UNIVERSITY OF COPENHAGEN
DEPARTMENT OF PHARMACY

PhD Thesis

Louise C. Druedahl

The current and evolving European regulation of biosimilars: views from industry and medicines agency regulators

Supervisor: Professor Anna Birna Almarsdóttir

This PhD thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 30 October 2020

Version for digital release

Author

Louise C. Druedahl, MSc. Pharm.

Copenhagen Centre for Regulatory Science (CORS) and Social and Clinical Pharmacy Group,
Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen

Thesis title

The current and evolving European regulation of biosimilars: views from industry and medicines agency regulators

Principal supervisor:

Prof. Anna Birna Almarsdóttir

Social and Clinical Pharmacy Group, Department of Pharmacy

Faculty of Health and Medical Sciences, University of Copenhagen

Co-supervisors

Assoc. Prof. Marco van de Weert

Drug Delivery and Biophysics of Biopharmaceuticals, Department of Pharmacy

Faculty of Health and Medical Sciences, University of Copenhagen

Prof. Marie Louise De Bruin

Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy

Faculty of Health and Medical Sciences, University of Copenhagen

Utrecht Institute for Pharmaceutical Sciences,

Utrecht University, the Netherlands

Prof. Timo Minssen

Centre for Advanced Studies in Biomedical Innovation Law (CeBIL)

Faculty of Law, University of Copenhagen

Dr. Hans Hoogland

Senior Regulatory Intelligence Specialist

LEO Pharma A/S, Denmark

Assessment Committee

Assoc. Prof. Christine Erikstrup Hallgreen
Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy
Faculty of Health and Medical Sciences, University of Copenhagen

Dr. Nikolai Brun
Director of Division, Medical Evaluation and Biostatistics
Danish Medicines Agency, Denmark

Prof. Allyson Pollock
Institute of Population Health Sciences
Newcastle University, England

List of Papers

This thesis is based on the following papers:

Paper I

Druedahl LC, Almarsdóttir AB, Kälvemark Sporrong S, De Bruin ML, Hoogland H, Minssen T, van de Weert M, Kesselheim AS, Sarpatwari A. *Biosimilar Manufacturing Challenges: A Qualitative Study of Manufacturer and Regulator Perceptions*. Preprint version.
Accepted, Nature Biotechnology, under the title: A qualitative study of biosimilar manufacturer and regulator perceptions on intellectual property and abbreviated approval pathways.

Paper II

Druedahl LC, Kälvemark Sporrong S, van de Weert M, De Bruin ML, Hoogland H, Minssen T, Almarsdóttir AB. *Finding a sound balance for biosimilar clinical requirements: Perceptions of industry and European national medicines agency regulators*.
Submitted.

Paper III

Druedahl LC, Kälvemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, van de Weert M, Almarsdóttir AB. *How to solve the question of biosimilar interchangeability? A qualitative study*.
In-preparation.

Preface

Dear Reader,

When I started this PhD journey, I had only scratched the surface of the field of biosimilars and its complexities. My preunderstanding was that little was known about biosimilarity and how it is delimited, admittedly I was rather skeptical about these products. Now, I see that I was limited in my understanding as I did not see how biosimilarity is evaluated on a case-by-case basis due to the complexity of biological molecules. Currently, I see biosimilars as relatively complex products from a costly development that have a much greater potential in society than is currently the case.

When I started this journey and using a cross-disciplinary approach, my mind was still thinking in silos about biosimilars through the lens of each discipline separately. Little did I know that my horizon would expand to view the intersections and complexities of when protein formulation, law, regulatory science, and pharmaceutical policy interact, overlap and complement each other in the understanding of biosimilars. This learning did not come easily, and I am forever grateful to all of those who helped me along the way to handle the frustrations and who opened my eyes to the richness offered by interdisciplinary research.

For me it has been a great decision to embark on a PhD journey. All moments with ups and downs have played a part in shaping me as a researcher and I have enjoyed it all. I am grateful for learning the handicraft of science and the opportunity to embed myself in my passion for research. For me, it has been a remarkable journey that in some ways can be described with this quote by Michel Foucault:

> *"I don't feel that it is necessary to know exactly what I am. The main interest in life and work is to become someone else that you were not in the beginning.*
>
> *If you knew when you began a book what you would say at the end, do you think that you would have the courage to write it?*
>
> *What is true for writing and for a love relationship is true also for life.*
>
> *The game is worthwhile insofar as we don't know what will be the end." [1] (p.9)*

With this thesis, I hope to contribute to the field of biosimilars, ultimately, to benefit patients.

Louise C. Druedahl, 30 October 2020

Abstract

Background

Regulatory approval of biosimilars, i.e., highly similar versions of originator biological products (the reference products), came about to foster competition and lower drug prices; however, the degree to which these goals have been achieved varies. Biosimilars provide opportunities to relieve healthcare system budgets and increase access to medicines, but reported challenges for these products include trade secret protection and complex manufacturing processes.
This PhD research is based within regulatory science but applies a cross-disciplinary approach by integrating knowledge about therapeutic proteins and their manufacturing, patent and trade secret protection, regulatory science, and pharmaceutical policy.

Aims

The overall aim of this thesis is to investigate how medicines agency regulators and the pharmaceutical industry view the current and future European regulatory landscape of biosimilar development and approval. The specific aims are:

- To identify key scientific, legal, and regulatory challenges in biosimilar development and their effect on biosimilar market entry (Study I).
- To determine the value and necessity of the European biosimilar clinical comparability trial requirements for establishing biosimilarity (Study II).
- To investigate the current European regulatory practices and the science underpinning interchangeability (Study III).

Methods

A qualitative approach was used to collect expert knowledge from medicines agency regulators and the pharmaceutical industry. Empirical data were collected from September 2018 to August 2019 via semi-structured, in-depth interviews for the conduct of the three studies. Twenty- three interviews were conducted with 25 participants, hereof eight EU national medicines agency regulators and 17 company participants. Sampling was purposeful and the participants were recruited using networking and snowballing as sampling strategies. Content analysis was applied by two analysts and audited by a third researcher.

Results

According to the participants, establishing biosimilarity for recombinant proteins is not scientifically challenging if there is access to biotechnology expertise. Further, that trade secrets are surmountable barriers to biosimilar development, but that patents are obstacles because of the large number of patents protecting each biological product. This is particularly relevant regarding the lack of an efficient search mechanism, a lack that leaves biosimilar developers with considerable uncertainty about the patent landscape protecting originator biologics.

Regarding the current regulatory requirements, participants predicted that the clinical trial requirements for comparable efficacy will be reduced. The arguments for and against this were both a matter of science and of aspects of competition, ethics and physicians' trust. Currently, the scientific discussion is fueled by advances in analytical testing of recombinant proteins and the knowledge generated from former biosimilar approvals.

Interchangeability was also a topic widely focused on by participants, who saw interchangeability as relating to regulatory practices, formal competences and trust and not only as a matter of science of likeness between two biological molecules. Biosimilar switching was largely supported by the participants. Some participants perceived substitution of biologics as an unexplored area filled with unknown potential risks, while others believed that there is sufficient scientific evidence to support it. According to the participants, the lack of scientific clarity of interchangeability might be resolved if the EMA, based on their expertise from biosimilar approvals, could hold a scientific and advisory opinion on interchangeability. The participants disagreed on whether EU countries should allow substitution of biologics; however, the company participants and most regulators were not in favor of this.

Conclusion

The European regulation of biosimilars is a success; nevertheless the participants from European national medicines agencies and the pharmaceutical industry portray a picture of biosimilars as a diverse and complex field undergoing rapid change. The current regulation may undergo changes regarding the biosimilar clinical trial requirements. Further, the European regulation of biosimilars is expected in the future to contain regulation for approval of biosimilars of recombinant orphan drugs; however, changes to the existing framework are likely to be needed for the next generation of follow-on products to gene- and cell-based therapies. Regulatory clarity on interchangeability of biosimilars would be a fruitful next step to ensure scientific grounds for either embarking on or refraining from realizing substitution of biologics in the near future.

Resumé

Baggrund

Den regulatoriske godkendelse af biosimilære lægemidler – dette vil sige meget ens versioner af originale biologiske produkter (referenceprodukter) – blev indført for at skabe konkurrence og for at sænke priserne på medicin. Successen med at bruge biosimilære lægemidler for at nå disse mål har dog være begrænset. Biosimilære lægemidler muliggør "luft" i sundhedssystemers budgetter og forøger tilgængeligheden af medicin, men tidligere rapporterede udfordringer for produkterne indbefatter beskyttelse fra forretningshemmeligheder, samt en kompleks produktionsproces.

Dette ph.d. forskningsprojekt er forankret indenfor regulatorisk videnskab, men applicerer en tværfaglig tilgang som integrerer viden om terapeutiske proteiner og disses produktion, beskyttelse fra patenter og forretningshemmeligheder, regulatorisk videnskab og farmaceutisk policy.

Formål

Det overordnede formål med denne afhandling er at undersøge hvordan lægemiddelmyndighedspersoner og ansatte i den farmaceutiske industri opfatter det nuværende og fremtidige europæiske regulatoriske landskab for udvikling og godkendelse af biosimilære lægemidler. De specifikke underformål er:

- At identificere essentielle videnskabelige, juridiske og regulatoriske udfordringer med udvikling af biosimilære lægemidler og disse effekt biosimilære lægemidlers markedspenetration (Studie I).
- At bestemme værdien og nødvendigheden af de europæiske krav til komparabilitets kliniske forsøg for biosimilære lægemidler hvad angår etablering af biosimilaritet (Studie II).
- At undersøge de nuværende europæiske regulatoriske praksisser og videnskaben som ligger til grund for udskiftelighed (Studie III).

Metode

En kvalitativ tilgang blev brugt til at indsamle ekspertviden fra lægemiddelmyndighedspersoner og ansatte i den farmaceutiske industri. Empiriske data blev for alle tre studier indsamlet mellem september 2018 og august 2019 via semi-strukturerede, dybdegående interviews. Treogtyve interviews blev foretaget med 25 deltagere, heraf otte deltagere fra EU nationale

lægemiddelstyrelser og 17 deltagere fra lægemiddelfirmaer. Sampling var strategisk og interviewpersonerne blev rekrutteret ved brug af networking eller sneboldemetoden. En indholdsanalyse blev udført af to forskere og auditeret af en tredje forsker.

