Product (VNR)	Package type and size	Wholesale price (€)	Reimbursement (€) *	Reimbursed price (€) **
Humira® (477362)	40 mg x 2 Prefilled pen	705.82	283.28	424.93
Yuflyma® (594328)	40 mg x 2 Prefilled pen	346.09	139.39	209.09

VNR= Nordic article number; *Including the reimbursement of the dispensing fee;
** Including reimbursed dispensing fee

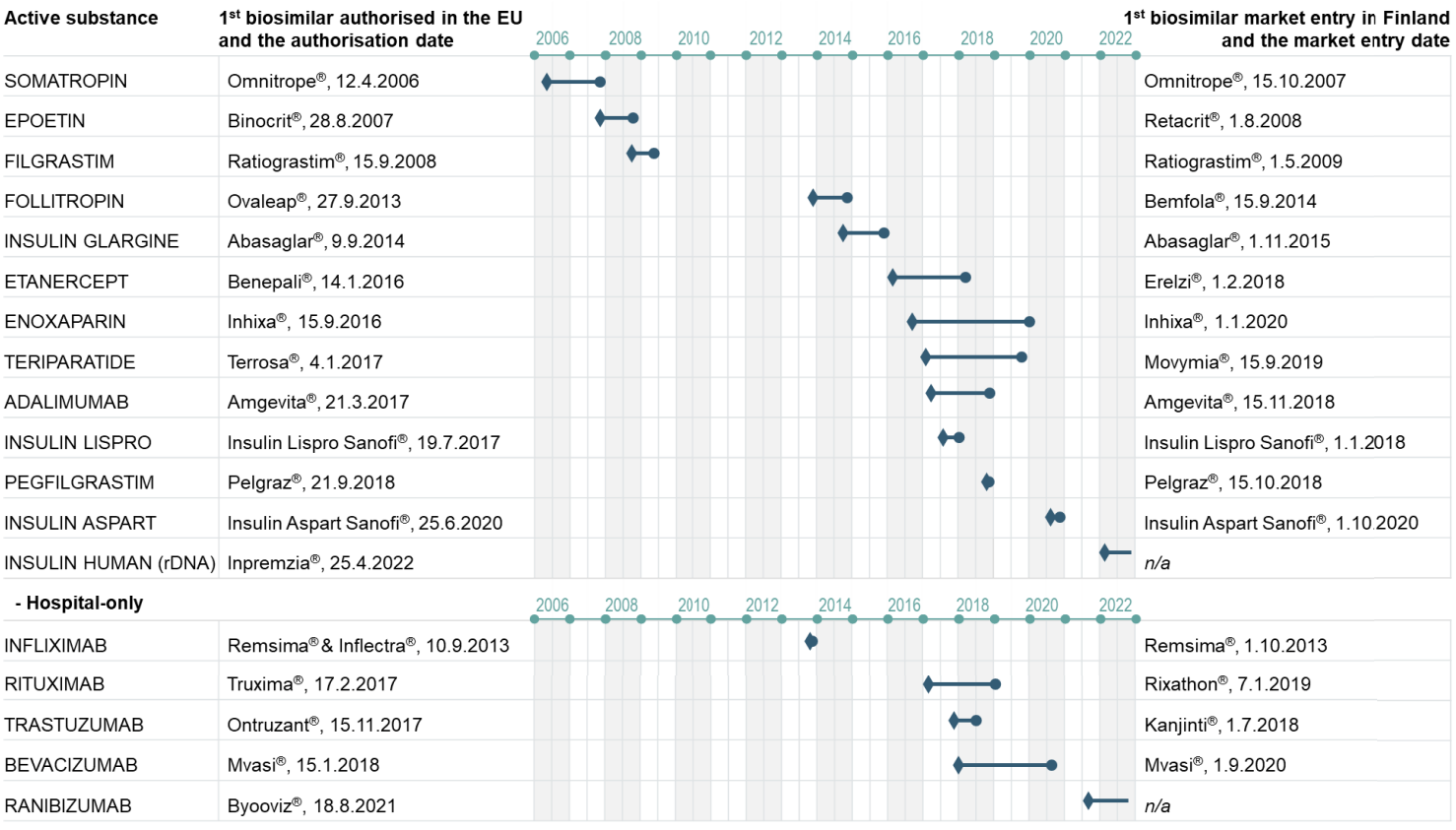

Figure 11. Visualisation of the biosimilar authorisation in the EU and the delay in the market entry in Finland after the EU authorisation. Please see Appendix 1 for the data collection description. For infliximab biosimilar, there is also a product that can be administered subcutaneously outside a hospital.

2.3.5.1 The objectives and measures to enhance biosimilar use in Finland

In 2016, the Council for Choices in Health Care in Finland (COHERE) outlined the principles for service choices of publicly funded services being 1) the significance of the health problem, 2) medical justification, and 3) ethics and economics [336]. Based on the principles, the most cost-effective option should be chosen from equally effective and safe health interventions addressing the same health problem. Applying the principles, COHERE Finland recommended that biosimilars be part of the publicly funded range of healthcare services following the principle of total expenditures [336].

In the Rational Pharmacotherapy Action Plan, the promotion of the use of biosimilars in outpatient care was among the very first actions implemented [24]. Both information and regulatory guidance were used. Information guidance introduced 1) an operating model on safe switching for healthcare organisations [337] and 2) basic information about biosimilars for patients [338]. The regulatory level guidance was implemented as an amendment to the Decree on Prescribing Medicines (2010/1088) by the Ministry of Social Affairs and Health [339]. According to the amendment, the prescriber is obliged to prescribe a lower priced, comparable alternative of biological medicine, and if not complying with this guidance, to justify the other choice in the patient records. This amendment has been in force since January 2017 [339].

While preparing the Rational Pharmacotherapy Action Plan, it was already estimated that the regulatory changes and information guidance implemented may not be sufficient to make any fast changes in biosimilar prescribing practices in outpatient settings [340]. According to a study by the Finnish Medicines Agency Fimea in 2018, the prescribers did not consider prescribing regulations sufficiently binding [315]. The study also found that if the physicians regarded price differences between the originator biologic and the biosimilar as too small, their willingness to prescribe biosimilars was reduced.

In 2020, the Social Insurance Institution sent a positive feedback letter to all doctors whose biosimilar prescriptions were filled in 2019 in Finland [48]. The positive feedback aimed to initiate a discussion about biosimilars and their prescribing. Thus, the letter was also published in the Finnish Medical Journal [341]. However, the feedback letter did not effectively affect prescribing of biosimilars [48]. The suggested reasons for the letter's ineffectiveness were that it did not seek to change doctors' prescribing practices and was not sufficiently focused on certain medicines. The prescribing feedback was repeated in 2022, targeting the guidance for those prescribers who had prescribed a biological product for which a lower-priced biosimilar would have been available in 2021 [342]. The results from the recent feedback letter have not been published to date.

2.4 SUMMARY OF KEY FINDINGS OF THE LITERATURE

- Rational pharmacotherapy is a complex concept aiming at effective, safe, cost-effective, high-quality, and equitable use of medicines. However, several factors can compromise rational and responsible prescribing and use of medicines. Over the years, more attention has been paid to the costs of medical therapies as more expensive medicines have entered the market. One factor compromising cost-effectiveness is the use of expensive brand medicines, although lower-priced medicines with similar efficacy, safety and quality would be available.

- Rational use of medicines has been promoted by long-term rational pharmacotherapy action plans in Finland. The most recent action plans have emphasised partnership and patient participation in medical therapy. In addition, influencing prescribing and use of medicines, identifying pharmacies as part of the health services system, and various medicines savings programs have been implemented. One of the most important initiatives to control drug costs was introducing generic substitution in the early 2000s. The practice was supplemented with a reference price system in 2009.

- Biologics are a versatile medicine group that strains healthcare budgets due to their exclusive prices and widespread use. However, their introduction has changed the treatment outcomes of many patients with severe and chronic diseases.

- Biosimilars approved in the EU are interchangeable with their reference product and another biosimilar of the same reference product and *vice versa*. Although biosimilars cannot be considered generic medicines due to their complex structure, the development philosophy between generic medicines and biosimilars have similar features.

- The uptake of biosimilars has been modest or even slow. Marketing efforts by the originator pharmaceutical industry, the way how prescribers are used to read the scientific publications based on randomised controlled clinical drug trials and the lack of economic incentives may increase the resistance to exchange patients' medication for lower-priced interchangeable biologics. Thus, new strategies to increase the uptake of biosimilars are needed.

3 AIMS OF THE STUDY

Biological medicines (biologics) have significantly improved treatment results in many severe chronic diseases. The use of biologics is increasing fast in both inpatient and outpatient care. Because biologics are expensive, they have challenged public medicine budgets in many countries. Alleviation of the increase in drug costs has been sought by trying to promote the use of biosimilars, i.e., clinically equivalent copies of original biologics, by different strategies, especially by trying to influence prescribing practices. Since these means have not been effective enough, automatic substitution in the pharmacy could be an option to increase the price competition among interchangeable biologics. This assumption is based on the cost savings obtained from generic substitution with small-molecule drugs. This study aimed to explore the potential of automatic substitution of biologics to enhance rational use of medicines in Finland with special reference to outpatient care.

Specific objectives of studies I-III were:

- To assess what impact the market entry of biosimilars has on the prices of the reference products and how the prices and market shares of biosimilars have developed in outpatient care in Finland, and to investigate whether biosimilars trigger price competition for biologics (I)

- To explore relevant Finnish stakeholders' perceptions of the automatic substitution of biologics with a special focus on medication safety and issues to be considered in the appropriate substitution model (II)

- To summarise available research evidence on practices, experiences, and perceptions of any relevant stakeholders on automatic substitution of biological medicines (III).

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

The academic dissertation consists of the following three original studies that applied nationwide retrospective register study (I), semistructured qualitative interviews (II) and systematic review (III) as methods (Figure 12).

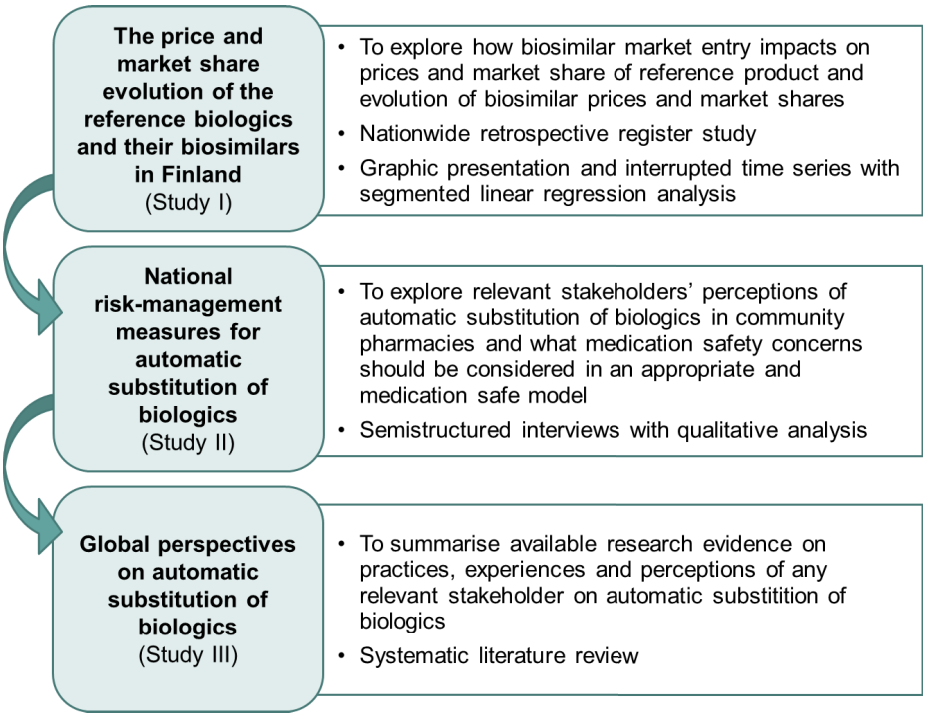

Figure 12. The outline of the studies I-III and the employed research methods.

4.2 THE IMPACT OF BIOSIMILAR MARKET ENTRY ON PRICES AND MARKET SHARES OF BIOLOGICS (STUDY I)

4.2.1 STUDY SETTING AND DATA COLLECTION

In Finland, the prices of outpatient prescription drugs are publicly available, but product-specific wholesale data are not. The data for this national retrospective register study were obtained from IQVIA Institute for Human Data Science, which has collected information on pharmacy wholesale sales of medicines since 2009 in Finland.

The biosimilars, their reference products, and two relevant insulin products (Toujeo® and Liprolog®) sold in Finnish community pharmacies between January 1, 2009, and August 31, 2020, were included in this study (Table 7). Toujeo®, an improved version of insulin glargine [343], and Liprolog®, an insulin lispro product from the same marketing authorisation holder as the insulin lispro reference product [307], were included to test whether competitors would have an impact on the market development of the insulin biosimilars.

The data were collected from the Finnish pharmacy wholesale data at the product level based on ATC codes [344]. For each product, the observation period started three years before the first biosimilar of the ATC group entered the market and continued until August 31, 2020. However, for the products for which the first biosimilar entered the market before January 1, 2012, the observation period started on January 1, 2009. The monthly updated data of ATC code, VNR, trade name, package description (package size, strength, dosage form), number of packages sold, and wholesale value (excluding value added tax, VAT) for the included products were received.

Reimbursement information and the reimbursement expiry dates for the products were obtained from the databases of Finnish authorities or official notifications or memos [329,345–347].

4.2.2 DATA PROCESSING

The data were processed and analysed with Microsoft Office Excel. Data on parallel import products, comprising only a small share of Finnish wholesale sales [348], were merged with the data of the product marketed by the originator's marketing authorisation holder (the same marketing name).

Table 7. *Included biologics and their status (originator, biosimilar or other) grouped by active substances with ATC codes, and therapeutic areas being listed by the date (bolded) of the first biosimilar entered the Finnish market before August 2020* [308,349,350].