Resultater

Ifølge interviewpersonerne, er det ikke videnskabeligt udfordrende at etablere biosimilaritet for rekombinante proteiner hvis der vel at mærke er adgang til bioteknologisk ekspertise. Desuden er forretningshemmeligheder overkommelige barriere for udvikling af biosimilære lægemidler, mens patenter virker forhindrende på grund af de store antal patenter, der beskytter hvert enkelt biologiske produkt. Dette gør sig især gældende i forhold til, at der mangler en effektiv søgemekanisme, hvilket efterlader udviklere af biosimilære lægemidler med en betydelig usikkerhed omkring patentlandskabet, der beskytter originale biologiske lægemidler.
I forhold til gældende regulatoriske krav, forudsiger interviewpersonerne, at kravene til kliniske forsøg til sammenlignelig effekt vil blive reduceret fremover. Argumenterne for og imod dette handler både om videnskab, men også omkring konkurrence, etik og lægers tillid. På nuværende tidspunkt er den videnskabelige diskussion drevet af fremgang inden for analytiske testning af rekombinante proteiner og den opnåede viden fra tidligere godkendelser af biosimilære lægemidler.
Udskiftelighed var også i fokus hos interviewpersonerne, der så udskiftelighed som relateret til regulatorisk praksis, formelle kompetencer og tillid: og ikke kun som et videnskabeligt spørgsmål om lighed mellem to biologiske molekyler. Et skifte til biosimilære lægemidler blev generelt støttet af interviewpersonerne, men nogle af dem anså substitution af biologiske lægemidler som et uudforsket område fyldt med ukendte, potentielle risici, mens andre mente at der er tilstrækkelig videnskabelig evidens til at støtte substitution. Ifølge interviewpersonerne kan den manglende videnskabelige klarhed omkring udskiftelighed muligvis blive løst hvis Det Europæiske Lægemiddelagentur (EMA), baseret på dets ekspertise fra godkendelser af biosimilære lægemidler have en videnskabelig baseret og rådgivende holdning til udskiftelighed. Interviewpersonerne var uenige om, hvorvidt EU lande bør tillade substitution af biologiske lægemidler. Samtlige interviewpersoner fra lægemiddelfirmaer og de fleste fra lægemiddelmyndigheder var imod dette.

Konklusion

Den europæiske regulering af biosimilære lægemidler er en succes, men interviewpersonerne fra nationale europæiske lægemiddelstyrelser og den farmaceutiske industri beskriver et billede af

biosimilære lægemidler som et diverst og komplekst felt i rivende udvikling. Den nuværende regulering vil muligvis ændres i forhold til krav til kliniske forsøg for biosimilære lægemidler. Derudover, vil den europæiske regulering af biosimilære lægemidler sandsynligvis kunne indeholde fremtidige godkendelser af biosimilære lægemidler til rekombinant medicin for sjældne sygdomme. Dog vil der sandsynligvis være behov for ændringer til det eksisterende ramme for efterfølgende produkter til gen- og cellebaseret terapi. Ydermere vil regulatorisk klarhed om udskiftelighed af biosimilære lægemidler være et formodentligt næste skridt for at sikre videnskabelige årsager til enten at gå i gang med eller at afstå fra at realiseret substitution af biologiske lægemidler i nærmeste fremtid.

List of Abbreviations

ADAs	Anti-drug antibodies
Biologics	Biological medicinal products
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, manufacturing and control
CQA	Critical quality attribute
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IPR	Intellectual property right
NAb	Neutralizing antibody
PD	Pharmacodynamic
PK	Pharmacokinetic
SPC	Supplementary protection certificate
US	United States of America
QbD	Quality-by-design
QTPP	Quality target product profile

Table of contents

Introduction

Biologics are complex molecules that exert highly specific actions in the body [2]. They treat illnesses such as cancers and autoimmune diseases [3]. Biologics have revolutionized the field of medicine by providing an increasing number of new types of therapies [4,5]. However, biologics are expensive and this expense is the main driver of rising drug costs [6]. The global biologics market is forecast to reach $452bn in 2022, a $175bn rise from 2017 [7].

Many countries have enacted abbreviated approval pathways for follow-on products to biologics, 'biosimilars', as a means of fostering competition and increasing access to biologics treatments, while continuing to incentivize innovative therapies [8,9]. The intention was to achieve a cost-lowering effect, analogous to that of generics for small molecule-drugs [10]. The EU was a frontrunner in introducing regulation for biosimilars and in defining these products as highly similar versions of an already approved biologic (the reference product) [8,11]. The first biosimilar was authorized in 2006 [8] and as of October 1, 2020 the European Medicines Agency (EMA) has approved 67 biosimilars for 17 reference products [12]. The US regulatory authorities introduced biosimilars in 2010 [13], and by June 2020, the EMA and the US Food and Drug Administration (FDA) had approved biosimilars for 16 and nine active substances, respectively [14].

In the EU in 2018, biologics accounted for 30% of drug spending, of which 1.5% was on biosimilars, and 21% (€12bn) of the amount spent on biologics was exposed to competition from biosimilars [15]. The uptake of biosimilars for top-selling products is fast, leading to substantial price reductions, for example, up to 89% for adalimumab [15]. However, the uptake varies across active substances and between EU countries, and access has not increased similarly for all types of active substances ranging from 3% for oncology treatments to 30% for epoetins [15,16]. Additionally, estimates indicate that only one-third of biosimilar sales exceed $100m, which is seen as the lower threshold for biosimilar development costs and a low investment return [15]. Moreover, the expensive development is a cost barrier to biosimilar development [17]. Other previously reported challenges for biosimilars include 1) complex manufacturing process, 2) intellectual property rights, 3) lack of fully accepted regulatory process by some stakeholders, 4) lack of incentives for physicians to prescribe, 5) uncertainty about substitution by pharmacists, and 6) strong ties of originator companies with physicians and patients [18].

There is currently an incomplete picture of how different stakeholders perceive the challenges and opportunities attached to biosimilars and how these relate to the regulation of biosimilars. The views of patients and physicians have been studied before with questionnaires [19– 25], but they do not

directly affect the regulatory process. By contrast, medicines regulators are central and industry is their client and, as such, the industry is heavily dependent on regulators' experience, views and expertise within the area of biosimilars. Investigating medicines regulator and industry perspectives will thus provide valuable information on the status of the field and where requirements for and the concept of biosimilars are moving. The primary focus of the research is the EU as it is the jurisdiction with the most extensive experience with biosimilars. The overall objective of this doctoral research is to answer the research question:

"How do medicines agency regulators and the pharmaceutical industry view the current and future European regulatory landscape of biosimilar development and approval?"

This doctoral research is within regulatory science but uses a cross-disciplinary approach to obtain multiple perspectives on the research question. Understanding this landscape requires knowledge about biosimilars from the aspects of therapeutic proteins and their manufacturing, the influence of patent and trade secret protection on their development, regulatory science to evaluate the regulation of biosimilars, and pharmaceutical policy to consider the societal consequences of how biosimilars are regulated. These aspects are dealt with in the following background section.

Background

Biosimilars are approved on the basis of biosimilarity rather than bioequivalence as for generics [26]. The many scientific differences between small-molecule and biologic drugs (such as large differences in manufacturing and molecular complexity) led to a need to change the European regulation to enable biosimilar approvals [11,27,28]. Biosimilarity describes the likeness between two biological products and the concept of comparing biotechnological products was first introduced by the FDA in 1996 [29,30]. The FDA provided guidance for manufacturers of originator biologics on product comparability pre- and post- manufacturing change to evaluate whether the change affected the safety, identity, purity, or potency of the product [29]. In a concept paper from 1998, the EMA discussed the same topic, but also the possibility of a scenario of comparability between recombinant proteins made by two different manufacturers [30].Thus, the scientific principles of comparability between products from different manufacturers rely on those applied regarding impact of manufacturing changes for biologics [11]. The realization that two manufacturers could create highly similar products from different processes was a key step because biologics have been described as "the process is the product" due to the considerable influence of the manufacturing process on the final product [10]. This step paved the way for the concept of biosimilarity and thus also for biosimilars as follow-on products to originator biologics.

Biologics can vary considerably in molecular size from relatively simple biologics such as insulin to larger, more complex molecules such as the monoclonal antibody adalimumab [31].

Biologics are a heterogeneous class of drugs, and other types of biologics other than recombinant proteins include vaccines, blood-clotting factors as well as gene- and nucleic acid-based therapies [4]. However, most biologics, including biosimilars, are often produced using biotechnological methods yielding recombinant proteins [27]. Therefore, the focus will be on these products for the remainder of this thesis.

The focus of this background section is firstly on the variability of proteins influenced by the complex manufacturing process for biologics. Thereafter, on intellectual property and trade secret protection of medicines and how this might influence biosimilar development. This is followed by the definition of biosimilarity and biosimilar approval requirements. Finally, the background of how the concept of biosimilarity relates to switching and substitution practices.

Variability in Protein-based Biologics

Biologics originate from living organisms; therefore, inherent variability can be expected in the final biological product [31–33]. This is in contrast to chemically-synthesized drugs, where exact copies can be made [31]. Proteins can vary due to several factors, for example, their expression in host cells, throughout manufacturing, and variations arising from storage and transportation [32]. This introduces some possible concerns regarding the activity of the drug, as this variability (especially in post-translational modifications) can affect pharmacokinetics (PK) and pharmacodynamics (PD) [34]. Some types of variability related to the manufacturing process and formulation include protein sequence (in principle not allowed for biosimilars), protein post-translational modifications (unavoidable), protein degradation products and process-related impurities (for example, host-cell proteins). Biologics have a potential for immunogenicity, and this can be linked to, for example, process-related impurities and hence require careful assessment [35]. Product variations are the case for both originator and biosimilar products [36]. The task for biosimilar manufacturers is to know the variation of the reference product and to make a highly similar product despite the proteins' inherent variation [32]. In this section, recombinant proteins and their manufacturing are first described, then how variations occur in these large molecules, followed by reverse-engineering as the main characteristic of biosimilar development.

Recombinant proteins and their manufacturing

A protein typically consists (a) chain(s) of more than 50 linked amino acids [37]. Such chains of amino acids form the basis for a protein's three-dimensional folding [37]. The three- dimensional structure of a protein is typically divided into primary, secondary, tertiary and quaternary structures and influences the protein's biological function [37]. Recombinant proteins are manufactured using recombinant DNA technology [38], see Figure 1.

Overall, recombinant DNA technology allows production of specific target proteins expressed via cell-based systems [39]. Firstly, the coding sequence for the target protein is incorporated into a vector and transferred to the chosen cell expression system [40]. From this cell, the target protein can be expressed and produced [40]. Thereafter, the chosen cell system is stored in a master cell bank for all future manufacturing of the protein [40]. To start production, a sample from the master cell bank stock is expanded to production scale [40].

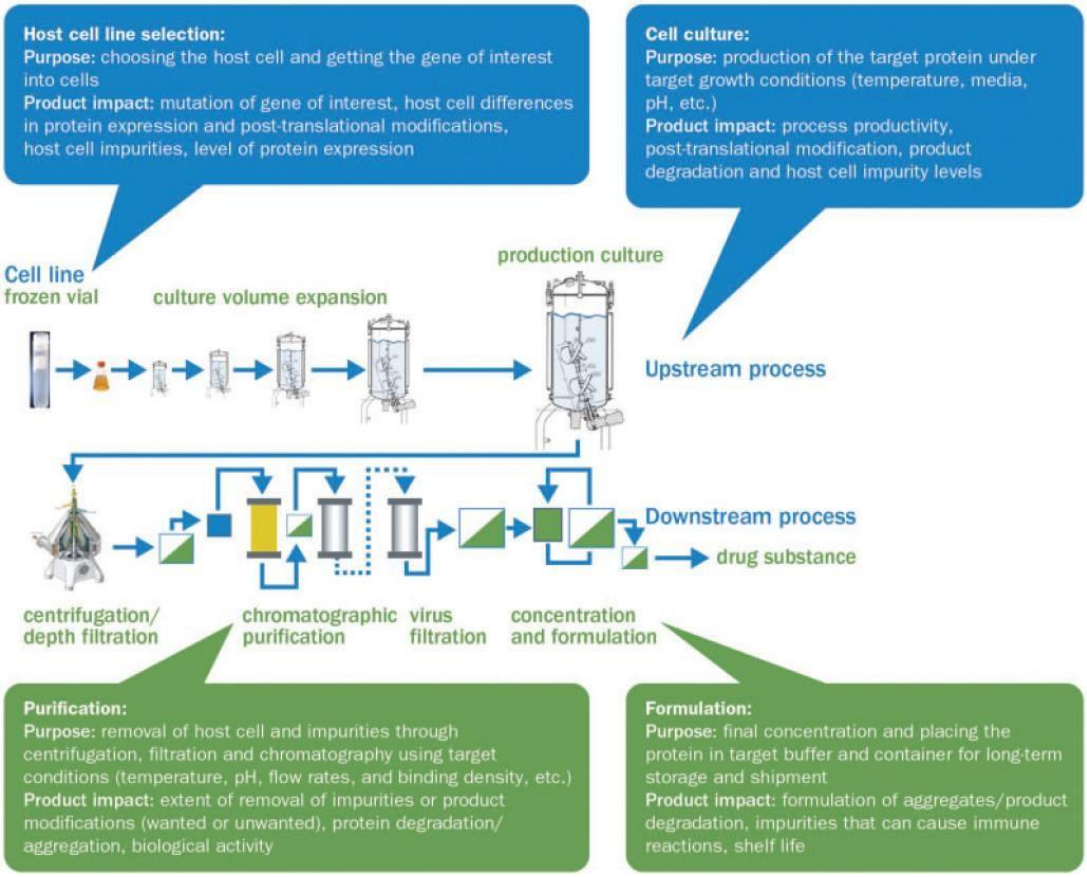

Figure 1. Recombinant protein manufacturing and the effects of the manufacturing steps on the final product. Used with permission from Vulto and Jaquez [32]**.**

The initial part of the manufacturing of a recombinant protein is expression and growth, as can be seen in Figure 1. The choice of host cell line is vital because different cell lines add different post-translational modifications to the target protein [32]. One of the most common post-translational modifications is glycosylation (carbohydrate moieties added to the protein molecule during expression) [41]. The specific glycosylation pattern varies between the type of host cells [32], and a protein with a complex glycosylation pattern can exist in over a hundred different variants even in a well-controlled production [42]. Glycosylation can influence both the biological activity and the immunogenicity of the product [41]. Further, different host cells will also result in various host cell impurities in the final product that will be specific for the given manufacturing process. During growth of the cells, optimized growth conditions (such as temperature, media and pH) are essential both for obtaining a high yield of the target protein, and for avoiding changes to the protein's structure [40].

For example, slight variations in the cell culture conditions can have a marked influence on glycosylation pattern and impurities [32].

After expression and growth, the cells have produced the target protein, which is harvested and then present in the bulk solution [40]. The subsequent manufacturing step is purification, see Figure 1, where the protein is often purified using several chromatographic steps [39,40]. The purpose of the purification is to remove degradation products and impurities, such as host cell residues, while maintaining the target protein [32]. Further, it is also an aim during purification to isolate the target protein from other variants produced by the cell expression system as well as degradation products [32]. Despite extensive purification during manufacturing, there will still be microheterogeneity in the final product, and batch-to batch variation for biologics is common [28,32].

After the purification has been completed, the target protein is formulated into the final drug product [40]. The final formulation must provide an environment in which the target protein can be stable despite both chemical and physical stress, in order to secure a reasonable shelf-life of the product [32]. Characterization of the final product is important for assessing whether manufacturing has been successful. The characterization should include a physicochemical characterization of the primary and higher order protein structures, molecular weight and quantity as well as characterization of purity and impurities, biological activity and if relevant the glycan profile of the protein [32,38].

Protein stability and control of variation

Throughout the manufacturing process, the target protein will be affected by various stresses and environment changes [39]. These changes can cause both chemical and physical instability for the proteins which can lead to protein degradation [32]. Chemical instability involves covalent modification of the protein molecule such as via deamidation, whereas physical instability includes protein unfolding and aggregation [43,44]. Aggregation is assembly of the target protein with itself or other protein structures, a process which is often irreversible [44]. Further, aggregation can occur during manufacturing, shipping and storage of the product [44]. There is much focus on the formation and presence of aggregates, and thus their minimization in the final product such as removal during the purification process, as they are implicated in immunogenicity [32].

Immunogenicity is linked to the presence of anti-drug antibodies (ADAs) and such unwanted immune responses can range from mild to life-threatening [35,45]. An ADA is termed a neutralizing antibody (NAb) if it binds to the therapeutic protein and inhibits the protein's biological activity [35]. ADAs have been associated with reduction of efficacy as well as adverse effects of a biologic [35,45].

A protein's sensitivity to changes in manufacturing parameters forms the basis for analyzing how different manufacturing steps affect the target protein [46]. One systematic approach to assuring the quality of the final product is quality-by-design (QbD) [47]. This approach aims to reduce product

variation by continuously monitoring a number of critical process parameters during manufacturing [48]. Process parameters are, for example, temperature or flow rate during chromatographic purification [48]. Critical process parameters are monitored because they are essential for the critical quality attributes (CQAs) [48]. Quality attributes describe desired physical, chemical, biological or microbiological characteristics of a molecule [49]. The CQAs are most indicative of the overall quality profile of the product, i.e. when these are within acceptable range it means that the whole quality profile is very likely to be acceptable [48]. The quality profile is the acceptable range to assure safety and efficacy of the final product [49]. Additionally, knowledge of different critical process parameters can reduce the risk of drift in the manufacturing process as well as unacceptable batch variation [46,48].

Protein characterization and reverse-engineering for biosimilars

A key difference between developing an originator biologic and a biosimilar is that the biosimilar development is steered by the characterization of the reference product [32]. This characterization is more extensive than that needed for originator biologics and generates a molecular fingerprint of the originator product [28,32]. It is done by analyzing several batches of the reference product, making it is possible to estimate its variation and thereby setting the frame for acceptable variation in CQAs for the biosimilar [31,32].

The tests needed for the reference product characterization are numerous. As an example, for the active substance etanercept, Cho et al. [50] used 61 test items, including orthogonal methods, to characterize the originator product. Orthogonal methods are methods that test a similar characteristic, but rely on different scientific principles [31]. A combination of these increases the validity of the overall analyses result [31]. An example of a test performed by Cho et al. is a size- exclusion experiment [50], see Figure 2.

Size exclusion is used to separate entities present in the product according to their molecular weight [50]. In Figure 2, there is a high-molecular weight (HMW) entity (HMW1) that is present in the originator product, but not in the biosimilar SB4 (highlighted in yellow box). Further, the peaks are shaped differently in the HMW2 area. Cho et al. [50] described that they analyzed the content of the HMW1 area using another method and that the component seen in the reference product is probably not of protein origin. In addition, that the shape difference in the HMW2 peaks is probably due to a low ability to separate the HMW1 and HMW2 peaks in the reference product [50]. Despite these visual differences, SB4 is an approved biosimilar of the originator biologic [50].

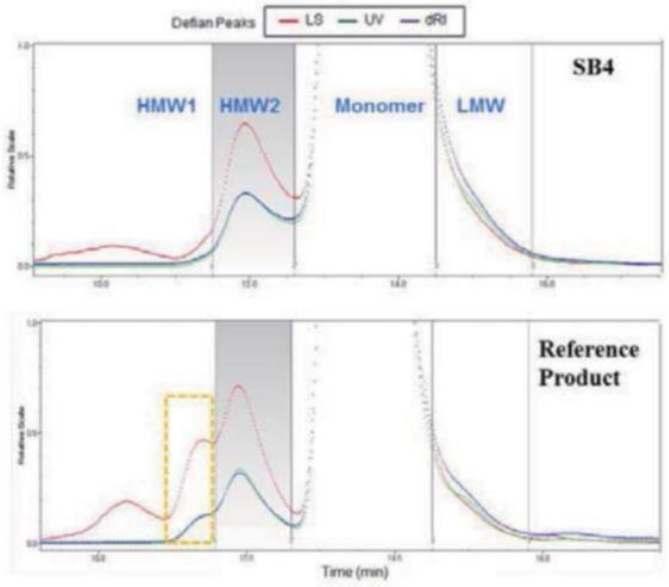

Figure 2. Size-exclusion test to compare the etanercept reference product and the biosimilar SB4. Used with permission from Cho et al. [50]**.**

The characterization of the reference product forms the limits of variation of the biosimilar [32]. Subsequently, biosimilar developers must make a product with a highly similar molecular fingerprint to the reference product by reverse-engineering the manufacturing process [28,32]. This has been associated as a challenge to biosimilar development because of the complex and difficult manufacturing process [18]. The reverse-engineering is needed because biosimilar developers do not usually have knowledge of the manufacturing process of the originator due to trade secrets [17]. For example, biosimilar developers do not know details of the cell system used for expression of the target protein [32]. The reverse-engineering is an iterative process that requires continuous modifications to growth conditions and purification processes until a biomolecule highly similar to the reference product is obtained [32]. Overall, the difficulties of reverse-engineering the manufacturing process of the originator product have been noted as a major hurdle to biosimilar development due to the trade secrecy protecting the originator process [17].