Active substance (ATC[1])	Trade name	Biologic status	Market entry in Finland	Examples of therapeutic areas
Somatropin (H01AC01)	Genotropin®	Originator	Feb 1 ,1994	Growth hormone deficiency
	Omnitrope®	Biosimilar	**Nov 15, 2007**	
Epoetin alfa/zeta (B03XA01)	Eprex®	Originator	Mar 1, 1991	Anaemia
	Retacrit®	Biosimilar	**Aug 1, 2008**	
	Binocrit®	Biosimilar	Nov 1, 2008	
Filgrastim (L03AA02)	Neupogen®	Originator	Aug 22, 1991	Neutropenia
	Ratiograstim®	Biosimilar	**May 1, 2009**	
	Zarzio®	Biosimilar	Jan 15, 2010	
	Nivestim®	Biosimilar	Aug 16, 2010	
	Accofil®	Biosimilar	Aug 15, 2015	
Follitropin alfa (G03GA05)	Gonal-F®	Originator	May 15, 1997	Infertility treatment
	Bemfola®	Biosimilar	**Sept 15, 2014**	
	Ovaleap®	Biosimilar	May 21, 2020	
Insulin glargine (A10AE04)	Lantus®	Originator	May 15, 2003	Diabetes
	Lantus Solostar®	Originator	Nov 1, 2007	
	Toujeo®	Other	July 1, 2015	
	Abasaglar®	Biosimilar	**Nov 1, 2015**	
Insulin lispro (A10AB04)	Humalog®	Originator	July 1, 1996	Diabetes
	Humalog Kwikpen®	Originator	Dec 1, 2008	
	Insulin Lispro Sanofi®	Biosimilar	**Jan 1, 2018**	
	Humalog JuniorKwikpen®	Originator	Apr 1, 2018	
	Liprolog®	Other	May 10, 2019	
Etanercept (L04AB01)	Enbrel®	Originator	Apr 2, 2007	Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, juvenile rheumatoid arthritis
	Erelzi®	Biosimilar	**Feb 1, 2018**	
Pegfilgrastim (L03AA13)	Neulasta®	Originator	Dec 31, 2002	Neutropenia
	Pelgraz®	Biosimilar	**Oct 15, 2018**	
	Ziextenzo®	Biosimilar	Oct 1, 2019	
	Pelmeg®	Biosimilar	Nov 15, 2019	
	Fulphila®	Biosimilar	July 1, 2020	
Adalimumab (L04AB04)	Humira®	Originator	Mar 1, 2004	Rheumatoid arthritis, uveitis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, ulcerative colitis, Crohn's disease
	Amgevita®	Biosimilar	**Nov 15, 2018**	
	Hyrimoz®	Biosimilar	Dec 1, 2018	
	Hulio®	Biosimilar	Dec 15, 2018	
	Idacio®	Biosimilar	Jan 1, 2020	
Teriparatide (H05AA02)	Forsteo®	Originator	July 28, 2003	Osteoporosis
	Movymia®	Biosimilar	**Sept 15, 2019**	
Enoxaparin sodium (B01AB05)	Klexane®	Originator	Apr 4, 1991	Venous thromboembolism
	Inhixa®	Biosimilar	**Jan 1, 2020**	
	Enoxaparin Becat®	Biosimilar	Jan 15, 2020	
	Ghemaxan®	Biosimilar	Apr 15, 2020	

ATC= Anatomical Therapeutic Chemical [344]

The amount of the active substance in each package was determined using the package description from the dataset or a Nordic Article Number (VNR) from FimeaWeb [308]. The consumption of active substances was measured as defined daily doses (DDD), which refers to the presumed average maintenance dose per day for a drug used for its primary indication in adults [351]. DDD updates in 2020 were used [344]. The total monthly product consumption (in DDDs) comprised all products with the same marketing name. The monthly consumption of each active substance was obtained by combining the monthly consumption of the reference product and its biosimilars.

The monthly wholesale weighted average price per DDD was used to describe drug prices. The value was calculated for each included product. A common weighted average price for biosimilars was calculated for those active substances with more than one biosimilar. All prices were converted to 2018 euros.

4.2.3 DATA ANALYSIS

4.2.3.1 Analysis of market and price evolution

The evolution of market shares and the wholesale prices of the included products during the study period were presented graphically. The results obtained from the subsequent analysis of their utilisation and price evolution were further synthesised with reimbursement information. The reference product's price evolution in relation to its price at the moment when its first biosimilar entered the market was summarised in a graph for those active substances for which the first biosimilar entered the market after January 1, 2012.

4.2.3.2 Statistical analysis

An interrupted time series analysis was applied to estimate the effect of biosimilar market entry on the price of the reference product. Interrupted time series analysis is a suitable method to study the long-term effects of interventions over time [352]. A segmented linear regression analysis, suitable to model an interrupted time series analysis and to estimate the effects of interventions on the variable under study, were used. The chosen method is suitable for analysing trends and levels of changes by comparing the values of the variables before and after the intervention.

The time series for each active substance was divided into two parts interrupted by the intervention. The intervention occurred when the decrease in the price of the reference product was observed in the graph. The biosimilar

market entry was considered an intervention if no price change was observed. Regression analysis was performed for reference products for which the first biosimilar entered the market after January 1, 2012. The statistical analysis was carried out with the R Studio (version 1.3.1093).

Two models were used in this study. A more appropriate model was selected for each active substance by analysis of variance and comparison of the values of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (described, for example, by Kuha [353]). If the AIC and BIC values were inconsistent, the model was selected based on the AIC value and analysis of variance. In the first model, the explanatory factors were time and the market entry of the biosimilar. Model 1 is in the form of equation (1):

$$(1) \quad Y_t = \beta_0 + \beta_1 \times time + \beta_2 \times intervention_t + \varepsilon_t,$$

where the Y_t is the average wholesale price per DDD of the reference product in month t; β_0 estimates the baseline level of the average wholesale price per DDD of the reference product per month at time zero; β_1 estimates the monthly baseline trend of the average wholesale price per DDD of the reference product before interruption; *time* is a continuous variable indicating time in months from the start of the observation period starting from zero; β_2 estimates the level change in the average wholesale price per DDD of the reference product immediately after the time series interruption; $intervention_t$ indicates time t and gets a value of 0 before and a value of 1 after the interruption; ε_t is the error term.

In the second model, the price was explained by time, biosimilar market entry, and a parameter describing the change in trend. Model 2 is in the form of equation (2):

$$(2) \quad Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention + \varepsilon_t,$$

where the parameters are otherwise the same as Model 1, but β_3 and time after intervention are added. β_3 estimates the monthly change in the trend of the average wholesale price per DDD of the reference product after the interruption, compared with the monthly trend before interruption and *time after intervention* is a continuous variable expressing the time in months after the interruption and receives the value 0 before the interruption.

Due to the potential autocorrelation of the time series analysis, the Durbin-Watson test [354] and the Newey-West method [355] were employed. In addition to the autocorrelation, Newey-West method considers heteroskedasticity. The results were autoregressively corrected and presented with a significance level of 0.01.

4.3 NATIONAL RISK-MANAGEMENT STRATEGIES FOR AUTOMATIC SUBSTITUTION OF BIOLOGICS (STUDY II)

The perceptions of Finnish stakeholders on the automatic substitution of biologics were explored using semistructured theme interviews. The theme interview is a suitable method for situations where it is desirable to elicit a wide range of views on a specific topic and if the phenomenon is previously unstudied [356].

4.3.1 INTERVIEW GUIDE AND ADDITIONAL INTERVIEW MATERIAL

Based on the study aim, literature, and the research group's experience and knowledge, an interview guide with four themes was developed (Study II: Supplementary Material 1). The guide was flexible, allowing a conversational and interactive approach in the interviews [357]. The themes were: 1) attitudes towards substitution, 2) medication safety upon automatic substitution of biologics, 3) prerequisites for the implementation of automatic substitution of biologics and any other specific issues to consider from different perspectives, and 4) implementation and monitoring. In the interviews, the tables of biosimilars on the Finnish market in August 2018 and EU-authorised biosimilars that were not launched in Finland were available.

The interview guide was tested in a pilot interview (n=1). Based on the pilot, the key term explanations relevant to the interview were added to the interview material. After this, the guide was adopted, but the possibility was left to modify it later, especially considering the different stakeholders' different roles. The pilot interview was included in the research data.

4.3.2 SAMPLING AND RECRUITMENT OF THE INTERVIEWEES

The study sample covered a full range of national stakeholders associated with biological medicines and their use ranging from the marketing authorisation to medicine distribution and patient care (Study II: Supplementary Material 2). The purpose of the interviews was to obtain rich and comprehensive insights from interviewees. The research group identified the stakeholders that were invited to participate. Purposive sampling was used to select the stakeholders to ensure the coverage of all relevant perspectives [358]. The following actors were included: community and hospital pharmacists, prescribers, nurses, patients/customers, pharmaceutical industry, pharmaceutical wholesalers, and different authorities regarding the distribution and pharmacotherapy process.

Interviewees were primarily recruited through interest groups, professional associations, and patient organisations. The chosen organisations were contacted by email. The timing for the interview was agreed upon by email or telephone. The invited organisations independently nominated the person or persons to participate in the interview. This influenced whether the interview was conducted as an individual, pair, or group interview. Direct recruits were made in situations where it was appropriate (e.g., authorities). A total of 38 interview invitations were sent.

4.3.3 DATA COLLECTION

Written informed consent was obtained from all interviewees. The interviews were audio recorded. The interviews were conducted in Finnish at places easily reached by the interviewees being sufficiently private to facilitate a free and confidential discussion.

At the beginning of each interview, the interviewer went through the most important terms (biosimilar, substitution and medication safety) used in the interview to ensure that the concepts would not cause any misunderstandings. Interviewees were encouraged to share their personal views and the possible positions of their background organisation on the topic.

4.3.4 DATA ANALYSIS

Audio records were transcribed verbatim by a professional transcriber, and transcripts were checked for accuracy. The data were pseudonymised before analysis. Inductive content analysis, which is applicable to research topics which are not well-known and are expected to yield new insights, was used [359,360]. Data from individual, pair, and group interviews were analysed in the same way, using the interview as the level of the analysis rather than analysing the views of each individual participant.

The data were read through several times, and sentences relevant to the research question were coded. Codes that had the same or similar meanings were combined. Combined codes were grouped into subcategories and further categories that formed, for example, perceived risk descriptions that were presented in a conceptual model. The data were mainly analysed by one researcher. The research group held several sessions where data, analysis and preliminary results were discussed to improve the trustworthiness of the qualitative analysis. The most representative quotations were reported. A checklist of the Consolidated Criteria for Reporting Qualitative Studies (COREQ) was utilised when applicable [361].

4.4 GLOBAL PERSPECTIVES ON AUTOMATIC SUBSTITUTION OF BIOLOGICS (STUDY III)

4.4.1 SEARCH STRATEGY AND DATA COLLECTION

This study applied systematic review as a method [362]. A systematic literature search was conducted on Scopus, MEDLINE (Ovid), CINAHL, and Web of Science in April 2021. These databases were considered to cover the relevant literature of interest. The peer-reviewed literature in English from January 1, 2006, to April 24, 2021, was included. This time frame was chosen to limit the literature search to the time since the biosimilars were authorised for the first time [363]. The search terms focused on the terms "substitution" and "biosimilar". Synonyms and kindred terms were identified with the help of two library information specialists to enable an extensive search since global biosimilar terminology is not established [255,364,365]. In all four databases, the following search query was used: (substitution* OR switch* OR interchang*) AND (biosimilar* OR "similar biotherapeutic*" OR "subsequent entry biologic*" OR "SEB" OR biogeneric* OR "follow-on biologic*").

An article was included if it met the predetermined inclusion criteria of being an original peer-reviewed study on the automatic substitution of biologics (Table 8). All kinds of studies, such as intervention studies, pilots or experiences, perceptions, or opinions of relevant stakeholders, including HCPs and patients, of an automatic substitution of biologics were accepted.

Table 8. *Predetermined inclusion criteria used for selecting articles for the systematic review. PICOS tool was applied to form the inclusion criteria* [362].

	Description of criteria
Inclusion criteria (PICOS)	
Participants	Patients, HCPs, or any other stakeholders related to the topic
Intervention	Pharmacist-led automatic substitution of biological medicinal products containing the same active ingredient
Comparison	Comparison was not required. Any scientifically rigorous research method was allowed
Outcome	Any outcome of the intervention (substitution), or experiences, perceptions or opinions of patients, HCPs, or other stakeholders about automatic substitution of biologics
Setting	Community and hospital pharmacies providing that a prescriber was not involved in the transition.
Exclusion criteria	
	Studies without any outcome measures, position papers, narrative reviews, letters, editorials, conference abstracts, meeting reports, switching studies, clinical trials, and real-world data reports on safety and/or efficacy of biosimilars, pre-clinical studies, molecular structure studies, and studies investigating the mechanism of action.

4.4.2 STUDY SELECTION AND DATA EXTRACTION

The database search yielded 2,880 citations (Figure 13). Once duplicates were removed, 1,363 potentially relevant citations were identified for further screening. Two researchers independently selected the studies based on titles and abstracts. Discrepancies were solved by discussion. The full texts of the potential articles were reviewed for final inclusion. The reference lists of the identified articles and relevant systematic reviews were hand-searched and screened for relevance. Finally, 27 articles met the inclusion criteria, of which 23 were surveys, and four studies were semistructured interviews.

Relevant data were extracted using extraction tables that compiled the following information: authors of the article, publication year, journal, affiliation types of the authors, study aim, study description, how substitution related issues were studied or asked, main outcomes, study limitations identified by authors, and funding sources with other relevant disclosures reported in the article. Extraction items were chosen by three researchers with consensus. When an article consisted of several study parts, only substitution-related parts were included in the analysis.

For data processing, the extracted information was classified according to the study type, continent, country, data collection period, the occupation or background of the participants, and their perceptions and experiences of automatic substitution of biologics. When the data collection period was not reported, it was set to the submission date of the article.

The identified perceptions and experiences of the study participants towards automatic substitution were categorised into three segments using the following criteria:

1) Negative perceptions: The studies with more than half of the participants opposing automatic substitution of biologics
2) Positive perceptions: The studies where more than half of the participants favoured automatic substitution
3) Uncertain perceptions: The studies where the participants' perceptions were uncertain or unclear.