Intellectual Property and Related Rights

Developing medicines requires large investments and involves both scientific and financial risks [51]. The protection of the resulting products and processes through intellectual property rights (IPR), trade secret protection and regulatory exclusivities are often essential in order for companies to take the necessary risks and recoup their investments [51]. Moreover, registered trademarks can protect distinctive signs such as logos, colors or names by providing exclusive rights over these [52]. Another increasingly important form of protection is data base protection rights and copyrights, which can

protect specific data and/or the organization of data, as well as original literary, scientific and artistic work such as texts or paintings [53,54]. However, protection by patents and trade secrets remains the most important for medicines and in particular for companies relying on biotechnology [55]. The following focuses on a general introduction to patents and trade secrets in the European context and thereafter on the relevance for biosimilars.

Patents

A patent provides the patent holder with a time-limited, exclusive right to the patented invention [56]. The patent grants the patent holder the rights to exclude others from commercial exploitation of the invention without consent, i.e. the invention cannot be commercially made, used, distributed, imported or sold [57]. A patent can protect, for example, an apparatus, a process or a product [56]. However, not all inventions are patentable because the invention must be eligible for patent protection (i.e. not thoughts or laws of nature), "*new, industrially applicable and involve an inventive step*" [56] and be sufficiently disclosed in the patent application [58]. The term of a patent is 20 years from the day the application was filed at the patent office (the priority date) in the relevant jurisdictions designated in the application [59]. The processing of the patent application may take about three to five years, but, if granted, the patent protection will be effective from its priority date [60].

An extension of the patent protection period of up to five years can be obtained via a supplementary protection certificate (SPC) [60–62]. Such extension was introduced in 1992 to compensate companies developing new medicines for the loss of on-market patent protection due to the time-consuming product development period and the clinical trials needed to achieve regulatory market authorization [63].

A valid patent prevents other companies from both patenting the same invention and making commercial use of the protected invention. Third parties that wish to make use of the patented invention must obtain a license from the patent holder, wait for patent expiry or attempt to get the patent invalidated in court. Nonetheless, there are three exceptions to the patent protection:

The research exception, which is a rule governed by national patent legislation [64]. The research exception allows use of a patented invention for the purpose of research [64]. However, the exact scope of this exception varies between jurisdictions both regarding research on and research with patented inventions, and what activities are regarded as "commercial" [64].
The so-called Bolar provision in Article 10.6, Directive 2001/83/EC that regulates medicines for human use [65]. The Bolar provision was introduced with Directive 2004/27/EC [66] as a means of circumventing the additional and unintended de facto protection of originator products arising

from inability to use the clinical trials with the originator product for development of follow-on products [64,67]. Before the Bolar provision, development of follow-on products could first be initiated after expiry of patents and supplementary patent protections in order to avoid patent infringement and thus prolonged the de facto period of protection further than the patent protection period itself [67]. The aim of the Bolar provision was to foster generic competition, to lower prices on medicines and to increase access to medicines [67]. In short, the Bolar provision aims to balance the incentives for drug development with public health [67]. Consequently, developers of follow-on products can experiment with patented inventions before the end of the patent protection term [68].

The SPC manufacturing waiver. To increase competitiveness in the EU, generic and biosimilar manufacturers are allowed to manufacture and stockpile their product to enable competitive launch in the EU on the day of the expiry of the SPC protecting the reference product. This is not considered as patent infringement as long as the manufacturing and stockpiling of the generic or biosimilar are started no more than six months before expiry of the SPC. [69]

In return for the patent protection, the patent applicant is required to disclose the invention i.e. to describe the invention sufficiently in the publicly available patent file for it to be replicated by a person skilled-in-the-art [58]. The patent rights' quid pro quo is that in exchange for the time-limited exclusionary right during patent protection, the patent holder must disclose the invention in the patent document and the invention falls into the public domain when the patent expires. However, it has been contested whether patents aid the spread of knowledge and whether the level of disclosure is adequate [51,70]. Nevertheless, enforcing further disclosure might cause inventors to limit use of patents and to a larger extent rely on the protection offered by trade secrets [51].

Trade secrets

In contrast to patent rights, trade secrets do not confer proprietary right to the information or creation covered by the trade secret [71]. Trade secrets are defined in the European trade secret directive, Article 2 as *"information which meets all of the following requirements:*

a. it is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question;

b. it has commercial value because it is secret;

c. it has been subject to reasonable steps, under the circumstances, by the person lawfully in control of the information, to keep it secret" [72] (p. 9).

The type of information can include drawings, prototypes, manufacturing processes, not patentable or not patented inventions, and genetic materials [73]. The type of information protected by a trade secret can be know-how that is difficult to codify in a patent description [51]. Moreover, it can also be strategic to keep information as a trade secret instead of disclosed as a patent [51]. Trade secrecy is intended to ensure certain information remains confidential and undisclosed [72]. However, as also included in the definition, it is important that the trade secret holder has taken reasonable steps (such as confidentiality agreements) to keep the information secret [55,72]. The legal framework protects the trade secret holder if a third party unlawfully, such as via theft or bribery, obtains the information protected as a trade secret [71]. This is reasoned because unlawfully obtaining the confidential and undisclosed information inhibits the trade secret owner from benefitting from their innovation as the first-mover [72]. Additionally, a trade secret does not prevent others from reverse- engineering or reinventing the trade secret protected knowledge.

The choice of patents versus trade secrets and the context of biologics

Patents and trade secrets offer different types of protection. For drug development it is important to decide early on what type of protection is preferable [74]. Considerations must be taken regarding 1) intent to license, 2) needs of third party communications/disclosures and 3) ability to keep the information confidential [74]. Trade secrets offer an advantage of potentially being time- unlimited and avoid acquiring costly patents; however, this relies on the information successfully being kept secret [74]. By contrast, patents offer early claims to the invention [55]. Another risk of trade secrets is if another company patents the same invention, leaving the trade secret holder to infringe such a patent by using their invention. In such cases, the trade secret holder would need to agree on a license, wait for patent expiry or attempt to get the patent invalidated in court [71]. In the context of biologics, a pharmaceutical company protecting a manufacturing process as a trade secret cannot claim infringement if another company reengineers the same process.

Biologics are typically protected with more patents than are small molecule drugs and the layered protection of multiple patents is referred to as patent ‘thickets’ [75,76]. The patents can protect, for example, composition-of-matter (active substance), dosage, formulations, indications and manufacturing [77,78]. Usually, the scope of the patent claims on a medicine will cover more than that covered by the marketing authorization. Where a marketing authorization may refer to the active ingredient(s), route of administration and the indication, the patent portfolio may also contain, for example, patents on manufacturing methods and use for other (second) indications [78,79]. These may also include patenting buffers that are not used to produce the product in the marketing authorization, but that may be patented as part of an invention to make it more difficult to produce

follow-on products [77]. However for biologics, trade secrets have been reported to be a more important protection than patents [51]. This is argued partly due to the possible challenges of reverse engineering a biological manufacturing process and partly due to the potential issues in proving process patent infringement [51]. Lack of access to the process information has been argued to block competition and foster innovation in newer, stronger analytical tools by biosimilar developers [17].

However, the innovations made by biosimilar companies may also be patentable [80]. Overall, there exists no hard evidence that trade secrets are delaying the development of new biosimilars [81].

The European Regulation of Biosimilars

This section gives an overview of the European system for regulating medicines followed by the European regulation of biosimilars.

All medicines must be authorized before being placed on the European market to protect public health [82]. The European system for approval of medicines is complex, partly for historic reasons. The most important legislation is the Directive 2001/83/EC, which is implemented in national laws in each member state, that describes the framework wherein national medicines agencies work [65].

Medicines can be authorized in the EU using four different authorization procedures: centralized, decentralized, mutual recognition and national marketing authorization procedures [82], see Table 1. The national agencies have (amongst other things) responsibility for all approval procedures that are issued on member state level (national, mutual recognition and decentralized procedures, see Table 1) [82]. The national agencies normally employ the scientific and administrative staff necessary for these tasks. The centralized authorization procedure and the establishment of the EMA is described in regulation 726/2004/EC [83]. An application for a centralized marketing authorization is evaluated by the EMA's Committee for Medicinal Products for Human Use (CHMP) [82]. Thereafter, the EMA sends a recommendation the European Commission that makes a legally binding decisions to grant or refuse the marketing authorization. A marketing approval is valid throughout the EU [82].

The EMA cooperates closely with the national regulatory authorities, which delegate experts to EMA Scientific Committees and Working Groups [82]. It will normally be these experts who act as (co-)rapporteurs and assessors in centralized procedures. For example, 55 out of 60 CHMP members were employed by national agencies or ministries of health in October 2020 (five members were affiliated to universities) [84]. Expertise is shared for assessment of medicines in Europe to capitalize from the scientific resources available in different EU countries [82]. The partnership between the EMA and national regulatory authorities is also known as the European medicines regulatory network. [82]

Table 1. European marketing authorization procedures. Information from documents by the European Medicines Agency [82,85]**.**

Marketing authorization procedures	Description
Centralized	- A centralized authorization is valid for all EU member states - One application sent to the European Medicines Agency - Valid in all EU member states and the European Economic Area (EEA) countries Norway, Iceland and Liechtenstein. - Compulsory for some types of therapies, such as: o new active substances for diabetes, biotechnology- derived medicines, advanced therapies and orphan drugs
Decentralized	- An authorization in two or more EU member states for a product not yet on the European market - The active substance must not fall under the scope of the centralized procedure
Mutual recognition	- Recognition of an authorization from one EU member state to another EU member state - Member states can rely on the other member states scientific assessment - The active substance must not fall under the scope of the centralized procedure
National	- An authorization valid in the national EU member state - The active substance must not fall under the scope of the centralized procedure

The European legislation and overarching scientific guideline for biosimilars came into force in 2003 and 2005, respectively [86,87]. This opened up for a legal possibility to obtain a marketing authorization for follow-on biologics. Prior to this, products would have been assessed in the then existing framework. One example is when Sandoz first applied in 2001 for approval of Omnitrope® as a generic product; it was refused by the European Commission because generic approval was considered inappropriate [88]. Following legal amendments, a second application led to biosimilar approval of Omnitrope® in 2006 [88].

A biosimilar marketing authorization application must be made via the centralized procedure if the proposed biosimilar is produced via biotechnological processes such as recombinant DNA technology [83]. The reference product must have been approved at least eight years before the clinical data of the reference product can be relied on in a biosimilar marketing authorization such as that laid down in Directive 2001/83/EC, Article 10(1) [65]. Further, a biosimilar cannot be placed on the market until a subsequent two years of market exclusivity for the reference product has passed [65]. This can be extended to a total of three years of market exclusivity if an additional indication

for the reference product is approved within the first eight years of approval, as laid down in Articles 10(1) and 10(5) [65]. Article 10(4) specifies biosimilars and the approval requirements as

"*a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines*" [65] (p. 23).

The basis for approval is a comprehensive comparability exercise between the proposed biosimilar and the reference product [11]. The reference product used for this must be authorized in accordance with Article 8 of Directive 2001/83/EC as amended [65]. High similarity of the biosimilar to the reference product must be demonstrated for quality characteristics, biological activity, safety and efficacy [11]. Any detected differences should not be clinically meaningful and be appropriately justified [11]. Further, the biosimilar active substance must be similar to the reference product in terms of molecular and biological likeness [11]. A biosimilar developer should not strive to improve efficacy as this is not in alignment with the biosimilar principle, but higher safety does not rule out biosimilarity [11]. A biosimilar will have its own product life cycle once biosimilarity has been established [11].

Currently, three overarching guidelines exist: one for biosimilars in general; one for quality guidance; and one for non-clinical and clinical guidance [11,89,90]. In extension of these requirements, there are eight product-specific guidelines, one for each of the active substances: recombinant granulocyte-colony stimulating factor; low-molecular weight heparins; recombinant human insulin and insulin analogues; interferon-beta; monoclonal antibodies; recombinant erythropoietin; recombinant follicle-stimulating hormone; and somatropin [91–98].

A recommended step-wise approach to biosimilar development

The EMA recommends developing biosimilars using a stepwise approach [11], see Figure 3. This includes starting with a comprehensive physicochemical and biological characterization of both the proposed biosimilar and the reference product. The EMA further recommends that the physicochemical, biological and non-clinical *in vitro* data should form the basis for designing appropriate *in vivo* studies and clinical studies. The aim is to determine residual uncertainty following each step and to design the following steps to address this uncertainty. [11]

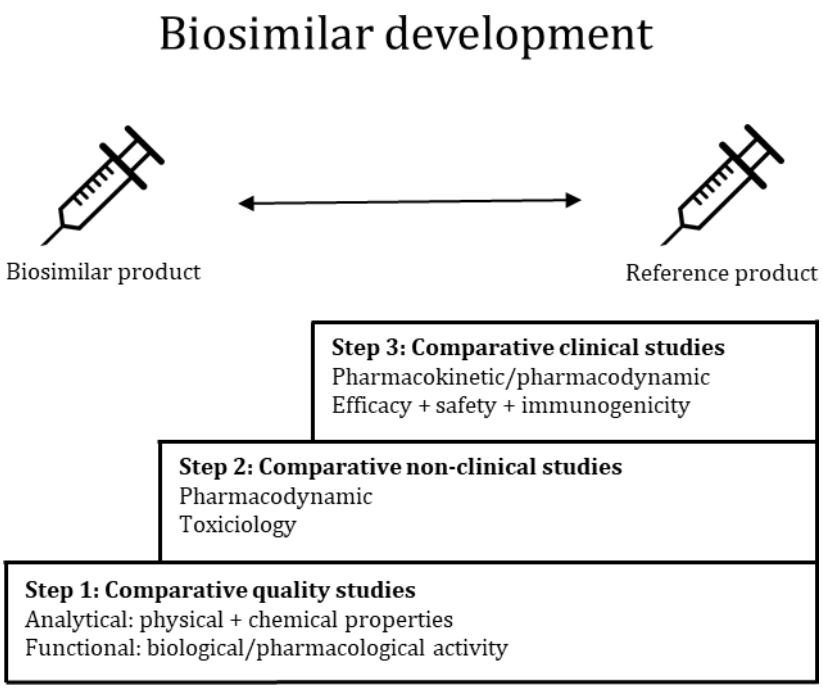

Figure 3. A stepwise approach to biosimilar development.
Inspired by the European Medicines Agency [181]**.**

Comparative quality studies

In Europe, for biotechnology-derived products, establishing comparable quality between a biosimilar and the reference product includes physicochemical and biological activity characterizations as well as quality attributes for specifications of the biosimilar product [89]. This necessitates development of a quality target product profile (QTPP) based on characterizations of the reference product and publicly available information [89]. Once developed, the biosimilar manufacturing process must yield a product with comparable molecular characteristics and quality attributes to the reference product [89]. A biosimilar is manufactured from its own process since, as previously mentioned, a biosimilar manufacturer will usually not have access to information about the manufacturing of the reference product [28,89]. For this reason, it is acceptable, for example, that the biosimilar has other process-related impurities than does the reference product [89]. To detect both similarities and differences as part of the comparability exercise it is important to use state-of-the-art, sensitive and orthogonal methods [89]. The analyses should include side-by-side comparisons of the biosimilar and reference products and where differences are detected these should be justified regarding their potential influence on efficacy and safety [89]. The quality analyses should also include:

- A physicochemical characterization to confirm the target amino acid sequence and physical properties and to determine primary and higher order structures of the active substance. The

posttranslational modifications should also be determined. This includes glycosylation patterns and comparisons of these with the reference product. [89]

- Determination of the biological activity of the biosimilar active substance via in-vitro assays. This aims to measure the biosimilar's ability to induce a particular biological effect in comparison to the reference product. Often several bioassays must be used to validate the results. [89,90]
- Measurements of purity and impurities, including assessment of whether these impact the quality of the biosimilar. This should include degradation pathways (such as protein aggregation) and the shelf-life of the product. [89]

Some challenges regarding establishing quality seem to be experienced by companies developing biosimilars according to an analysis conducted by Cilia et al. [99]. The authors report on objections raised by regulators to the quality assessment as part of biosimilar marketing approvals in the years 2006–2015 [99]. For 22 approved biosimilars, they found 32 'major objections' and 1042 'other concerns' [99]. Of the 32 major objections, the most frequent for drug substance was related to biocomparability of the active substance (four) and for drug product, the most frequent were related to process validation (three) and reference standards (three) [99]. However, it is unclear whether products approved later than 2015 would have fewer objections than products approved during 2006–2015. Nonetheless, the findings by Cilia et al. indicate that companies might experience some initial challenges regarding comparative quality when establishing biosimilarity.

Comparative non-clinical and clinical studies

Another part of the comparability exercise is to establish clinical biosimilarity, which is done via a PK study and, if feasible, a PD study as well as clinical efficacy and safety trials. These studies should be conducted to make comparisons between the biosimilar and reference product. The PK studies are used to measure possible differences in bodily responses with regard to absorption, possible distribution and elimination. If feasible, PD studies should be added to the PK study. The selected PD markers should be surrogate markers that relate the effect on the marker to a clinical outcome for patients. [90]

In some cases, clinical biosimilarity can be demonstrated from quality and PK and/or PD profiles of both biosimilar and reference products [11]. However, if necessary, clinical comparability can be established via a clinical study for comparable efficacy [90]. This is typically conducted with a randomized, parallel group study design, which preferably is double-blinded [90]. Further, such a trial needs to be adequately powered and conducted in a representative population in an indication approved for the reference product [90]. Safety of the biosimilar is measured during PK and/or PD

studies and in the comparable clinical efficacy trial [90]. Adverse events known from the reference product must be compared with the biosimilar in terms of type, severity and frequency [90]. It is also essential to test for immunogenicity both pre- and post-approval [90]. Additionally, manufacturing differences between reference products and biosimilars and their possible influence on safety must be described [90] and impurities and excipients in the biosimilar must not give rise to concern [11]. Overall, it is important to note that clinical data cannot justify differences on the quality level [90].

Immunogenicity

The study of immunogenicity as part of a marketing approval is to determine the clinical impact from the presence of an immune response from the product. Immune responses may occur both rapidly and/or evolve slowly. Rare side effects and slowly induced immune reactions from biologic treatment are difficult to detect in clinical trials; therefore, continuous evaluation of immunogenicity post-marketing is necessary. Assessment of immunogenicity should include evaluation of data from studies of PK, PD, safety and efficacy. However, specific immunogenicity studies are rarely needed, but are incorporated into PK/PD and/or safety and efficacy studies. The factors influencing immunogenicity relate to patient-specific differences, concomitant treatments or product-related aspects. An immune response can result in loss of efficacy or serious acute effects such as anaphylaxis. [45]

Immunogenicity became a focus for follow-on biologics after changes to an originator erythropoietin product caused an increased incidence of pure red cell aplasia [100,101]. For a biosimilar, similar or less immunogenicity than the reference product is acceptable [90]. Specifically for biosimilars, it is important to detect and characterize all immune responses and antibodies emerging from the biosimilar product and not only those seen for the reference product [45]. Further, these responses should be correlated to PK, PD, safety and efficacy [45]. The product level differences between biosimilar and reference products include product- and process-related impurities, anti-drug antibodies, protein aggregates, excipients, or the interaction of the active substance with the specific container system [45]. In the EU, for approval of biologics, it is required to include a risk assessment of immunogenicity to support the immunogenicity testing carried out both pre- and post-approval [45]. Biosimilars are developed to have the same variation as the originator biologic as previously mentioned. However, some variation is still permitted between biosimilars and reference products such as that shown by Halim et al. [36] for erythropoietin in a comparison of two originator products with two biosimilars. The four products varied regarding content, isoform profile and potency, both between products and also in batches of the same product [36]. This shows that while products can be highly similar, biologics can still vary slightly.

Interchangeability of Biosimilars

Another legal aspect and a question that relates to the understanding of biosimilarity is the interchangeability of biosimilars in clinical practice. Interchangeability becomes practically relevant after biosimilar development and approval because it sets the basis for how to use medicines. Interchangeability is understood differently in the EU and the US, but in the EU the term interchangeability refers to the act of exchanging one medicine for another with the same clinical effect [102]. More specifically, this exchange can be made by either a physician or a pharmacist; the exchange is termed switching or substitution, respectively [102]. Thus, if a physician changes a patient's treatment from a reference product to its biosimilar, it is a switch. If regulation allows that a pharmacist exchanges a reference product to its biosimilar, it is termed substitution. It is characterized as automatic substitution if a pharmacist can conduct this exchange without informing the prescriber.