The legislative status of substitution of biologics in the country of the study was extracted from the literature, where available. No statistical analysis was performed.

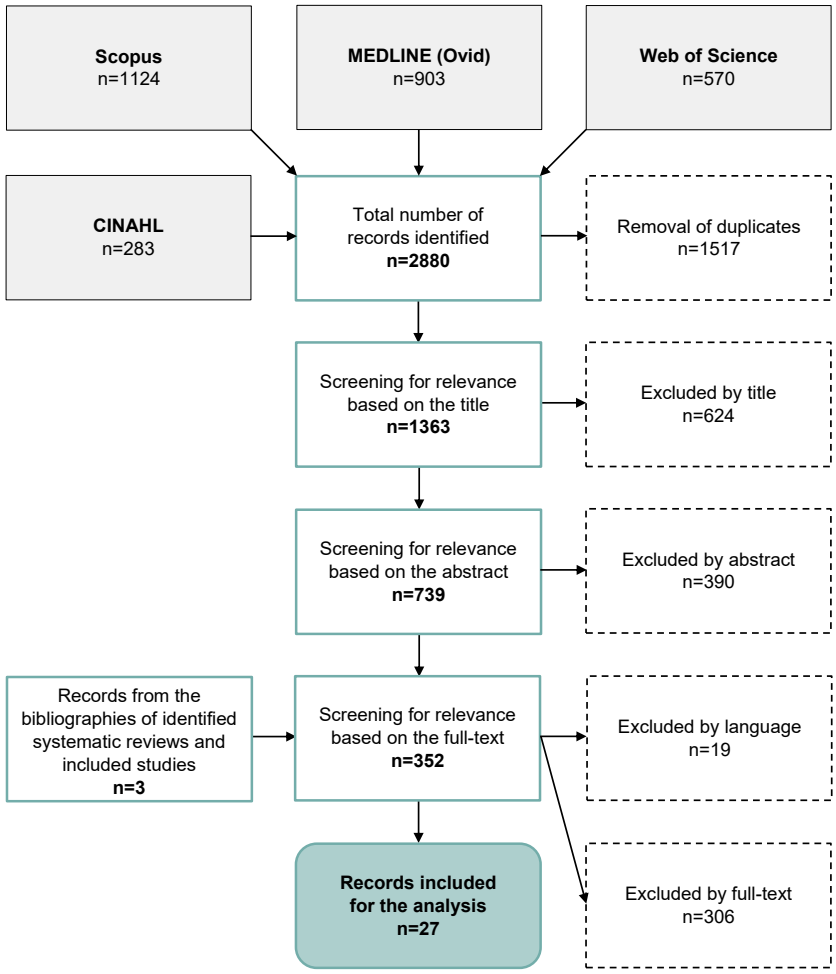

Figure 13. Flow chart of study selection.

4.4.3 QUALITY ASSESSMENTS

Each survey was systematically evaluated for method-specific quality features by seven main questions (Study III: Supplementary Material 1) derived from the Survey Assessment Guide [366]. Each main question had a maximum of eight sub-questions. The main questions were scored depending on the distribution of sub-questions that fulfilled the requirement. The total quality of the included surveys was calculated based on the scores obtained from the main questions, the maximum being seven points. A survey quality was classified as high if the total score was from 4.5 to 7 and low if the total score was from 0 to 2.5. All identified studies were included in the further analysis regardless of their methodological quality.

The quality of each semistructured interview study was assessed using a 10-item Critical Appraisal Checklist [367] to ensure that included qualitative interviews were of applicable quality (received more than 8/10 points from the checklist) (Study III: Supplementary Material 1). However, the quality of the qualitative interviews was not compared. One researcher carried out the quality assessment. All the research group members carefully reviewed the assessment before approval.

4.5 RESEARCH ETHICS AND DATA CONFIDENTIALITY (STUDIES I-III)

The original studies were conducted complying with the Finnish National Board of Research Integrity TENK guidelines for the ethical principles to conduct research and good scientific practices [368,369]. Applied methods did not require ethical pre-evaluation as the data of these studies (I-III) did not contain personal health information, identifiable patient information or medical interventions for patients.

Study I was a retrospective register study consisting of sales statistics of pharmaceutical products in outpatient care in Finland.

In the stakeholder interviews (Study II), all interviewees were adults and were asked for informed consent. All data were carefully managed to respect the anonymity of the participants and confidentiality. The study complied with the confidentiality requirements of that time.

Patients or the public were not involved in the planning or designing of the studies. However, in the interviews (Study II), the patients participated as representatives of their patient organisations.

5 RESULTS

5.1 BIOSIMILAR MARKET SHARE AND PRICE EVOLUTION OF THE REFERENCE PRODUCTS AND THEIR BIOSIMILARS (STUDY I)

5.1.1 BIOSIMILARS' MARKET SHARE EVOLUTION

The sales of the first biosimilars of insulin glargine, enoxaparin, adalimumab, insulin lispro, and etanercept started in the first month when entering the market (Table 9). Biosimilars for other active substances that entered the market during the observation period were not sold during the first month.

At the end of the observation period, the total use of the reference product and its biosimilars, measured by DDD, was the highest for insulin glargine, followed by enoxaparin, adalimumab, insulin lispro, and etanercept. The biosimilar uptake varied between active substances (Table 9, Study I: Supplementary Material). At the end of the observation period in August 2020, the epoetin and filgrastim biosimilars had a 100% market share, while the enoxaparin, insulin glargine, and teriparatide biosimilars had low market shares of 6%, 6% and 0%, respectively. The biosimilar market shares for the other seven active substances were between these. Non-biosimilar competitors Toujeo® and Liprolog® had gained remarkable market shares (32% and 49%, respectively). After the introduction to the market, their uptakes were the same or more efficient than biosimilar uptake of the same active substance.

Six active substances had multiple biosimilars on the market during the observation period (Table 9). The first biosimilar of the active substance had the largest market share by the end of the observation period, except filgrastim, whose second biosimilar had the largest market share.

Table 9. *Summary of the uptake, use, and price differences of biosimilars compared to their reference products in Finland from January 1, 2009 (somatropin and epoetin) or the first biosimilar market entry (other active substances) to August 31, 2020. The active substances are in the order in which their first biosimilars entered the market.*

Active substance	Status at the moment of BS market entry		Status at the end of the observation period in August 2020						
	BS sold in the 1st month	The price difference: RP and BS	The price difference: RP and BS	The reimbursement status for the RP	BSs market share	BS market share distribution			
						1st	2nd	3rd	4th
Somatropin	-	-	3%	✓	73%	73%			
Epoetin	-	-	-	✗ (Ended Mar 31, 2011)	100%	100%	0%[f]		
Filgrastim	✗	30%[a]	-	✗ (Ended Mar 31, 2013)	100%	3%	69%	24%	5%
Follitropin	✗	30%[a]	10%	✓	24%	23%	0%		
Insulin glargine	✓	15%	1%	✓	6% (4%[d])	6%			
Insulin lispro	✓	26%[b]	28%	✗ (Ended May 31, 2019)[c]	99% (51%[e])	99%			
Etanercept	✓	30%	12%	✓	30%	30%			
Pegfilgrastim	✗	30%[a]	6%	✓	38%	37%	0%	1%	0%
Adalimumab	✓	30%	22%	✓	35%	18%	11%	5%	1%
Teriparatide	✗	31%[a]	-	✓	0%	0%			
Enoxaparin	✓	42%	28%	✓ (Ending Nov 30, 2020)	6%	6%	0%	0%	

BS= biosimilar; RP=reference product, - = information not available; ✓ = Yes; ✗ = No; a = the first sale month, b=pooled price difference of different packages in weighted average prices; c = Some of the products were no longer reimbursed since Sept 30, 2018; d = The market share of the biosimilar on the market, including also Toujeo®; e = The market share of the biosimilar on the market, including also Liprolog®, f = Product no longer on the market.

5.1.2 BIOSIMILARS' PRICE EVOLUTION

Seven of the first biosimilars were 26–31% lower-priced than the reference product when the biosimilar was first sold (Table 9, Study I: Supplementary Material). The outliers were the first insulin glargine biosimilar (price difference of 15%) and the first enoxaparin biosimilar (price difference of 42%). For all active substances, apart from enoxaparin (22% increase in combined wholesale weighted average price), biosimilar prices either remained steady or decreased over the observation period from January 1, 2009 (somatropin and epoetin) or the first biosimilar market entry (other active substances) to August 31, 2020.

In those active substances with only one biosimilar (somatropin, insulin glargine, insulin lispro, etanercept, and teriparatide) or two biosimilars (follitropin and epoetin) (Table 9), the prices of the biosimilars generally had only minor changes. The exceptions were somatropin biosimilar, whose price decreased by 27% in September 2010 and the first epoetin biosimilar, whose price fluctuated before 2013 (Study I: Supplementary Material). Filgrastim, pegfilgrastim, adalimumab, and enoxaparin had more than two biosimilars on the market (Table 9) and their prices varied more. The prices of the filgrastim biosimilars began to vary in 2017 when the prices of the biosimilars either stayed stable or decreased (maximum price decrease of 63%). The price of the first pegfilgrastim biosimilar decreased by 14%, and the third biosimilar by 7% over the observation period. The price development of the second and fourth pegfilgrastim biosimilars is unknown because these products were not sold over the observation period, and the wholesale weighted average price could not be calculated. The prices of the first three adalimumab biosimilars decreased by 19–23%, and the fourth biosimilar price stayed stable.

5.1.3 THE IMPACT OF BIOSIMILAR MARKET ENTRY ON THE REFERENCE PRODUCT'S PRICE

The relative changes in the wholesale weighted average prices of the reference products were further analysed for the eight active substances (Figure 14) whose first biosimilar entered the market after January 1, 2012. For enoxaparin, teriparatide, insulin lispro, adalimumab, and etanercept, the price of the reference product remained relatively stable before the biosimilar entered the market. For insulin glargine, pegfilgrastim, and follitropin, the price of the reference product was higher three years before the biosimilar market entry compared to the price at the time of the biosimilar market entry.

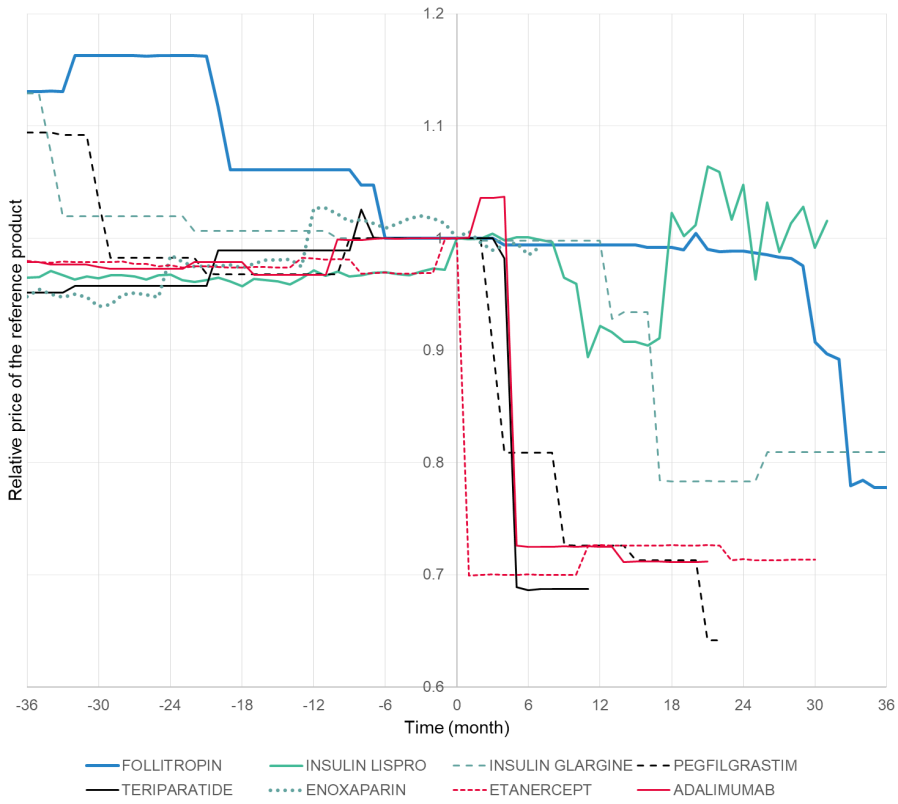

Figure 14. Development of relative prices of reference products for eight active substances. The observation period began three years (36 months) before the first biosimilar entered the market and continued for three years (36 months) after that. The relative prices of the reference products are standardised to be 1 when the first biosimilar entered the market (at 0 months). The price decreases before biosimilar market entry for insulin glargine (-33 months) and follitropin (-19 months) reference products occurred in 2013 due to mandatory price reductions for all medicines outside the reference price system [370].

Compared to the time before biosimilars entered the market, larger changes in the prices of the reference products were observed after the biosimilar market entry (Figure 14). For all active substances, except enoxaparin and insulin lispro, the price of the reference product decreased permanently after the biosimilar entered the market. With enoxaparin, whose observation period was eight months after biosimilar market entry, no changes in the price of the reference product were observed. The price of insulin lispro reference product decreased at first, but after 18 months, it increased higher than at the time of biosimilar introduction. At the end of the observation period, insulin lispro reference product was no more in the reimbursement scheme (Table 9).

For those active substances whose biosimilars entered the market after 2017, the prices of the reference products fell shortly after the biosimilars entered the market compared with the price decreases for insulin glargine and

follitropin (Figure 14). The insulin glargine reference product price decreased in December 2016 and again in April 2017. The follitropin reference product price decreased between March to June 2017.

In the interrupted time series analysis, Model 2 was a better fit for seven reference products, as adding the monthly change in the average wholesale price per DDD trend after interruption to the model improved the model's suitability for them. Model 1 was only used for the teriparatide reference product. The changes in the price level of the reference products after the interruption (the price decrease of the reference product or biosimilar market entry) were statistically significant for six reference products (follitropin, insulin glargine, pegfilgrastim, adalimumab, teriparatide and enoxaparin) and statistically insignificant for two reference products (insulin lispro and etanercept) (Table 10). The change in the price level of the etanercept reference product after the interruption was not statistically significant, although the price drop can be seen in Figure 14. However, without the Newey-West method [355], the change in the price level was a statistically significant result ($p<0.01$), and similarly, Model 1 yielded a statistically significant result ($p<0.01$) using the Newey-West method. There were statistically significant price trends of the reference products before the interruption of the time series and statistically significant changes in the price trends of the reference products after the interruption of the time series (Table 10).

Table 10. *Impact of biosimilar market entry on the reference product price (in euros) per DDD. Active substances are listed by the date the first biosimilar entered the Finnish market. Results are presented with a 95% confidence level (CI), and statistically significant p-values (p<0.01) are bolded.*

Active substance	Compared to time series interruption	Estimate (€/DDD)	95% CI (€/DDD)	P
Follitropin^	Level before (β0)	28.269	26.376; 30.161	**<0.001**
	Trend[a] before (β1)	-0.078	-0.122; -0.034	**<0.001**
	Level change after (β2)	-3.254	-4.539; -1.970	**<0.001**
	Trend[a] change after (β3)	0.086	-0.002; 0.174	0.055
Insulin glargine^	Level before (β0)	1.270	1.241; 1.298	**<0.001**
	Trend[a] before (β1)	-0.001	-0.002; -0.001	0.003
	Level change after (β2)	-0.185	-0.283; -0.086	**<0.001**
	Trend[a] change after (β3)	0.001	-0.002; 0.004	0.503
Insulin lispro^	Level before (β0)	0.749	0.740; 0.759	**<0.001**
	Trend[a] before (per month) (β1)	0.001	0.000; 0.001	0.048
	Level change after (β2)	-0.054	-0.095; -0.013	0.011
	Trend[a] change after (β3)	0.004	0.001; 0.006	0.006
Etanercept^	Level before (β0)	31.279	31.092; 31.465	**<0.001**
	Trend[a] before (β1)	-0.000	-0.016; 0.016	0.989
	Level change after (β2)	-8.725	-21.699; 4.250	0.184
	Trend[a] change after (β3)	0.021	-1.069; 1.112	0.969
Pegfilgrastim^	Level before (β0)	44.290	41.183; 47.398	**<0.001**
	Trend[a] before (β1)	-0.078	-0.210; 0.054	0.241
	Level change after (β2)	-5.646	-8.150; -3.142	**<0.001**
	Trend[a] change after (β3)	-0.327	-0.513; -0.141	**<0.001**
Adalimumab^	Level before (β0)	32.331	31.857; 32.805	**<0.001**
	Trend[a] before (β1)	0.039	0.011; 0.067	0.007
	Level change after (β2)	-9.460	-10.403; -8.517	**<0.001**
	Trend[a] change after (β3)	-0.080	-0.113; -0.047	**<0.001**
Teriparatide*	Level before (β0)	10.254	10.155; 10.354	**<0.001**
	Trend[a] before (β1)	0.016	0.012; 0.020	**<0.001**
	Level change after (β2)	-3.544	-3.706; -3.382	**<0.001**
Enoxaparin^	Level before (β0)	1.499	1.481; 1.517	**<0.001**
	Trend[a] before (β1)	0.004	0.003; 0.005	**<0.001**
	Level change after (β2)	-0.043	-0.065; -0.021	**<0.001**
	Trend[a] change after (β3)	-0.007	-0.008; -0.006	**<0.001**

[a] Trend per month, CI = Confidence interval, DDD = Defined daily dose, ^ Model 2 was applied in statistical analysis, * Model 1 was applied in statistical analysis.

5.2 PREPARING FOR THE IMPLEMENTATION OF AUTOMATIC SUBSTITUTION OF BIOLOGICS: RISK MANAGEMENT ON THE NATIONAL LEVEL (STUDY II)

5.2.1 STUDY PARTICIPANTS

A total of 32 interviews with 62 participants were performed between August and November 2018 (Table 11). There were individual (n=17), pair (n=7) and group (n=8) interviews. Each pair and group interview included participants only from one stakeholder group. All interviews were conducted face-to-face with a mean duration of 55 minutes (ranging from 30 to 98 minutes). In three interviews, there were some participants (n=4) via Skype or over the telephone. Most of the contacted stakeholder organisations (n=38) agreed to participate in the study (n=32, 84%). Six contacts did not lead to an interview. Three invited stakeholders refused to participate due to a lack of knowledge or experience on the topic, and two participants dropped out since a suitable interview time was not found (group interviews). No response was received for one invitation. The participants' characteristics are summarised in Table 11.

Table 11. *Characteristics of the interviewees (n=62) participating in the interviews (n=32).*

Background of the interviewees (n=62)	Number of interviews (interviewees)
Community pharmacists	**8** (15)
National and/or local professional associations	
Practitioners (pharmacy owners, pharmacists (MSc/BSc))	
Authorities	**7** (18)
Legislation	
Evaluation of interchangeability of generics	
Supervision of pharmacies	
Pricing or reimbursement	
Pharmacovigilance	
Prescribers	**7** (7)
Professional associations	
Practitioners from medical specialty societies	
Pharmaceutical industry and wholesalers	**6** (8)
National interest groups	
Pharmaceutical companies and wholesalers	
Patients/customers	**2** (5)
Patient associations	
Hospital pharmacists	**1** (6)
Hospital drug formulary management	
Nurses	**1** (3)
Specialist nurse associations	
TOTAL	**32** (62)

5.2.2 GENERAL PERCEPTIONS OF SUBSTITUTION OF BIOLOGICS

Practically all participants in the interviews (n=32) preferred physician-led switching as a primary method for enhancing the use of biosimilars, whereas varied attitudes regarding the automatic substitution of biologics in community pharmacies were elicited. In half of the interviews (n=16), the position of the attendees was positive toward the substitution at the pharmacy level. In 25% of the interviews (n=8), interviewees had the opinion that there was not enough experience with biosimilars, and they saw risks that should be solved prior to initiating automatic substitution in community pharmacies. Automatic substitution of biologics was deemed as a totally inappropriate procedure in some interviews (n=8). Some negative comments reflected a distrust of the quality, safety, and efficacy of biosimilars in general. Positive and negative attitudes were both found among all stakeholders, including patient representatives, and all types of interviews (individual, pair or group interviews). Treatment naïve patients were perceived to be the most suitable for substitution.

5.2.3 POTENTIAL BENEFITS OF THE AUTOMATIC SUBSTITUTION OF BIOLOGICS

Cost savings were clearly the most often identified potential benefit of automatic substitution (Table 12). In addition to cost savings in healthcare (n=17), the participants identified several other benefits that might be achieved by implementing the substitution of biologics. More patients can receive treatments if savings result in the increased number of patients on biological treatment (n=5), initiation of biological treatment in an earlier phase of the disease (n=3) or introduction of novel treatments for new patients (n=2). Price reductions may also increase patients' willingness and ability to use biologics (n=5) if the price reductions are substantial. Continuity of treatment was also identified as a potential benefit, for example, in the case of medicine shortages (n=4).

Table 12. *Potential benefits of substitution at the community pharmacy as identified in the interviews (n=32).*

Benefit	Description of the benefit
Savings	• Society saves on drug costs (n=17)
More patients can receive treatments	• Lower prices can improve patients' willingness and ability to use self-injectable biologics (n=5) • Patients have better access to biological treatments (n=5) • Patients may start biological treatment in an earlier phase of their disease (n=3) • New drug treatments can be introduced without compromising sustainability of pharmacotherapy (n=2)
Continuity of treatments	• Treatment can continue smoothly with another product if there is a medicine shortage (n=4) • Decreasing prices can increase the pharmacy's willingness to keep the products in stock (n=2) • Patients may receive a three-month dose of reimbursed medication at the same time if the price of the product falls sufficiently (n=1) • Treatment can continue smoothly with another reimbursed product if there is a change in the reimbursement status of the patient's current medicine brand (n=1) • Immediate availability could improve if pharmacies were aware of the product that must be dispensed (n=1)

5.2.4 THE PERCEIVED MEDICATION SAFETY RISKS AND THEIR MANAGEMENT

Most of the risks with biologics' substitution identified in the interviews (n=32) were related to the interruption or complication of patient's pharmacotherapy because of issues such as inadequate knowledge of the administration device (n=19), medicine availability problems (n=12) or patient's distrust of the biosimilar medicine itself (n=11) (Table 13). For example, differences in packages and complex naming (n=11) can introduce a risk for duplicate therapy. Traceability of the dispensed product name and batch number (due to long-term side effects; n=8, or unavailability of the dispensed product name or batch number; n=5) and insufficient availability of healthcare contacts (n=12) were also identified as medication safety risks in substitution in several comments. Lack of appropriate counselling for patients in the pharmacy and the inconsistencies between the pharmaceutical product-specific patient information materials were mentioned as risks in some interviews.

Several methods to minimise medication safety risks were proposed in the interviews. Medication and device counselling provided by pharmacists (n=23), infrequent substitution interval (n=15), and better knowledge of biosimilars among HCPs (n=13) were identified as potential remedies in multiple interviews.

Table 13. *Perceived medication safety risks and methods to manage them as identified in the stakeholder interviews (n=32).*

Potential risk	Descriptions of perceived risks with manifestation	Methods to minimise the risk as identified in the interviews (n=32)
The patient's medication is interrupted or complicated temporarily or permanently	**The patient does not know how or is unable to use the administration device correctly (n=19)** - The patient feels that the new administration device is difficult to use. - Patient fails to administer the medicine, or he/she is not able to repeat the administration - New administration device is not suitable for the patient (handicap, visual impairment) - Too wide a range of different devices is available **The medicine is not available at the right time (n=12)** - The pharmacy does not have the product in stock - There is a medicine shortage **The patient does not trust the new medicine (n=11)** - The patient has benefited significantly from the original product and does not want to change. - The patient receives conflicting messages from different HCPs. - The substitution will surprise the patient at the pharmacy. - Patient is suspicious due to different product appearance and trade names. **The patient experiences ADRs after the substitution (n=11)** - Reactions to excipients - Nocebo-effect	- Pharmacy provides medication counselling including device counselling with optional injection training (n=23) - The interval between product substitutions should be longer for biological drugs than for generic medicines (n=15) - Further training of HCPs on biosimilars (n=13) - Consistent, positive attitude towards substitution across healthcare and pharmacies (n=9) - A motivating conversation with the patient by a doctor and nurse (n=8) - Ensuring at every pharmacy and healthcare visit that the patient can use the device correctly (n=8) - Medication monitoring (n=8) - The patient knows where to contact in case of problems (n=7) - Prescriber can prohibit substitution if necessary (n=7) - Evaluation of the interchangeability of devices in a regulatory process (n=6) - Dispensing of biologics based on an appointment or pre-order (n=6) - Switches and substitution are avoided if the patient's medication has not stabilised (n=6) - Evaluation of biological medicines suitable for substitution by the regulatory authority (n=6) - Post-marketing surveillance of medicines (n=5) - Regional co-ordination / co-operation between healthcare and pharmacies (n=4) - Substitution policy prevents shortages by supporting pharmaceutical companies to anticipate the market (n=3) - Mandatory reserve supplies of biological medicines (n=2)

Potential risk	Descriptions of perceived risks with manifestation	Methods to minimise the risk as identified in the interviews (n=32)
	- Large-scale substitution may reveal problems that were not previously detected **Concern about losing the medicine's effectiveness (n=8)** - The development of drug antibodies is accelerated by repetitive switches - There is no large-scale experience on repetitive switches	- Providing reliable medicines information sources for patients (n=2)
The patient uses two products with the same active substance	**Based on the appearance or name of the product, it is not possible to determine whether the active substance is the same (n=11)** - Different appearance of packages - Different trade names - Generic names can be confusing - Patient recognises only the established brand name **The patient does not understand that substitution has taken place (n=8)** - Patients with polypharmacy, the elderly, patients with impaired cognition **The patient has two prescriptions for the same active substance (n=3)** - The patient has a prescription for the original product and another prescription for the biosimilar	- Demonstrating administration devices in medication counselling (visuality) (n=9) - Prescriber can prohibit substitution (n=7) - Printing medication lists to patients and reviewing their medication (n=1) - The new product is marked with a label that indicates the substitution (n=1) - The new product is not delivered too early, so the patient does not have two products at the same time at home. (n=1) - Pharmacist invalidates the previous prescription when substituting (n=1)
The traceability of the product is compromised	**The biological drug can have long term side effects (n=8)** - The product that caused a side effect cannot be traced **In case of a side effect, the product cannot be traced (n=5)** - The physician is not aware of what brand and what batch the patient has used - Patient refers only to the originator's brand name	- The interval between substitutions should be longer for biologics than for generic medicines (n=15) - Promoting two-way information sharing between pharmacy and healthcare services (n=10) - Switches and substitution are avoided if medication has not stabilised (n=6) - Introduction of a drug certification system (automatic registration of the dispensed package and batch) (n=6)

Potential risk	Descriptions of perceived risks with manifestation	Methods to minimise the risk as identified in the interviews (n=32)
		- Development of information systems so that the batch number of the delivered product is also registered in the electronical prescription center (n=4) - Prescriber can check the brand name of the supplied medicine at the electronical prescription center (n=3)
The patient cannot get into healthcare in case of problems	**Healthcare is overloaded due to substitution (n=12)** - Substitution increases patient contact with healthcare - Patients with substituted medicine would be in closer follow-up - The patient contacts the physician to obtain a substitution refusal	- Further training of HCPs on biosimilars (n=13) - Consistent, positive attitude towards substitution across healthcare and various pharmacies (n=9) - A motivating conversation with the patient by a doctor and nurse (n=8)
The patient does not receive substitution-related advice from a pharmacy	**'On behalf of the patient' customers (n=5)** - For example, a relative can apply for a medicine on behalf of a patient **New methods to dispense medicines (n=1)** - The patient can apply for a medicine from the "smart box" when convenient	- Medication counselling with both visual and written material (n=7) - Prescriber can prohibit substitution (n=7)
The patient is distracted by the support material he receives	**There may be differences in written material received by the patient (n=2)** - Material for various products is accumulated **The availability of additional materials may vary by product (n=2)** - Pharmaceutical company supplies additional product-specific material such as web pages, storage, and shipping boxes, etc.	- Generic and harmonised risk minimisation materials (n=2)

Note: 'Patient perspective' can be either the patient representative's view or another stakeholder representative's assumption on the patient's view.
ADR= adverse drug reaction, HCP = healthcare professional

5.2.5 SUBSTITUTION FREQUENCY

The interviewees were asked about the optimal substitution interval for biologics. Only three interviewees agreed that the current generic substitution interval of three months (e.g., how often the medicine could be substituted in the pharmacy) would be suitable for biologics, and none recommended having an interval of one month. The most commonly suggested interval for substitution was 12-24 months (n=13). In some interviews, the participants did not want to mention any precise frequency but mentioned that it "should be done rarely". Both the validity period of a prescription and the adjusted reference price intervals for biologics were suggested to determine the interval of biologics' substitution.