The European context

In the EU, it is determined by each member state whether a biosimilar can be switched or substituted for the reference product [83]. A study from 2017 showed that substitution of biologics is not a general practice in Europe [103]. Because of the national responsibility, the EMA is not allowed an official position on interchangeability of biosimilars, including switching and substitution [104].

However, several national medicines authorities have issued statements on the concepts [105]. On the one hand, the Finnish and the Danish Medicines Agencies (FIMEA and DKMA) see switching from reference products to biosimilars as unproblematic [106,107]. However, where the Danish agency does not voice its opinion on substitution, FIMEA takes a subtle position on substitution regarding it as possible if carefully planned [106,108]. On the other hand, the Irish and Belgian Medicines Agencies (HPRA and FAMHP) view switching as possible, but this is not the case for biosimilar substitution [109,110]. Additionally, in a scientific paper, several European regulators provided their personal perspective that a switch between a reference product and its biosimilar in the EU is safe; however, they did not take a position on automatic substitution [111]. Even though the EMA has not voiced an official opinion, their immunogenicity guidance states that risk of delayed immune reactions may increase when biologic therapies are repeatedly switched among products within a product class [45]. This can be interpreted as cautiousness toward multiple switching of biosimilars.

The US context and requirement for switching studies

In contrast to the EU, in the US a biosimilar may be automatically substituted for the reference product if the biosimilar meets the requirement that there is not an increased risk from alternating between the reference product and the biosimilar compared with if no alternation was made [112]. The FDA generally expects that a clinical study, termed a 'switching study', is needed to demonstrate that a biosimilar is interchangeable (i.e. substitutable in a European context) [112]. The FDA decides the need for a switching study depending on the structural complexity and known immunogenicity profile of the biological active substance [112]. This is illustrated in the FDA guidance for biosimilar insulin products, where a switching study would generally not be needed to determine the interchangeability of insulin biosimilars [113]. This was decided on the basis of insulin being a relatively small, structurally uncomplicated and well-characterized biomolecule that can be thoroughly evaluated using analytical tools, leaving little or no residual uncertainty regarding immunogenicity [113].

In applicable cases, a switching study is recommended for determining whether switching two or more times between the reference product and its biosimilar leads to differences in safety or diminished efficacy [112]. The suggested study design starts with a treatment period with the reference product, followed by a randomized two-arm period [112]. This includes a 'switching arm' where patients experience switches between the proposed interchangeable biosimilar and the reference product and a 'non-switching' arm with patients receiving the reference product [112]. In general, the endpoints in a switching study should measure changes in clinical PK and/or PD as consequences of switching [112]. These endpoints are deemed more sensitive than efficacy endpoints; however, a switching study should also assess safety and immunogenicity [112]. The immunogenicity assessment should include assessment of occurrence of anti-drug antibodies and neutralizing antibodies [112]. The studied condition should be an indication approved for the reference product and in a population that would allow extrapolation of interchangeability to other conditions [112].

However, it is unknown how a switching study leading to a US interchangeability designation would look in practice as no biosimilars had received the designation as of October 1, 2020. Further, for substitution to occur in practice, each US state needs to formalize biologic interchangeability in state laws [114]. At present, 40 US states require prescriber notification if substituting biologics: therefore, in practice, they do not currently allow automatic substitution [115].

The debate on switching and substitution

Another part of the debate, apart from jurisdictional differences, covers the opinions of pharmaceutical companies and the scientific debate.

There are different opinions regarding substitution of biosimilars in the pharmaceutical industry when looking at position statements from pharmaceutical companies. For example, Sandoz, a company with biosimilar medicines, has issued a position that there is no scientific basis for either creating a separate category or implying a difference between biosimilars and interchangeable biosimilars in the US [116]. Further, the company states that there are no product changes, and thus no molecular changes, made between approval of the biosimilar and the interchangeability designation [116]. Accordingly, no quality difference exists between the two categories of biosimilars [116]. Further, Sandoz adds that the argument that multiple switches pose an additional risk lacks support from scientific data [116]. In contrast to this is the position of Pfizer, a company with both originator biologic and biosimilar medicines, but mainly originator biologics. Pfizer argues that the requirements for substitutable biosimilars should exceed those for biosimilar approval [117]. The pharmaceutical industry at large has also issued statements on substitution of biosimilars. The European Federation of Pharmaceutical Industries and Associations (EFPIA), whose members are most often originator companies, holds the position that substitutability of biosimilars cannot be assumed and that the consequences of multiple switches are unknown [118]. In addition, Medicines for Europe, whose members are primarily biosimilar companies, has issued a statement that individual patient factors are the reason that substitution of biosimilars should not take place per default [119].

The scientific debate on switching and substitution of biosimilars has largely centered around questions of whether these practices are linked to increased immunogenicity owing to differences in impurities between biosimilar and reference product or to changes in efficacy [120– 123]. Overall, immunogenicity can be influenced by several factors, typically allocated into three types: treatment-, patient- and product-associated factors [35]. Treatment factors include the likelihood of an immune response differing depending on the route of administration (such as intravenous vs. subcutaneous) [35]. Patient factors include whether a patient received concomitant medicines that might lower the function of that person's immune system and thus increase the likelihood of an immune response from the biologic [35]. Product-related factors include aggregates or contaminants present in the biologic [35]. Overall, the risk of differences in immune responses, and thus immunogenicity, varies between population groups and individuals, as well as between products and product categories [45]. A recent systematic literature review from 2020 based on 170 studies found that no robust data showed major safety issues emerging from switching from a reference product to its biosimilar [120]. However, the findings largely depended on studies of infliximab, which accounted for 100 of the 170 included studies [120]. Further, many of the included studies had methodological difficulties in assessing the frequency of rare safety effects or diminished efficacy [120]. Only six studies addressed

multiple switches, but these did not report clinically meaningful differences in efficacy, safety or immunogenicity [120].

There clearly exist contrasting views on switching and substitution of biosimilars both between EU and US jurisdictions as well as among the pharmaceutical companies. The body of scientific evidence does not indicate issues related to switching, but the question of science justifying substitution is largely unanswered. Overall, it becomes a matter of trust and belief in science and biosimilars regarding whether substitution could and should be possible. Both switching and substitution are practical questions of how to use medicines, but they are also scientific concepts slowly evolving the understanding of biosimilarity.

Aims

The overall aim of this thesis is to investigate how medicines agency regulators and the pharmaceutical industry view the current and future European regulatory landscape of biosimilar development and approval. The specific aims are:

- To identify key scientific, legal, and regulatory challenges in biosimilar development and their effect on biosimilar market entry (Study I).
- To determine the value and necessity of the European biosimilar clinical comparability trial requirements for establishing biosimilarity (Study II).
- To investigate the current European regulatory practices and the science underpinning interchangeability (Study III).

Study Design and Methods

Investigation of the overall aim requires research of knowledge from medicines agency regulators and participants from the pharmaceutical industry, thus to collect expert knowledge as research data. Expert knowledge is distinct from other types of knowledge (such as everyday knowledge) by not being accessible to everyone [124]. A person can acquire expert knowledge from three factors: 1) experience and education; 2) the responsibility a person holds; or 3) a certain position in a process [125]. An expert is defined as *"an institutionalized authority to construct reality" [Hitzler, Honer and Maeder, 1994 in Meuser and Nagel* [124]*]* (p. 19) or phrased in another way a *"person who is responsible for the development, implementation or control of solutions/strategies/policies"* [125] *(p. 181).* Both medicines agency regulators and the pharmaceutical industry are stakeholders that play a key role in the regulation of biosimilars, either by developing, executing and controlling the regulation as a regulator or by working in the industry providing inputs to regulatory processes by supplying scientific evidence via marketing authorization applications, scientific advice or documents open for consultation.

This research adopted a qualitative research approach to capture expert knowledge to investigate the overall aim. Qualitative interviewing is a recommended way to access expert knowledge [124]. An interview can collect uncodified knowledge when the participant can unfold and nuance his/her point of view and reflections [124,125]. Moreover, interviews enable insight into how people make meaning of and experience the world [126]. This allows exploration and interpretation of such world views and thus facilitates research beyond the researchers' perspective which is needed to investigate the overall aim.

Research Design

The research builds on a regulatory science approach to evaluate the performance of the regulations of biosimilars [127]. For this, empirical data were collected via semi-structured, in-depth interviews [128].

Of the specific aims, one was purposefully investigated and the other two were data- driven as they were identified as important from the data. From early on, the target was purposefully to research how and what challenges establishment of biosimilarity, including the influence of intellectual property and trade secret protections as reported in the literature [17,18,51]. This area became the focus of Study I. Additionally, a broader investigation of the performance of the regulation of biosimilars was conducted. From this, it became evident that the evolution of the biosimilar clinical

trial requirements as well as the differing regulatory practices and scientific understanding of interchangeability were topics in focus by participating regulators and the pharmaceutical industry. Therefore, these two areas became the focus for Studies II and III, respectively.

Sampling and recruitment

To capture the different nuances of the overall aim it was decided to interview experts from (or as consultants to) medicines agencies or pharmaceutical companies with at least one EMA- or FDA-approved originator biologic or biosimilar. Eligible participants could work in jurisdictional or national medicines agencies in the US or EU and company participants in departments of regulatory policy/affairs, legal and CMC (chemistry, manufacturing and control). Further, eligible participants needed to have knowledge about and prior experience with biologics. Regulators from the US were included as eligible participants to compare regulatory opinions of biosimilars between the EU and US. The sampling included both current and former employees of the workplaces. Thus, the sampling was purposeful to obtain a wide range of experiences and perspectives. The participants were recruited using the sampling strategies networking and snowballing.

Data collection instrument

Three interview guides were developed to facilitate a cross-disciplinary investigation of the overall aim. Interview guide I (Appendix I) used the fields of law and therapeutic proteins and their manufacturing to investigate challenges with establishing biosimilarity and a biosimilar manufacturing process including the role of intellectual property and trade secret protections.

Interview guide II and III (Appendix II and III) used the fields of regulatory science, law and pharmaceutical policy to investigate the overall performance of the system regulating biosimilars as well as legal challenges related to biosimilars.

The guides were developed with inspiration from informal meetings with EU national medicines agency regulators and representatives from the pharmaceutical industry as well as the interview guides used for investigating the use of conditional marketing authorizations by Hoekmann et al. [129]. The interview guides were all designed on general topics as advised for expert interviews without closed questions and a preset, strict structure for the interview [124]. The shared field wherein the participants work is essential for comparability of the interviews [124].

Data collection

The interviews were time-wise longer by using all three interview guides rather than scheduling multiple interviews with the same experts. This was because of an expectation that the different nuances related to the overall aim would be highly connected, and it was considered unlikely to

research each of them individually. Further, each expert would likely have a view on the different aspects.