Participants suggested an association between substitution frequency and medication safety, and pharmaceutical market attractiveness (Table 14). It was suggested that a long substitution interval may increase medication safety compared to shorter intervals. On the other hand, pharmaceutical companies' interest in entering the local pharmaceutical market may be compromised if the substitution interval is too long.

Table 14. *The impact of the length of the biologic substitution interval (how often substitution could occur) on medication safety and the attractiveness of the Finnish pharmaceutical market as expressed in the stakeholders' interviews (n=32).*

Substitution interval	Medication safety	Attractiveness of pharmaceutical market
Short	**Positive impact on** • Continuation of treatment in case of shortages of a particular product **Negative impact on** • Device expertise of the patient • Traceability of the product and batch number • Management of support material for the patient • Concerns on immunogenicity	**Negative impact on** • Predictability of pharmaceutical market • Stock management in pharmacies **Uncertain impact on** • Competition between products
Long	**Positive impact on** • Device expertise of the patient • Traceability of the product and batch number • Management of additional patient materials **Negative impact on** • Continuity of treatment in case of shortages	**Positive impact on** • Predictability of the pharmaceutical market • Stock management in pharmacies **Negative impact on** • Competition between products (prevents rapid reaction to price changes)

5.2.6 TASKS AND RESPONSIBILITIES OF THE PATIENTS AND HEALTHCARE PROFESSIONALS

In the interviews, participants suggested that automatic substitution will bring new tasks to community pharmacists (Figure 15). Lack of information sharing between community pharmacists and nurses who are involved in patient counselling was noted in several interviews. It was highlighted by interviewees that this information pathway should be developed for effective and consistent counselling on administration devices for patients. Multiple interviewees stated that collaboration between teams in healthcare and pharmacies should be improved before introducing automatic substitution of biologics. On the other hand, the role of patients as partners was discussed in several interviews.

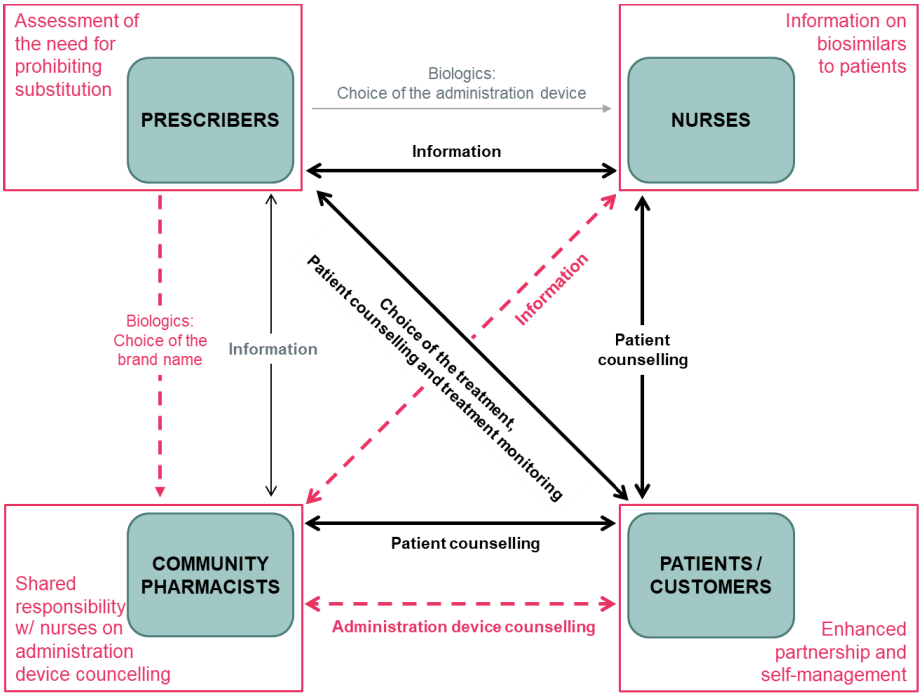

Figure 15. Existing interactions (black lines) between patients and HCPs in biological medicine treatment in Finland and new tasks (red boxes) and new interactions (red dashed lines) between patients and HCPs induced by automated substitution of biologics identified in the stakeholders' interviews (n=32).

5.3 GLOBAL PERSPECTIVES AND EXPERIENCES ON BIOLOGICS' SUBSTITUTION (STUDY III)

5.3.1 CHARACTERISTICS OF INCLUDED STUDIES

The systematic search resulted in the inclusion of 27 original articles, of which 22 were non-interventional surveys, one with an intervention study, and the remaining four studies were semistructured interviews (Table 15, Table 16, Study III: Supplementary Material). No study was designed as a comparative study or a study reporting practical or clinical treatment outcomes on biologics' automatic substitution.

The majority (56%, 15/27) of the included studies (11 surveys; 4 semistructured interviews) were conducted in Europe (Table 15, Table 16). The study participants were mainly either physicians (n=12), pharmacists (n=5), patients (n=4), payers (n=1), or various stakeholders (n=5). All semistructured interviews had participants for various stakeholders and were from Europe (Table 16). In 44% of the studies (12/27), the data collection had begun in 2015 or earlier. Almost one-third of the studies (8/27) were conducted in countries that allowed limited pharmacist-led automatic substitution of biologics, or substitution was not explicitly prohibited at the time of data collection. Most studies (81%, 22/27) had a primary focus other than the automatic substitution of biologics. Substitution or replacement of biologics was mentioned as an objective only in five studies, of which one was a qualitative study focusing on the automatic substitution of biologics.

In most studies, the authors were affiliated with academia, a government authority, a hospital or university hospital, or a hospital pharmacy (Study III, Supplementary material 2). Three studies (11%) did not report any government-, academic-, or health system-affiliated authors. The pharmaceutical industry was reported as one of the affiliations in three studies. Studies that reported any funding were partly or fully funded by either a public sector, i.e., government authority, university grant or bursary (3/27), research fund, pharmaceutical industry (5/27), or a lobbying organisation (3/27). One study [371] had received both public and pharmaceutical industry funding. In the rest of the included studies, authors declared no funding was received for the study, or the funding was not reported in their article. However, potential conflicts of interest among authors were reported in 63% (17/27) of the studies. Half of the studies conducted among prescribers (6/12) were funded by a pharmaceutical company or a lobbying organisation.

Table 15. *Included surveys (n=23) according to main regional categories (Europe, North America, and other) organised by research method, year of data collection, country, the legislative status of automatic substitution at the time of the study, quality of the study, number of participants, and their perceptions/experiences of automatic substitution of biologics, and the other main outcomes of the study.*

Year of data collection	Continent Country	Legislative status of automatic substitution of biologics[#]	Prescribers	Pharmacists	Patients	Other	Medical specialty	Quality of the study	Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available).	Reference
	EUROPE									
2018	Spain	◆			87		-	High	+ Reported patient satisfaction when substituting an originator prefilled syringes to pens of biosimilar etanercept in the hospital pharmacy: 23% were extremely satisfied; 28% very satisfied; 23% satisfied, and 26% partly satisfied or not at all satisfied.	Barbosa et al., 2021 [372]
2017	France	✓			629		-	Mod	– 3% approved substitution made by a pharmacist.	Frantzen et al., 2019 [373]
2017	Poland	↔		260			-	Mod	– 17% would offer substitution of biologics.	Łukasik and Nowicki, 2018 [374]
2017	Poland	↔		61			-	Mod	– 23% agreed that biosimilars should be used to substitute original medicine. 75% agreed to have a doctor's permission for substitution.	Pawłowska et al., 2019 [375]
2015-16	Ireland	X	102	143			De, E, G, HO, Np, Nu, R, O	High	– < 5% medical specialists considered substitution appropriate, 35-43% with physician consent. 14% of pharmacists indicated to be comfortable with substitution.	O'Callaghan et al., 2017 [371]
2015	France	✓		802			-	High	+ 53% approved substitution made by a pharmacist.	Beck et al., 2017 [376]
2015	Not specified	◆	118				G	Mod	– 90% disapproved substitution made by a pharmacist, 13% approved the substitution of new prescriptions.	Danese et al., 2016 [377]

2013	France	✓	116				R	Mod	–	81% disapproved substitution made by a pharmacist.	Beck et al., 2016 [378]
2013	Not specified	◆			383		-	Mod	–	1% accepted the substitution made by a pharmacist.	Peyrin-Biroulet et al., 2017 [379]
2013	Not specified	◆	307				G	Low	–	64% were against automatic substitution, 18% approved substitution for new prescriptions.	Danese et al., 2014 [380]
2013	France, Germany, Italy, Spain, the UK	✓XXXX	470				De, E, HO, Np, Nu, R	Low	–	95% considered from very to somewhat important to have sole authority to decide the biologic product.	Dolinar and Reilly, 2014 [381]
	NORTH AMERICA										
2016-17	U.S. (States not specified)	◆	297				De, G, R	Low	–	17% would be comfortable with pharmacy-level substitution without physician knowledge.	Teeple et al., 2019 [382]
2015	U.S. (National, District of Columbia, Florida, North Carolina, Maryland, Pennsylvania)	◆◆✓XXX	97				De	Mod	–	94% considered it very or somewhat important that the prescriber should have a control. 88% considered that substitution would occur in the future.	Barsell et al., 2017 [383]
2014	Canada	X	81				R	High	–	88% would feel concerned or very concerned if substitution would be possible.	Grabowski et al., 2015 [384]
2014*	U.S. (States not specified)	◆				8[a]	-	Low	?	Half of the participants were reluctant to initiate the practice of automatic substitution.	Cohen et al., 2014 [385]
	OTHER										
2019*	Tunisia	X	107				HO	Low	–	52% were in favor of a justified substitution and interchangeability, 4% were in favor of a systematic substitution, 7% were in favor of systematic interchangeability, 23% against substitution and interchangeability.	Hadoussa et al., 2020 [386]
2019	Pakistan	◆		305			-	High	?	59% neither agreed or disagreed with statement "Being a pharmacist, I can safely switch to biosimilar without physician permission (8% agreed or strongly agreed; 32% disagreed or strongly disagreed).	Shakeel et al., 2020 [387]
2018	Australia	✓			132		-	High	+	25% were worried about pharmacist-led substitution without consulting the prescriber	Kovitwanichkanont et al., 2020 [388]

2017	Korea, Japan, China, other Asian countries	◆◆◆◆	151				G	Mod	–	87% disagreed with the automatic substitution of the originator with a biosimilar by a pharmacist. 44% disagreed automatic substitution in any case. Disagreement was highest among prescribers in Korea (62%).	Park et al., 2019 [389]
2016	France and Canada	✓X		229			-	Mod	+	25% considered that only physicians could proceed with the interchangeability of biosimilars.	(Adé et al., 2017) [390]
2016	Russia**	◆	206				G, HO, R	Mod	–	53% were negative, 25% were neutral and 22% were positive about substitution.	Karateev and Belokoneva, 2019 [391]
2016	Australia	✓	160				De, E, HO, G, Np, Nu, R	Low	–	90% considered it critical or very important to have sole authority to decide the biological product. 51% did not accept substitution for patients with chronic disease. 53-81% of respondents considered that clinical trial data on safety and efficacy after switch(es) is suitable evidence demonstrating that biosimilar is suitable for substitution on pharmacy level.	Murby and Reilly, 2017 [392]
2015*	Argentina, Brazil, Colombia, Mexico	◆XXX	399				De, E, HO, Np, Nu, R, O	Low	–	>80% considered it critical, or very important to have sole authority to decide the biological product.	Gewanter and Reilly, 2015 [393]

*Manuscript submission year (if data collection time was not indicated)
** Not following the European legislation on biosimilars, thus categorized in "Other"
# At the time of the study. Please note, legislative status does not indicate if the substitution practice is implemented.
✓ Substitution is allowed in some circumstances, ↔ Substitution is not specified / not specifically prohibited, X Substitution is not allowed, ◆ Information is not available in consulted sources.
a Payers, De = Dermatology, E = Endocrinology, Di = Diabetes, G = Gastroenterology, HO = Hematology/Oncology/Medical oncology, Np = Nephrology, Nu = Neurology, R = Rheumatology, O = Other, n/a = Not specified
Quality evaluation, please see Study III: Supplementary Material 3

High= high quality, Mod= moderate quality, Low = low quality, + Perceptions mainly positive, ? Uncertain /mixed perceptions, – Perceptions mainly negative

Table 16. *Included semistructured interviews (n=4) organised by research method, year of data collection, country, the legislative status of automatic substitution at the time of the study, quality of the study, number of participants, and their perceptions/experiences of automatic substitution of biologics, and the other main outcomes of the study.*

Year of data collection	Continent Country	Legislative status of automatic substitution of biologics #	Prescribers	Pharmacists	Patients	Other	Medical specialty	Quality of the study		Experiences and perceptions on automatic substitution of biologics, and the other main outcomes (if available).	Authors
	EUROPE										
2018	Finland	↔	7[a]	9[a]	2[a]	14[a1]	n/a	Not scored	+	50% had a positive attitude to substitution, 25% suggested that risks should be solved before implementing the substitution, 25% deemed substitution as an inappropriate model. Treatment-naïve patients were suggested the most suitable for substitution.	Tolonen et al., 2019 [394]
2017-18	Austria, Belgium, Croatia, Denmark, France, Ireland, Italy, Malta, Poland, Portugal, The Netherlands, UK, Spain, Switzerland, and pan-European perspective	◆	9	10	9	16[b]	E, G, HO N, R	Not scored	?	Both emotional (lack of trust and experience, loss of prescriber's control over treatment, fragile landscape regarding biosimilars) and practical (no pharmacists' mandate to substitution, insufficient communication systems between prescriber and pharmacist) barriers were identified. Most prescribers and pharmacists were not against pharmacist substitution providing the prescriber is informed about change and the treatment is under prescriber's control, but it was noted that participants disagreed automatic substitution also in the future. Addressed barriers, patient and product specific exceptions, and efficient system for reporting adverse events, are needed for the future to organise substitution in practice.	Barbier et al., 2020 [395]
2017	The UK	X	11	4		7[c]	Di, G, R	Not scored	–	The majority of participants had a negative attitude. A minority of the participants considered that substitution may occur in the future.	Aladul et al., 2018 [396]

2012-13	Belgium	X	2	3	1	13[d]	n/a	Not scored	?	Biosimilar substitution was considered more acceptable for treatment naïve patients.	Dylst et al., 2014 [397]

At the time of the study Please note, legislative status does not indicate if the substitution practice is implemented.
✓ Substitution is allowed in some circumstances, ↔ Substitution is not specified / not specifically prohibited, **X** Substitution is not allowed, ◆ Information is not available in consulted sources.
[a] Number of interviews, [a1] Interviews with authorities (n=7), representatives from industry and wholesalers (n=6), nurses (n=1)
[b] Patient (representative) (n=9), regulator (n=7)
[c] Nurses
[d] Authority (n= 4), academic (n=3), industry (n=6)
E = Endocrinology, Di = Diabetes, G = Gastroenterology, HO = Hematology/Oncology/Medical oncology, Np = Nephrology, R = Rheumatology, n/a = Not specified

5.3.2 PERCEPTIONS AND EXPERIENCES OF AUTOMATIC SUBSTITUTION OF BIOLOGICS

Most of the included studies (18/27) reported negative perceptions of the automatic substitution of biologics (Figure 16, Table 15, Table 16). Surveys conducted among prescribers (12/12) reported mainly negative perceptions of the study participants. Negative perceptions were also reported among pharmacists (2/5), patients (2/4), and mixed stakeholders (2/5). Except for one study, all studies that received funding from the pharmaceutical industry (Abbvie, Janssen, Pfizer, Sandoz) or a lobbying organisation (Alliance for Safe Biologic Medicines) (n=9) reported negative substitution perceptions of the study participants.

Five studies reported positive perceptions, and four mixed or uncertain perceptions. Of the studies with positive findings, two surveys were conducted among pharmacists, one among patients and one interview study among various stakeholders. In the only identified intervention study (no control group) conducted in a hospital pharmacy, patients did not report decreased satisfaction with their medication after substitution.

Most identified studies measured automatic substitution-related issues with a few structured questions. In two qualitative interviews with a prospective approach (Table 15), elements required for implementing automatic substitution of biologics were identified. In both studies, barriers and risks related to biologics' automatic substitution, such as the necessity of communication between HCPs, pharmacists' competency to counsel the patient in case of a change of the administration device, and a need for a reliable pharmacovigilance system, were identified. It was mentioned that making patient or product-specific exceptions (for example, "dispense as written") should be possible if needed. Substitution interval (i.e., how often the patient's medicine could be substituted), a clear mandate from a competent authority, and HCPs' and patients' trust in biosimilars should be addressed before implementing the substitution in practice.

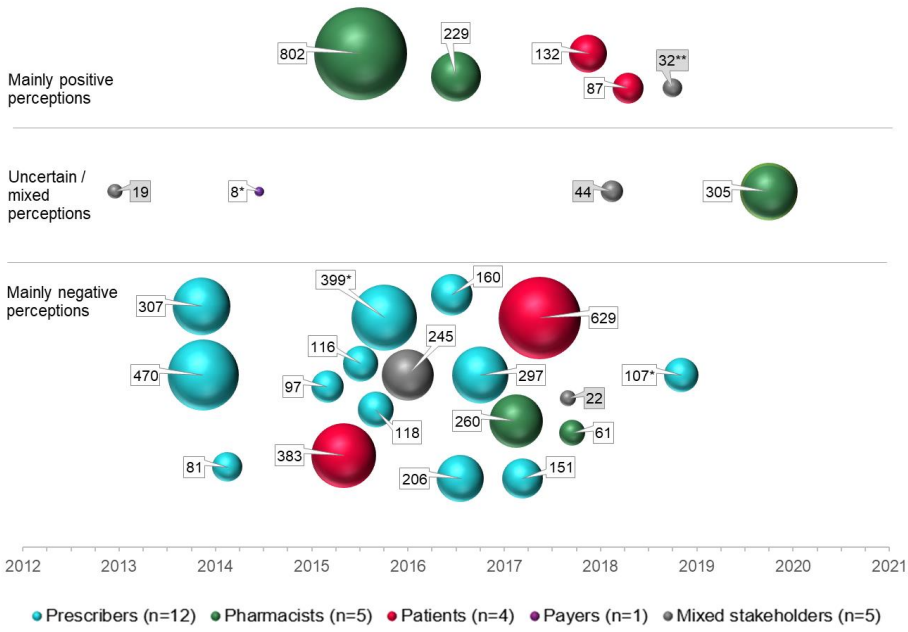

Figure 16. Perceptions of automatic substitution of biologics: the summary of the findings of the included studies (n=27). Each bubble describes one study. The bubble is centred in the middle of the data collection period as per year (*data collection time was not reported; bubble is centred by the date of manuscript submission). The colour of the bubble indicates the type of study participants as prescribers (n=12), pharmacists (n=5), patients (n=4), payers (n=1), and mixed stakeholders (n=5). The area of each bubble and the included numeric value describe the number of study participants (**units of analysis). White and grey backgrounds indicate the study type as surveys and interviews, respectively. The bubble is located in one of three segments depending on the perceptions of the participants on the automatic substitution of biologics.

5.3.3 QUALITY OF THE STUDIES

Of the included surveys (n=23), six (26%) were assessed as of high quality and six (26%) as of low quality (Study III: Supplementary Material 3). The rest of the surveys (n=11) were of moderate quality. The quality of the included surveys was compromised by a non-systematic approach in developing the questionnaire (22/23), which may increase the risk for ambiguous skewed questions, the lack of questionnaire testing (18/23), and potential response bias (18/23) (i.e., the risk that participants do not represent the target population, or the response rate is low). The study participants did not represent the defined population of interest in the study design in 14/23 of the surveys, and the response rate was poor in 8/23 or not reported at all in 10/23 of the surveys. The accurate data collection time was missing in three surveys.

The quality of the semistructured interviews (n=4) was assessed as appropriate for qualitative research. Interview reports lacked information on researchers' relationships with participants and the accuracy of the data collection process.

Half of the high-quality surveys (3/6) and one semistructured interview (1/4) reported mainly positive perceptions of the automatic substitution of biologics.

6 DISCUSSION

This study provides quite a recent picture of the market situation of biological medicines in outpatient care in Finland. The findings indicate that the market share of biosimilars has remained modest, and there is still a lack of price competition between biological products. Thus, there is a need to find new, more effective ways to promote the use of biosimilars so that biological treatments can be made available for as large number of patients as possible within the public healthcare budget limits.

Based on this study, automatic substitution could serve as a potential strategy to enhance the relative use of biosimilars and increase price competition between interchangeable biological products, even though reported experiences of the procedure's implementation in pharmacies were not found in scientific literature. Our stakeholder study showed that the implementation of automatic substitution of biologics in outpatient care requires careful planning that extends beyond technical implementation. Aspects to be considered relate to community pharmacists' competence and skills in advising patients with devices needed for the subcutaneous administration of biological medicines, which is their common administration route. As counselling medications requiring subcutaneous administration in outpatient care has been nurses' task so far, redefining tasks and intensifying cooperation, particularly between nurses and community pharmacists, are needed. There is also a need for joint guidelines and procedures with prescribers and community pharmacists on the principles of substituting biologics. Closer cooperation with patients is also required. For example, a possible substitution should be discussed between the prescriber and the patient with an assessment of whether the patient's condition and medical treatment are in balance for the transition to interchangeable medicine. Medical and practical reasons should also be considered when deciding on the general substitution interval for biologics. The three months substitution intervals currently used in generic substitution seem to be too short for biologics.

6.1 EVOLUTION OF THE USE OF BIOSIMILARS AND PRICE COMPETITION BETWEEN BIOLOGICS DURING 2009-2020 (STUDY I)

6.1.1 PRICES AND MARKET SHARES OF REFERENCE PRODUCTS AND THEIR BIOSIMILARS OVER TIME IN THE OUTPATIENT SETTING

The national retrospective register study provided several findings on the price and market share evolution of the reference products and their biosimilars in Finland during 2009-2020. First, biosimilar market entry reduced the price of its reference product in outpatient care in Finland, mainly due to the national pricing policy and public reimbursement scheme concerning the market entry of the first biosimilars. Second, biosimilar prices usually remained stable or decreased during the observation period depending on the number of competing biosimilars. Thus, the number of biosimilars seems to factor into increasing price competition. Third, the market shares of biosimilars were relatively minor compared to the market shares of the reference products, with significant variations between different active substances. The results indicate that previous national strategies and actions to increase the use of biosimilars have been ineffective. The same has been found in other recent studies from Finland [48,348].

Study I showed that the utilisation of biosimilars varied significantly between different biological agents, and the uptake is still modest among some active substances in outpatient care in Finland. Similar variation in biosimilar use has been observed between active substances elsewhere in Europe [49]. Despite the mandatory price reductions, the savings may not be gained if the patient's medication is switched to another competitor, such as a new modified version or a follow-on drug. In Study I, the new competitor with a more concentrated formulation of the insulin glargine gained significant market share after entering the market. A recent study on the Finnish pharmaceutical market showed that some patients treated earlier with a reference product were switched to new versions after the biosimilar market entry [348]. Thus, the generation of slightly modified new versions of the reference product is used to block the biosimilar competition.

The biosimilar prices mainly remained steady or decreased during our study period 2009-2020 in Study I. The price regulation of reimbursable biologics also affected the biosimilar prices, as the first biosimilar to be reimbursed had to be at least 30% lower priced than the reference product since 2017 [26,220]. In addition, the first biosimilar set the maximum price level for subsequent biosimilars. Our results show that introducing new biosimilars triggered a slight price reduction among the previous biosimilars if there were more than two biosimilars on the market. This finding may indicate that one or two biosimilars do not yet trigger price competition

between interchangeable products when the prices are in the public domain. Instead, much higher reductions are seen in the closed tendering of hospital drug formularies [301,332].

Study I showed that changes in the pharmaceutical pricing and reimbursement legislation in Finland in 2013 and 2017 seemed to explain almost all significant reference product price changes observed in our data [26,220,370]. In 2013, the wholesale prices of all medicines outside the reference price system were reduced by 5% [370]. In 2017, the amendments to Health Insurance Act (2004/1224) required price control for both the price of the first biosimilar entering the reimbursement scheme and the price of the reference product after the biosimilar has entered the market [26,220].

Since 2017, a single decline in a reference product price occurred relatively soon after the first biosimilar market entry due to mandatory price regulation. After that, only minor changes in the prices of the reference products were seen. Similar results concerning the decrease of the reference product prices after the biosimilar market entry have been reported previously in Finland and other European countries [48,398]. Four reference products (insulin lispro, filgrastim, epoetin, and enoxaparin) were no longer covered by the public reimbursement scheme at the end of the observation period, or a bit later since permanent price reductions were not executed [329,347].

The mandatory price reduction of the reference product may also curb incentives to switch to biosimilars by limiting price differences between products. Although using best-value biologics (BVBs) contributes to short-term savings, it may weaken the incentives of pharmaceutical companies to bring biosimilars to the market [2,398,399]. Further, companies developing biosimilars may not be willing to face tough public competition because several companies also have original biologics [236], which they want to be profitable even after the expiration of patents and data protection. Further, companies that market originator medicines may dump their prices in unpublic competition to prevent biosimilars from entering the market [398].

6.1.2 THE EFFECTIVENESS OF THE PREVIOUS AND CURRENT BIOSIMILAR POLICIES IN ENHANCING THE RATIONAL AND RESPONSIBLE USE OF MEDICINES IN FINLAND

In addition to price and reimbursement regulations amendments, the most significant change to enhance biosimilar use in Finland was the obligation to prescribe a lower-priced, comparable alternative to a biological medicine [339]. This was also the most important, quickly implemented change based on the Rational Pharmacotherapy Action Plan in order to obtain immediate cost savings [24,340]. Since the regulation on prescribing biosimilars has not resulted in the desired change in prescribing behaviours, the next potential measure could be the automatic substitution of biologics.

The effectiveness of the previous and current biosimilar policies to enhance the rational and responsible use of medicines in Finland can be evaluated with the results of Study I. Finland's biosimilar strategy has relied heavily on the biosimilar information provided by the Finnish Medicines Agency Fimea and the steering effect of pricing and reimbursement legislation [400]. These strategies mainly target on prescribing of biosimilars. Several studies have explored initiatives and policies that may influence biosimilar uptake [300,398,401–403]. Compared to other European markets, the biosimilar policy in outpatient care in Finland seems relatively ineffective [48,398]. Although the primary goal should not be the increased use of biosimilars but the use of medically appropriate best-value biologics (BVBs), the biologics market must be healthy and attractive for pharmaceutical companies to launch and maintain biologics in the market to reach sufficient price competition [2].

The impacts on biosimilar uptake of the efforts made in 2017 by mandating the prescriber to justify the choice if not prescribing the lowest-priced biologic were not seen in Study I [339]. However, it is possible that the outcomes of this intervention were hidden behind the more powerful intervention of pricing biosimilars and their reference products enacted in 2017 [26,220]. The interview study among Finnish physicians conducted by the Finnish Medicines Agency Fimea found that prescribers did not consider this degree-level regulation very binding [315]. Prescribers have received feedback on their biosimilar prescribing practices, as Social Insurance Institution has sent two feedback letters on biosimilars [48,342]. The positive feedback letter did not affect prescribing of biosimilars [48]. The consequences of the 2022 letter have not been published to date. Nevertheless, sharing biosimilar information alone does not seem to be sufficient to enhance the biosimilar uptake, as balanced information has to compete against misinformation and disparagement of biosimilars, and the use of biosimilars does not introduce immediate benefits to the prescriber, the patient, or the local healthcare institution [315,316].