Before initiating the research, the interviewer (LCD) used the scientific literature to embed herself in the field to enable richer interviews. The perspective of the interviewer is academic, which was considered fruitful as she neither had been working in industry or in a medicine agency after graduation as a pharmacist. It is important to note that for expert interviews, the competency that the interviewer presents influences the willingness of expert participants to share their expertise [124]. Thus, "going naïve" as a common interview technique may not always be feasible for expert interviews because the interviewer can come across as incompetent [124]. Therefore, it is essential that the interviewer builds knowledge within the field where the participants have their expertise [124].

The interviews were conducted face-to-face, by telephone or online call between September 2018 and August 2019. The respective participant chose the media/location. All participants were interviewed for their personal perspectives based on their current or previous professional work experiences and were not interviewed as formal representatives of their workplace. The interview technique included extensive probing to encourage participants to nuance and expand their responses to the open questions. Further, the technique to "go naïve" was only used to make implicit participant responses explicit, such as *"I'm not sure I understand, could you please put some more words on that?"*. All but one interview were recorded, but extensive notes were taken during the unrecorded interview. The interviews were transcribed verbatim, and each transcript was validated by reading it while listening to the interview recording. The transcripts (or notes from the non- recorded interview) were sent for commenting and approval by the respective participant.

Analysis

Content analysis was used to analyze the data [124,130]. A combination of an inductive and deductive approach was used. Transcripts were read line-by-line and the meaning of all the text was considered. Text segments relevant for the purposeful aim and the broad investigation of the performance of the regulation of biosimilars were marked, and a code capturing its meaning was assigned. The context of the expert was assessed when evaluating the meaning and significance of the statements. Two analysts (LCD and Prof. Sofia Kälvemark Sporrong (SKS) at Social and Clinical Pharmacy, University of Copenhagen and at Social Pharmacy, Uppsala University, Sweden) independently conducted the coding.

This initial coding was extensively discussed and from this the specific aims for Study II and III were identified. Thereafter, for all three specific aims, all codes were reconsidered, compared and merged into overarching categories that captured the meaning of the included codes. From this, LCD and SKS developed a consensus list. LCD used the list to analyze all the transcripts and made the preliminary analyses for Studies I-III. The preliminary analyses and a subset of transcripts were audited [130] by Prof. Anna Birna Almarsdóttir (ABA) for all three studies. The analyses were finalized differently between Studies I-III:

- For Study I: LCD discussed and interpreted the coding results with Ass. Prof. Ameet Sarpatwari at Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, USA.
- For Studies II and III: LCD, SKS and ABA discussed and interpreted the coding results.

Thereafter, all other co-authors provided their inputs for the analyses using their wide range of expertise (within the fields of law, medicine, pharmaceutical policy, protein formulation, social science, regulatory science, and a company perspective). This was done by commenting on drafts of the Papers I-III and/or one-on-one conversations with LCD.

Ethics

No ethics approval was required according to Danish law [131], however, ethical considerations were met. Information about the study was sent to the participants and all participants provided written informed consent. All participants are anonymous and all material is stored confidentially. All data collection and processing were carried out with compliance to European General Data Protection regulation (GDPR). The Faculty of Health and Medical Sciences at the University of Copenhagen approved the processing of personal data in this study (SUND-2018-09). No token of incentive to participate was given.

Summary of Findings

Twenty-three interviews were conducted with 25 participants from pharmaceutical industry and EU national medicines agency regulators, see an overview of the participants' expertise in Table 2. No one from the FDA or the EMA was able to participate. The median interview time was one hour and two minutes. The original research conducted as part of this thesis is disseminated in three studies, and the results are summarized in the following section.

Table 2. Participant affiliations and expertise.

Participant group characteristic	Interviewed participants (n=25)	Non-participation (n=4)
Workplace		
EU national medicines agency *	8 (32)	1 (25)
European Medicines Agency (EMA)	0 (0)	1 (25)
US Food and Drug Administration (FDA)	0 (0)	2 (50)
Originator-only manufacturers**	5 (20)	NA
Originator and biosimilar manufacturers***	4 (16)	NA
Biosimilar-only manufacturers****	8 (32)	NA
Primary expertise of company participants		
Regulatory policy/affairs	10 (40)	NA
Chemistry, manufacturing, and control	3 (12)	NA
Law	4 (16)	NA
Recruitment strategy		
Networking	18 (72)	2 (50)
Snowballing	7 (28)	2 (50)

** From seven different EU countries. ** From two companies. *** From two companies. **** From seven companies.*

Study I – "Challenges in Biosimilar Manufacturing" (Paper I)

The first study addresses scientific, regulatory and legal challenges for biosimilar development. The three key findings relate to trade secrets, patents and regulatory flexibility vs. companies' need for certainty of what is required.

Trade secrets were generally viewed as a surmountable barrier to biosimilar development. Participants indicated that the science behind reverse-engineering the originator biologic is

challenging, although doable when companies have expertise in biotechnology, and when such expertise is available outside originator companies. The participants did not believe that disclosure of trade secrets for QbD measures for the originator product manufacturing would facilitate biosimilar development. The reason is that the manufacturing process is company specific and differences in process parameters, such as host cell and growth conditions would render the information close to useless. Moreover, new scientific knowledge about the biologic active substance's characteristics and function is gained from biosimilar development.

Participants were more concerned about the barriers caused by patents protecting originator biologics. This concern arises from the large number of patents protecting originator biologics as well as a lack of efficient search mechanism to identify them. Moreover, participants recounted that it is scientifically challenging to work around the patents, but that it is possible once the relevant patents are identified. Uncertainty and monetary risk for biosimilar companies were seen as consequences of the difficulty in mapping the patent landscape.

The clarity of the regulatory requirements for biosimilars was raised by participants as a challenge to biosimilar development. The requirements were known by biosimilar companies, but they were not always certain how best to fulfill them. Regulators expressed that ambiguity provided them with regulatory flexibility because it helped to avoid reliance on outdated methods. Company participants explained that the ambiguity made them seek regulatory scientific advice multiple times during biosimilar development. Of particular concern was whether clinical trials would be necessary for a particular biosimilar product in development. Despite the EMA guideline permitting clinical comparability trials to be waived, the participants believed that negotiation with the EMA on this matter to be impossible.

Study II – "Clinical Trial Requirements for Biosimilars" (Paper II)

In the second study, participants predicted that the clinical trial requirements for comparable efficacy would be reduced. The reasons were both a matter of science as well as aspects of competition, ethics and physicians' trust. Currently, the scientific discussion is fueled by advancements in analytical testing of recombinant proteins and the knowledge generated from former biosimilar approvals.

Arguments were raised for and against reducing the requirements. Those for reducing the requirements included the following points:

- Analytical science is sufficiently developed.
- Biosimilar development costs would be lower.
- Biosimilars for more originator biologics would be attractive to develop.

- Conducting clinical trials is often not scientifically needed and would therefore be unethical.

Those against reducing the requirements included the following points:

- Clinical trials are scientifically needed for establishing comparable efficacy and immunogenicity.
- Originator companies would be disincentivized by too easy introduction of competition with biosimilars
- Physicians could become more reluctant than currently to prescribe biosimilars.

Overall, regulators expressed a need to be convinced and to trust that new clinical requirements for biosimilar approval would not lower the European standard for highly similar quality, safety and efficacy compared to the reference product. Overall, participants did not expect that a reduction in the requirements would result in lower prices on biosimilars.

Study III – "Interchangeability of Biosimilars" (Paper III)

The third study showed that participants see interchangeability relating to regulatory practices, formal competences and trust, rather than it being merely a matter of science of likeness between two biological molecules. Biosimilar switching was overall supported by the participants, but their views differed on substitution of biologics. Some perceived substitution as an unexplored area filled with unknown potential risks, while others believed there was enough scientific knowledge to support it.

Nonetheless, switching studies were not seen as the solution to obtaining sufficient scientific knowledge for interchangeability of biosimilars. In addition, participants disagreed with the US delineation between the biosimilar and interchangeable biosimilars. The scientific aspect of interchangeability of biosimilars is unclear. It was suggested that it could be resolved if the EMA, based on their expertise from biosimilar approvals, could hold a scientific and advisory opinion on interchangeability. The participants disagreed on whether EU countries should allow substitution (i.e. by pharmacists) of biologics; however, the company participants and most regulators were not in favor of this.

Discussion

This section starts with a discussion of the findings divided into several parts and then a discussion of the methods and theory follows. The discussion of findings starts with a discussion on the current and evolving regulatory landscape of biosimilars followed by a more in-depth focus on two upcoming regulatory discussions and ending with a theoretical perspective on biosimilars as both reality and visions of the future.

Discussion of Findings

The current and evolving regulatory landscape of biosimilars

The concept of biosimilarity is well recognized scientifically, but the results of this thesis also point to current challenges.

The findings of this thesis suggest that the main challenge for biosimilar development of recombinant proteins appears to be related to patent protection, and not necessarily to trade secrets or a complex manufacturing process, as previous scholars have shown concerns about [17,18,81]. This could be because the importance of trade secret protection in the field of recombinant proteins has diminished over time as scientific knowledge has grown. Thus, trade secret protection most likely continues to be a valuable protection in scientifically less established fields compared with that of recombinant proteins. There are many patents protecting each biological medicine in layers of protection by individual patents [132], and they can be difficult to identify due to lack of an efficient search mechanism. However, when identified patents protecting, for example, a product's formulation can then usually be scientifically worked around, such as found in Paper I. The patent landscape, according to Moorkens et al. [133], indicates that secondary patents (protecting for example indications) are hindrances to biosimilar development, but that earlier patent litigation has cleared patent obstacles for biosimilar developers. Thus, patents are likely barriers to biosimilar development as there remains an uncertainty whether all relevant patents have been identified and it requires financial resources to pursue litigation.

The biosimilarity concept appears to be continuously evolving, starting with the establishment of the concept in the biosimilar overarching guideline [11]. The initial molecules were relatively small biologics. Since then, there has been a scientific journey to enable biosimilars of monoclonal antibodies (unpublished results). At present, there are discussions on reducing or waiving biosimilar clinical trial requirements. Further, the biosimilarity concept regarding interchangeability is not yet fully explored and there is a lack a detailed scientific understanding of whether biosimilars can be

substituted and if not, the scientific reason for or against it. Both these discussions are scientific, but they also include political and ethical aspects (see below).