The need to incite competition in the market is imperative not only for short-term savings but for the future. At the end of July 2022, 70 biosimilar products were approved in the European market, and the marketing authorisation applications of ten biosimilars were under evaluation by the EMA's Committee for Medicinal Products for Human Use (CHMP) [236,404]. In addition, nearly 140 original biologic drugs are expected to lose their exclusivity over the next ten years, opening more opportunities for developing and launching biosimilars [49]. Thus, more effective ways to increase biosimilar uptake are needed.

6.2 HOW THE IMPLEMENTATION OF AUTOMATIC SUBSTITUTION OF BIOLOGICS CAN BE CARRIED OUT SAFELY: STAKEHOLDER VIEWS (STUDY II)

Study II provided several aspects that need to be considered before implementing automatic substitution in practice. Based on the stakeholder interviews, education of healthcare professionals and patient counselling, suitability of administration devices, possibility to rule out the substitution, appropriate substitution interval, and traceability of the dispensed product are the key elements in the substitution.

6.2.1 EDUCATION OF HEALTHCARE PROFESSIONALS AND PATIENT COUNSELLING

Study II indicated that the HCPs need a wealth of detailed information on biosimilars, which is consistent to previous findings [50,318,405,406]. The outcome of substitution may be negatively influenced if the provided information is ambiguous or not sufficiently detailed [406]. The attitudes of the prescribers or other providers towards substitution have been shown to have an impact on the patient's acceptance to transition the medication and its perceived outcomes [226,407]. In generic substitution, lack of appropriate information has been shown to be confusing and raise doubts regarding the quality, safety, and efficacy of the generic product [408–410]. Regarding the experience of generic substitution, it is important to provide consistent information to patients about biosimilars, the reasons for the substitution and the dispensed product.

Study II identified potentially new roles for community pharmacists to facilitate safe and effective substitution of biologics. Patient counselling on any biological medicine is usually given by the prescribers and nurses in Finnish healthcare units. Community pharmacists are obligated by law to ensure that the patients know the appropriate use of medicinal products, including administration devices [8]. Thus, all suggested new roles are already within the current mandate of the Finnish pharmacies. Nevertheless, it seemed that introducing the substitution of biologics would require a major effort to educate and train community pharmacists in dealing with biologics, their administration devices and patient counselling. This finding was confirmed in the Finnish context in a study by Kaunisto et al. [411]. Based on the knowledge gaps in pharmacies, the Association of Finnish Pharmacies, in cooperation with the University of Helsinki and HUS Pharmacy, launched a scheme in which the knowledge of community pharmacists regarding biological medicines is increased [412]. Further, in the undergraduate curricula of pharmacists and all other HCPs, more attention should be paid to rational and responsible use of biologics and biosimilars.

Supportive information sources of biological treatments for patients were product-specific risk minimisation materials, as identified in Study II. Based on the assessment by the regulatory authorities, the marketing authorisation holder may be required to produce risk minimisation material, such as patient "alert cards" used to manage the adequate monitoring of treatment [280]. In general, the risk minimisation material of biosimilars should be consistent with the information of the reference product. To avoid confusion among patients, these materials should be as harmonised as possible [280]. Further, general information on biosimilars and their interchangeability is available in local languages and can be tailored to the needs of the pharmacies [413]. Ideally, pharmacies and local healthcare units should collaborate in developing patient counselling materials and techniques to increase synergy and avoid overlapping work.

6.2.2 ADMINISTRATION DEVICES

Study II indicated that patients' knowledge of the use of the administration devices is one of the key factors to the success of substitution. All administration devices for biosimilars and their reference products have been tested for usability at the time of marketing authorisation [16]. However, different administration devices can prevent transitioning [396]. In some cases, there may be clinically relevant differences in the usability of different devices, as experienced by certain patient groups. For instance, substitution may involve the use of a different type of device, such as an autoinjector instead of a prefilled syringe. Thus, to ensure safe substitution, the national authority must assess the suitability of administration devices for substitution in all relevant patient groups. The risk for clinically relevant problems when using different administration devices can be minimised with adequate patient counselling, including device training and good communication among the participants in the pharmacotherapy process (Figure 16). Community pharmacists should be able to provide the necessary device training if the patient or caregiver is unfamiliar with the new device to ensure the appropriate product administration.

6.2.3 RULING OUT THE SUBSTITUTION

Study II indicate that there may be situations where substitution of biologics is inappropriate. For instance, the patient may not have reached an optimal treatment response with the present medicine. In this case, substitution needs to be postponed until a rational decision can be made to substitute or switch, or prescribe a product with a different active substance (swapping). Substitution may also be inappropriate if the patient will not be able to use the new product due to physical handicap or other relevant reasons. Nevertheless,

patients and healthcare providers may consider a new device easier to use [320–323]. It is important that the physicians must present a clinically sound justification if they wish to prohibit the substitution. However, ruling out the substitution is not a new concept as, according to the local legislation, prescribers can prohibit generic substitution [226,229,414,415].

6.2.4 SUBSTITUTION INTERVAL

One of the concerns in Study II related to substitution was the frequency of transitions. The stakeholders seemed to favour longer substitution intervals for practical and safety reasons. Frequent transitions could overload the pharmacies in patient counselling and increase the risk of medication errors and potential transition-related adverse events, such as the nocebo effect. Multiple transitions may confuse patients and their caregivers [396]. Troubleshooting may also be difficult in cases of frequent transition or substitution and adverse drug reactions (ADRs) with long latency, such as immunogenicity and loss of efficacy. A long substitution interval may also increase the predictability of the market and simplify the logistics and the management of the stock in the pharmacies, especially for expensive biologics with limited shelf life. Thus, the optimal substitution interval for biologics should be determined by several theoretical and practical factors. The draft of the government's proposal in the summer of 2022 to unify all the biologic prescriptions as being valid for one year is a step towards a one-year substitution interval controlled by the validity of the prescription [416].

6.2.5 TRACEABILITY

One of the suggested risks in Study II was the traceability of the dispensed product. This concern has also been raised in some previous literature [417]. In contrast to general perception, the traceability of biosimilars and their reference products is already adequate [281]. The main challenge in the traceability of all biologics is the poor reporting of the batch numbers by HCPs. In contrast, the pharmacies in Finland are already obligated to record the batch numbers of all dispensed biologics [418]. Thus, traceability could be optimised at the pharmacies. The fact that the information related to substitution is not automatically transferred to patient records is a concern. Nonetheless, in Finland, a prescriber can find the dispensed medicine's brand name in the electronic prescriptions archive [419]. In addition, traceability could be further improved if the unique identifiers of prescription medicine packages introduced due to the prevention of falsified medicines were recorded in the electronic archive of prescriptions [418–420].

However, mere information about the products delivered to the patient is not necessarily enough, as participants in Study II indicated that medication

should be monitored. Combining information on trade names used in the treatment and even batch data with patient outcome data to monitor potential changes in patient outcomes would increase confidence among those involved in pharmacotherapy. For example, in Denmark, patient treatment outcomes have been followed in the national DANBIO registry, which has increased confidence in both biosimilars and the system, resulting in high biosimilar uptake [250,294,303,304]. The work to develop and establish national healthcare quality registers has also started in Finland [178,421].

6.3 THE STAKEHOLDERS' PERCEPTIONS AND EXPERIENCES OF AUTOMATIC SUBSTITUTION OF BIOLOGICS (STUDIES II AND III)

At the time of Studies II and III, the automatic substitution of biologics in community pharmacies was implemented only in a few countries, such as Australia. The regulatory framework allowed substitution in some countries although most of them were not implemented it into the practice.

The identified negative perceptions of automatic substitution of biologics may reflect the respondents' general mistrust of biosimilars and a breach of prescribing autonomy. According to recent studies, stakeholder perceptions of biosimilars are largely cautious, and their knowledge of biosimilars is scarce [50,314,395]. This mistrust can be intentionally generated or enhanced by biased opinion polls to influence biologics market shares. Feeding the ongoing debate with evidence from opinion polls indicating that physicians are against the substitution may be powerful in enhancing mistrust in biosimilars. Potential risks related to the interchangeability of biosimilars and their reference medicines have often been used as an argument in scientific debate [276,296]. However, no evidence has been found to support the assumption that a switch between biological medicine and its biosimilar has a negative impact on the efficacy, safety, or immunogenicity of the biological treatment [258,264,296,422].

Negative perceptions of the substitution of biologics among HCPs can influence public opinion, particularly the opinions of patients benefitting from the treatment with biologics, including biosimilars. These perceptions may reinforce patients' negative beliefs and induce adverse events or other unwanted treatment outcomes (also known as the nocebo effect) [297]. In prescriber-led switching, the nocebo effect has been suggested to be managed by shared-decision making between a prescriber and a patient [423]. However, other potential methods may also minimise the nocebo effect [424,425], which may be appropriate when considering automatic substitution. The fact that biologics substitution is generally not allowed reflects old legislation and

perceptions from the era before biosimilars. The past regulatory policies may increase negative perceptions.

The negative and suspicious perceptions concerning the automatic substitution of biologics seem to follow the same pattern seen previously with the generic substitution of small-molecule medicines [223]. Although the substitution of biologics is not fully comparable to that of small-molecule chemical drugs, the experiences of implementing generic substitution could be helpful in implementing the substitution of biologics. As known today, generic substitution has become a widely recognised and implemented procedure providing significant direct drug cost savings to medicine users and public budgets, especially if combined with the reference price system [200,206,426].

6.4 LESSONS LEARNED FROM THE IMPLEMENTATION OF GENERIC SUBSTITUTION

It is essential to see the similarity between the philosophies of generics and biosimilars. Thus, the widely used anti-biosimilar phrase "similar but not the same" does not distinguish between generic (e.g., different salts), biosimilars, or new versions of any biological drug associated with a change in the production process [427]. This is a critical aspect to demystify biosimilars and harness the history of generics to help explain the resistance to substituting biosimilars.

The current discussions on inciting the biosimilar uptake have a similar tone as discussions on generics in the early 2000s. Somewhat positive attitudes of prescribers toward biosimilars are not realised as active transitions of patients to biosimilars [48,50], as seen in biosimilar market shares in Study I. This conflict between knowledge and practice may be explained by the theory of cognitive dissonance that Festinger introduced in the early 1960s [428]. Most prescribers admit that current data demonstrate the therapeutic equivalence and interchangeability of biosimilars but still insist on data that are irrelevant for biosimilars instead of transitioning patients to a best-value biologic (BVB) [429].

Before generic substitution was introduced in 2003 in Finland, governmental attempts were made to influence physicians' prescribing behaviour [214,215]. The generic substitution was completed with a reference price system, as substitution alone did not steer strongly enough what brands were dispensed to the patients, especially in the case of expensive and highly reimbursed medicines [28]. Thus, when considering the biologics substitution, it is imperative to consider the introduction of a reference price system at the same time.

Pharmaceutical companies strive to maintain their product demand after a patent and data exclusivity [430]. Industry efforts to maintain demand have been varied and creative, including biobetter and me-too medicines [255]. There is also active but often subtle lobbying against generic and biosimilar medicines in originator manufacturers' tool packs, typically masked in patient safety concerns [431]. This phenomenon was also observed in Study III, where a significant share of the identified articles were opinion-poll-type questionnaires with convenience sampling not representing the populations of interest.

6.5 RATIONAL USE OF BIOLOGICAL MEDICINES

Rational pharmacotherapy is effective, safe, cost-effective, equitable, and of high quality [24]. In the EU, all biosimilars are evaluated through a strict marketing authorisation procedure to ensure that only effective, safe, and high-quality medicines enter the market [4,5,7]. Although several authorities and professional societies have positioned biosimilars approved in the EU to be interchangeable with the reference product and corresponding biosimilars, the statements have not led to the active prescribing of biosimilars in outpatient care which was observed in Study I [48,50,264,432]. The slow introduction of biosimilars endangers the cost-effectiveness and equality of rational pharmacotherapy in particular. Scientifically unfounded use of a more expensive medicine is inappropriate, particularly if clinically equivalent medicines are available. The lower prices of medicines can incite changes in treatment practices enabling more and more patients to start biological treatments at an earlier stage of their disease as identified in Study II. This boosts patient equality.

Evidence-based medicine relies on robust data on the safety and efficacy of medicines from randomised clinical trials. Prescribers are experienced in reading and interpreting phase III clinical efficacy data, but similar data are unavailable for biosimilars. Thus, prescribers and other HCPs may experience conflicts if they do not thoroughly understand the scientific concept of biosimilars [316]. This highlights the further need for educating HPCs on biologics and biosimilars in undergraduate and continuing education settings. In the past, good experiences to influence prescribing were gained from Rohto workshops [143]. A similar collaborative approach could be appropriate to enhance the prescribing of lower-priced biologics. However, information steering may remain ineffective if prescribers or their institutions do not have financial incentives to switch patients' medicine [300,401,433]. The recent social and healthcare reform [165] enables local structures to guide the prescribing of medicines. In the future, it may bring budgetary guidance to prescribing in outpatient settings.

The other option to promote the rational use of biologics is a top-down structural approach which obligates increasing the use of lower-priced biologics by legislation. The legislative interventions can cover, for example, prescribing, dispensing or reimbursements. Good experiences with generic substitution and the gained savings encourage considering to promotion of biosimilars in the dispensing phase. Finnish community pharmacies with highly educated staff have good conditions for implementing the automatic substitution of biologics as long as the national process is carefully planned with stepwise implementation. The goal of a careful approach should be to ensure medication safety throughout the process and to avoid potential risks identified in Study II.

Rather than substituting biologics in community pharmacies, the transition between interchangeable biologics would be much easier if the prescriber decided on the brand to be used in the treatment already at a patient appointment. This would allow the prescriber to take a comprehensive review of the patient's health status and discuss a brand choice decision with the patient. The initiation of the treatment with the most affordable interchangeable biological product is already in daily practice [48]. Instead, the incentives implemented until the end of the data collection period for this dissertation in Finland have not motivated prescribers to switch between products for patients already within biologic therapy (Study I).

Currently, the community pharmacy must dispense medicines based on biologics' prices, and patient counselling is conducted without access to sufficient patient data. If the substitution of biologics is introduced on a large scale in Finland, community pharmacists must have adequate access to electronic patient information in order to provide comprehensive support for patient self-management. This could also serve as a two-way communication path between healthcare units and community pharmacies. The change to allow adequate information sharing should be part of creating up-to-date electronic medication data in the national patient database system [167].

6.6 RELIABILITY AND VALIDITY OF RESEARCH METHODS

The strengths of Study I were the use of comprehensive nationwide data and the application of a robust scientific method suitable to analyse the impact of the interventions on the biologics market in outpatient care. In addition, a long observation period that covered almost the entire time biosimilars have been on the Finnish market was employed. Further, Study I was the first comprehensive nationwide analysis of biosimilars and their reference products from the Western markets.

Study I had some limitations. First, the other competitors of biosimilars, such as improved or modified versions and follow-on products, were excluded, except for two insulin products. Competitors with the same or a similar mechanism of action may impact the biosimilar market development. This perspective should be considered in pharmacoeconomic studies focusing on one or a few indications treated by biologics since broader inclusion criteria were unsuitable for the complete nationwide data used in Study I. Further, the effect of competitors should be noted as a potential bias in the statistical analysis. A reference product's price change could have been due to the market entry of any competitor and not precisely due to a biosimilar, as assumed in Study I. However, the graphs of the market shares and price evolutions in Study I supplement material support assumptions made in Study I.

Secondly, some extrapolations were needed when using wholesale data and wholesale weighted average prices instead of retail sales data. However, since the prices of biologics are relatively high, it can be assumed that community pharmacies are hesitant to store a lot of expensive medicines and the use of wholesale data is representative. In addition, the sales prices of prescription medicines are based on wholesale prices being the same in all Finnish community pharmacies. The use of the wholesale weighted average price may skew the prices if the monthly wholesale is minor and targeted to small package sizes. The defined daily doses (DDD) were used in Study I. DDDs describe the presumed average adult maintenance dose per day when a drug is used for its primary indication. These are not necessarily equal to the prescribed medication doses for patients. However, DDDs can be used to compare drug utilisation regardless of different strengths or package sizes between products and active ingredients. Additionally, the use of DDDs and ATC codes enables the international comparison of the results, increasing the findings' generalisability. However, the national context should be noted as biosimilar policies vary across Europe.

Although a wide range of stakeholders participated in the interviews in Study II, the community pharmacists and authorities constituted majority of the participants. Compared to other stakeholder representatives, the limited number of patients and nurses may have skewed the results. This may have been partially compensated by the views expressed by non-patients as "patient perceptions". However, there is often a difference between what patients actually think and what HCPs believe patients to think.

In Study II, the views of different professions were grouped together. This was because the aim of this study was to explore views from different stakeholders to build up a model for the automatic substitution of biologics rather than to compare differences in opinions between stakeholder groups. The individual and pair/group interviews were intentionally merged because the stakeholders nominated a varying number of representatives to be interviewed. In each interview, the participants represented only one stakeholder group, which might have mitigated differences in the dynamics of these approaches. The challenge to combine these two methods led to the

decision to analyse the data on the level of the interviews, not by each interviewee. In general, qualitative research is not suitable for drawing generalisable conclusions from observations. In Study II, including altogether 32 interviews, the strength of the perceptions was presented with the number of interviews representing the result. Finally, similar to all qualitative research, it is not possible to fully remove researcher bias in Study II. It should be noted that the results reflect the local circumstances in Finland and may not as such be applicable to other EU countries. However, the majority of issues covered in Study II are common to many European healthcare systems.

The systematic review in Study III applied a robust scientific method to collect comprehensive evidence on automatic pharmacist-led substitution of biologics. The strength of Study III was that two library information specialists participated in designing the search queries. Two researchers screened and selected the articles, and the quality of the included surveys was systematically assessed. The major limitations concern the amount and quality of research evidence found. The research evidence was mainly based on surveys of low to moderate quality without generalisable results due to convenience sampling and small sample sizes not representing the populations of interest. The applied survey instruments and measures were not tested or validated, and most studies did not have the automatic substitution of biologics as their primary objective. The level of evidence is low or very low generated in this type of studies.

Further, the healthcare systems in different countries and continents vary, allowing for various local combinations of physician-led switch and pharmacist-led automatic substitution. For example, biological medicines may be dispensed from a hospital pharmacy instead of a community pharmacy, and the transition from biologic to another interchangeable biologic may be coordinated by a multidisciplinary healthcare team. In the identified intervention study [372], prescriber informed the patients about the upcoming transition, and a substitution practice was conducted in a hospital pharmacy. On the other hand, these different dimensions in organising the substitution and variations in the prescriber's participation in the transition procedure may help find the optimum future procedures for safe automatic substitution practices, while substitution in community pharmacies is not widely allowed.

Although the data collected for this study covered the timeframe till the very recent years, it is still only a picture of that time. The interviews in Study II were conducted in the autumn of 2018, after which several changes in the national biosimilar policy were made.

6.7 PRACTICAL AND POLICY IMPLICATIONS

With advanced analytical methods, clinical trials and post-marketing experience, the understanding of biosimilars has dramatically increased in recent years. At the moment, the attitudes of prescribers, other HCPs, and patients significantly influence the deployment of biosimilars. The conflicting perceptions on the issue indicate the need for consistent and balanced information on biosimilars, especially their switching and substitution, but also the changes in biosimilar policies. Study I confirmed that although Finnish prescribers have quite positive views on biosimilars [315], the implemented initiatives have not been effective enough in promoting biosimilar uptake as the reference product had the highest market share at the end of the observation period in the several active substances. Therefore, new, more effective methods to incite biosimilar uptake and trigger price competition should be considered.

Generic substitution is a proven method to increase price competition among medicines and contain pharmaceutical costs in Finland [204,218]. Considering the practical aspects of substitution (Study II), it may be appropriate to implement the substitution of biologics with a stepwise approach before adopting the policy on a full scale. Effective and transparent communication campaigns to increase the knowledge and, thus, trust among patients, prescribers, pharmacists, and nurses are needed to prevent unintentional and intentional misinformation and the nocebo effect. Practical, safety and economic aspects should be monitored and studied during the first phases of implementation in order to obtain a comprehensive understanding of substantial benefits and risks as well as market dynamics associated with implementing substitution of biologics.

The optimal substitution frequency and deployment of the reference pricing system are essential elements in successfully implementing biologics' substitution. The substitution frequency of one year seems to be the most suitable from practical and safety perspectives (Study II). However, biologics are a heterogenous group of products, and some products (such as filgrastim) may suit for even shorter frequency. Relevant potential risks related to substitution can be prevented or mitigated by planning, execution, and testing. However, many of the perceived risks are not explicitly related to the substitution of biologics. As was seen with generic medicines, the full economic potential of substitution was missed in medicines with high reimbursements, as there was no financial incentive for patients to allow the substitution [28]. Thus, including the biologics also to reference pricing system should be considered. However, the rules for reference pricing of generic medicines may not be applicable.

6.8 RAPIDLY EVOLVING LANDSCAPE OF BIOSIMILARS IN FINLAND

Although the data for this study were collected up to recent years, it is still only a snapshot of the quickly evolving landscape. The interviews for Study II were conducted in autumn of 2018, after which various stakeholders, especially prescribers, have gained more practical experience with biosimilars. Several changes have also been made to the national biosimilar policy in Finland. In May 2022, the Ministry of Social Affairs and Health set up a working group to consider the implementation of automatic substitution of biologics in Finland [434]. Later in 2022, the Government gave two important proposals to the Parliament regarding biologics, both on prescribing [435] and automatic substitution [436]. Drafts for both proposals were subject to public consultation [416,437].

The law of the first proposal focusing on prescribing practices were approved in December 2022, and they came into action at the beginning of 2023 [435,438]. The prescribers are obligated by law (previously by degree) to prescribe the most lower-priced biological medicine. A prescriber can diverge from this only for patient-specific medical or therapeutic reasons. Any deviations must be justified in the prescription. According to the law, prohibiting the substitution must also be recorded in the biologic's prescription. The duty to supervise prescribing practices was assigned to healthcare units. Further, Social Insurance Institution was appointed as a supervising authority. In the same context, the validity period of all biological prescriptions was unified to one year.

During the public consultation on the draft of the government's proposal on the automatic substitution of biologics, the wide range of stakeholders gave critical statements [437]. In particular, the substitution interval of three months was deemed too short. Also, the inclusion of all interchangeable biologics in the automatic substitution and reference price system received criticism.

The government issued the proposal for the automatic substitution of biologics at the end of 2022 [436]. In the proposal to the parliament, the substitution interval was defined as six months, and some insulins were given a two-year transition period. According to the government's proposal, the amended Medicines Act and Health Insurance Act defining the legislative framework for automatic substitution of biologics would enter into force at the beginning of 2024. Thus, the practice of automatic substitution of biologics would start in pharmacies on April 1, 2024.

6.9 FUTURE RESEARCH

Economic, clinical, and humanistic (i.e., patient satisfaction, quality of life) outcomes of any changes in national biosimilar strategy and policies should be evaluated by parallel, ongoing monitoring and research. A wide range of research methods suitable for assessing the state of rational pharmacotherapy should be employed [101]. For example, studies utilising multiple databases, such as reimbursements, use, and pricing of biologicals for specific indications, combined with patient-reported outcomes, are needed to understand the overall impact of any biosimilar policy changes. However, the need for research should not limit or delay but support the national policy evolution of rational use of biosimilars.

Further, research on the knowledge of HCPs on biosimilars is needed to follow up on the evolution and identify the potential knowledge gaps in the field. In studies to be conducted among HCPs, a particular focus should be on interventions for both undergraduate training and continuing education 1) to increase the skills of all participants in the medication use process to communicate with one voice on biologics and 2) to improve the readiness of pharmacists to provide counselling on biologics. Study II pointed out that patient counselling by community pharmacists is essential in ensuring medication safety in biologics' substitution. Despite the emerging biologic substitution experience in some countries, the content of the information that community pharmacists should provide to patients and caregivers has neither been studied nor reported. Especially, studies exploring patient perspective and experience with biologics' automatic substitution are needed.

As indicated in Study I, the genuine price competition may need more than two biosimilars on the market, and the market dynamics of different biosimilars need future studies in Finland. Biosimilars have been in hospital formularies for years, and some good experiences have also been published in the Finnish context [332]. However, little is published about the savings generated by biosimilar uptake in hospital formularies. Although the tendered prices are not publicly available, research on biosimilars' impact on healthcare budgets in inpatient care is also needed. Further, merging the data from different patient care settings would provide interesting information on the overall costs of biological treatments.

7 CONCLUSIONS

- The prices of the reference products seem to decrease, and biosimilar prices seem to remain stable or decrease after the biosimilar market entry. However, legislation and initiatives implemented until August 2020 did not support price competition between biosimilars and reference products. As a result, biosimilars had a minor market share among some of the biologics in Finland, with significant growth potential in the future.
- Even though automatic substitution of biologics has been suggested to be a potential strategy for controlling growing healthcare costs, the identified international research evidence on practices, experiences, and perceptions of any relevant stakeholders on automatic substitution of biological medicines is mainly based on opinion polls and surveys, yielding results that are neither generalisable nor suitable for guiding policymaking.
- Perceptions of the Finnish stakeholders on automatic substitution of biologics in community pharmacies were more positive than in previous international studies. However, several reservations were presented, and risk mitigation measures were deemed necessary. The identified medication safety risks can be mitigated by an appropriate substitution procedure developed in collaboration with relevant stakeholders, including patients, and piloted in pharmacies. The risks were suggested to be prospectively managed before the large-scale implementation of the automatic substitution of biologics.
    - Substitution interval (e.g., how often the medicine could be substituted in the pharmacy) was suggested to impact both medication safety and pharmaceutical market attractiveness.
    - Relevant product information, presentations and administration devices were identified as critical factors to be assessed by the national authority on each product before listing the product as substitutable.
    - Consistent and unbiased information is needed for all substitution stakeholders, including patients.
    - The substitution introduces new tasks and communication needs to those involved in the actual medication use process, particularly to community pharmacists who will be responsible for substitution and counselling the patients.
- Economic, clinical, and humanistic (i.e., patient satisfaction, quality of life) outcomes of substitution and any other changes in national biosimilar strategy and policies should be evaluated by parallel, ongoing monitoring and research.

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APPENDICES

Appendix 1. Data collection of the EU-authorised biosimilars and their market availability status in Finland (Figures 10 and 11)

The data of authorised biosimilars in the EU were searched on the European Medicines Agency's website[1] on July 30, 2022. Search filters were selected as follows:

- Medicine: European public assessment reports (EPAR);
- Authorisation status: Authorised;
- Medicine type: Biosimilar.

The search resulted in 70 biosimilars.

From the product details, items of (marketing) name, active substance, anatomical therapeutic chemical (ATC) code, and the date of issue of marketing authorisation valid throughout the EU were extracted to Microsoft Excel.

The market availability status of the identified biosimilars was searched from the basic register downloaded from the website[2] of the Finnish Medicines Agency Fimea. The datasets were updated on July 25, 2022.

The date of market entry was extracted from the dataset of 'Pakkaus_0' for each biosimilar regardless of the type of the biosimilar package or if the package is still available in Finland. The market entry and exit dates, if available, were combined with the data extracted from EMA's website. If any market entry date was not given, the biosimilar was deemed with status "not brought on the Finnish market". In addition, ATC codes of identified biosimilars were reviewed to identify any nationally authorised biosimilars. For identified items, their biosimilar status was checked from FimeaWeb, a pharmaceutical product database provided by the Finnish Medicines Agency Fimea[3].

1 European Medicines Agency. Medicines. Search. https://www.ema.europa.eu/en/medicines Accessed July 30, 2022.

2 Finnish Medicines Agency Fimea. Basic register [in Finnish]. https://www.fimea.fi/laakehaut_ja_luettelot/perusrekisteri. Accessed July 30, 2022.

3 Finnish Medicines Agency Fimea. FimeaWeb. https://www.fimea.fi/web/en/databases_and_registers/fimeaweb. Accessed July 31, 2022.