The results of this thesis regarding the biosimilar clinical trial requirements are a contribution to the discussion in the scientific literature. Webster et al. [134] propose a framework that does not per default require clinical trials for comparable efficacy, but only if prompted by the rest of the biosimilar comparability exercise. Further, Webster et al. describe PD markers as confirming the established analytical similarity of a biosimilar. This contrasts with the findings of this thesis where regulators see PD markers as the next step to further reduce or waive clinical trial requirements for comparable efficacy. However, Frapaise and Allocati et al. [135,136] encourage reassessment of the biosimilar clinical trial requirements. Nonetheless, the results of this thesis show that both EU national medicines agency regulators and industry find the discussion important, and the EMA Regulatory Science Strategy [137] indicates that the EMA wishes to develop the biosimilar clinical trial requirements by 2025. This can potentially aid biosimilar market entry by reducing the clinical trial burden [138].

Interchangeability and substitution of biologics

The findings in this thesis show that substitution of biologics is an important topic, a topic that is likely to receive intense focus in policy discussions in the near future. An essential perspective in this policy discussion is patients' and physicians' view on and trust in interchangeability of biosimilars.

Specifically for interchangeability, Peyrin-Biroulet et al. [20] found that 30% of patients would accept a change from the originator to a biosimilar product if it was approved by the physician. However, only 1% would approve if the pharmacist (independently) substituted the product [20].

Overall, patients' main concern is the safety regarding biosimilars [21], but Gasteiger et al. [22] found that female gender and short-term treatment with an originator product were associated with a perception of biosimilars as less safe [22]. For rheumatology, Van Overbeeke et al. [21] found that rheumatologists were more cautious about biosimilar interchangeability than were patients, and that 28% of rheumatologists distrusted biosimilars, regarding them as not interchangeable with the originator product. Further, several studies have found that the majority of medical specialists would be uncomfortable with substitution of biologics [25,139,140].

This situation is not surprising if compared with the previous experiences of physicians and patients with generics as follow-on products for small-molecule drugs. Initially, half the physicians distrusted the interchangeability of certain types of generics, for example, beta-blockers [141]. Later, those in established healthcare systems accepted interchangeability of generics and understood that generic

substitution has high value for society [142,143]. Currently, patients overall seem to trust generic substitution; nevertheless, concerns about inferior quality exist due to a perception of low quality connected to low price [144,145]. However, some patients experience better effects from generics [145], but others are reluctant to use generic substituted medicines due to nocebo effects (negative effects due to patients' expectations) [146]. This aligns with a few participants in this research who report that patients' nocebo effects are present in biosimilar use (unpublished results). Further, in the literature, scholars have argued that nocebo effects are present and are a hindrance to substitution of biologics rather than a scientific problem [147,148].

In comparing the biosimilar situation with generics, one could assume that physicians and patients might initially be opponents of substitution due to its unfamiliarity; however, at least for generics, trust has been gained over time. Thus, full acceptance prior to implementation of substitution of biologics should not be expected. For substitution of biologics to occur regulators need to decide how they scientifically view interchangeability of biosimilars and to voice this opinion. To instill trust in physicians and patients in interchangeability, regulators need to show certainty and trust in the substitution of biologics.

The scientific question of likeness was also present when generic substitution was introduced [149]. This was central to the political debate between proponents and opponents of generic substitution, who used parts of science to support their standpoints [149]. This led to the emergence of pharmacokinetics to establish similarity for generics to small-molecule drugs, which is now considered basic science [149]. Similar initiatives for biosimilars may have to be driven by governmentally funded science projects [149]. This is likely even more pertinent for biosimilars as the findings of this research show that the pharmaceutical industry overall is not in favor of substitution of biologics, and as such is unexpected to be a driver of it.

The acceptance of generics and the introduction of generic substitution in Europe largely happened in the wake of the economic crisis starting in 2008 [150]. The economic pressure provided incentives to lower costs, also in the healthcare sector [150]. In relation to biosimilars, the large influence of COVID-19 on the world's economies might provide a similar push toward acceptance of biosimilars and promote use of these products [151]. A further driver might be that non-medical switching of an originator product to a biosimilar has not been associated with increasing use or costs of health care services [152]. Overall, this can provide an incentive to investigate how interchangeability of biosimilars could be scientifically acceptable, i.e. making clear, scientific decisions on this. The connection between the use of products and economic crisis aligns with the results of this thesis, i.e. that interchangeability is more than a scientific question of likeness between biological products.

From a societal perspective, it is attractive to obtain medicines at prices that allow treatment of more patients and free resources to invest in innovative medicines. However, such desires should not affect regulatory decisions on approval requirements as these should be based on sound, scientific arguments. This points to ethics in relation to reducing clinical trial requirements and substitution of biologics, and these can be evaluated using ethical principles such as the four (beneficence, nonmaleficence, respect for autonomy and justice) defined by Beauchamp and Childress [153].

The evaluation of risk assessment regarding interchangeability of biosimilars resembles the thinking of Ulrich Bech as part of his theory of risk society [154]. In this theory, risk is associated with a modern, man-made, technological invention and as such the threat to both individuals and society must be evaluated. Further, seeing that these risks are unavoidable, they must be minimalized to a 'tolerable' level in a societal perspective. A discrepancy between risk perceptions depends on whether the perceiver is an expert or lay person, assuming the former relies on scientific knowledge and the latter on personal experience. The link between the two types of risk assessment is argued to be the level of knowledge; accordingly, if the lay population knew what experts know, they would evaluate risks in the same way. [154] Such thoughts are seen in the results of this thesis when participants argue that physicians and patients need education to understand biosimilars and the concept of biosimilarity. However, the knowledge of interchangeability is more difficult to communicate when regulators have yet to make up their minds. A crucial aspect is to remember that there will always be a risk and that currently there is no hard evidence against the substitution of biologics.

Future biosimilars

The concept of biosimilarity will most likely continue to evolve because of the ever- increasing understanding of biosimilars. Further, because new types of biological products are being developed and marketed, it spawns questions of how biosimilars to these can be made. One example is biosimilars to orphan drugs and another, in the more distant future, is follow-on products for gene- and cell-based therapies, although these might be given another term than biosimilars when they emerge. Currently, the next step appears to be biosimilars to orphan drugs which is discussed below.

Orphan drugs treat rare diseases and biosimilars to these could be developed as 56 out of the 156 EMA-approved orphan drugs are biologics [155]. Of these biologic orphan drugs, 14 have already lost their market exclusivity, and 34 more are expected to by 2029 [155]. Nonetheless, two challenges are identified for orphan drug biosimilars: 1) a regulatory challenge and 2) lack of economic incentives.

A regulatory challenge is the reliance on comparability clinical trial data for establishing clinical biosimilarity. Clinical trials for biosimilars have a mean of 376 enrollees according to data from Allocati et al. [136], which is markedly more than trials for, for example, originator orphan drugs for cancer, which have a mean of 92 enrollees [156]. It is unrealistic and unaligned with the biosimilar concept that clinical data supporting biosimilar approval exceed the amount gathered for the originator orphan drug. Thus, the regulatory flexibility to accept smaller clinical studies than that usually expected for originator product orphan drugs [157] will likely also be needed for approving biosimilars to orphan drugs. An alternative approach could be to rely more on non-clinical data to predict a drug's performance in the clinic, for example, analytical testing. This was argued in the results, and it should be investigated whether this also could apply to biosimilar orphan drug approvals. This will presumably be applicable only for orphan drugs that are recombinant proteins.

There is also a challenge regarding economic incentives to develop biosimilar orphan drugs. According to Dowlat [158], some drugs with only orphan designation have a market value of €1 billion, which might not be attractive for biosimilar developers compared with developing biosimilars for the orphan drug indications of blockbuster medicines. Further, only 12% of the 42 biologics orphan drugs mentioned above are estimated to have a European market size larger than €100 million per year [155]. Moreover, the total patient population is limited and strong loyalty is seen for patients and physicians to the originator product [155,158]. Additionally, orphan drugs are likely to be a larger part of the future regulatory picture because of the shift in drug development toward more specialized targeting of diseases and smaller patient populations [159]. Investments in correlating quality and PKPD data to the product's performance in the clinic could pave the way for orphan drug biosimilars [160]. However, from a societal perspective, orphan drugs cost about $200,000 per patient per year [161] and if the current regulations fail to incentivize biosimilar orphan drug development, there should be initiatives providing sufficient incentives. The alternative is a market where originator orphan drugs obtain monopoly because no competition is introduced; this does not favor patients.

It often takes years for regulations or guidelines to be drafted and come into force. For this to happen, there is a need to look at how biosimilar orphan drugs should be made and regulated, if they should. In this matter, it is key to focus on scientific rather than political arguments, even though regulatory flexibility may be needed for realization of biosimilar orphan drugs.

The imaginary of biosimilars: reality and vanguard visions

The theoretical perspective provided in this section serves as a framework to understand the results of the thesis in a wider context. Further, it is important to frame policy problems as identified in Studies I-III because *"they fundamentally alter people's perceptions of what is real in the world*

around them" [162] *(p. 24)*. This means that how we talk, interact and act around policy, shapes both people's understanding of the current world and of the future. Therefore, it is pertinent to notice the ongoing vanguard visions and in particular imaginaries, as they are likely to shape the reality of the future of biosimilars.

Emerging technologies and changes in scientific principles are results of technological visions and expectations [163]. Thus, technology, including biosimilars, is not a result of serendipity but a result of visions and expectations of how technology could be. In this section, the emergence of biosimilars as products, as well as the results of this research, are viewed within the context (or theoretical framework) of the theory of sociotechnical imaginaries as developed by Sheila Jasanoff [164]. According to Jasanoff, sociotechnical imaginaries are

"…collectively held, institutionally stabilized, and publicly performed visions of desirable futures, animated by shared understandings of forms of social life and social order attainable through, and supportive of, advances in science and technology" [164] *(p. 4).*

Sociotechnical imaginaries are visions of the future that can be utopic — a positive imaginary of how science and technology can foster social progress — or dystopic — negative imaginary of fears of the harm that an invention or lack of innovation can inflict [164]. However, imaginaries are more than visions of advancements in science and technology, they also contain an idea of how life should be in society's shared understanding [164]. According to both Jasanoff and Hilgartner, imaginaries are created when 'vanguard visions' of single persons or smaller groups gain wider support and are collectively adopted [164,165]. For example, members of a group can connect by shared imaginaries of futures to realize or avoid these [164]. Vanguard visions undergo transformations as they evolve and if vanguards turn into imaginaries, it becomes a co-production of shared visions of the future [165]. The imaginary can be shared among groups, communities, their leaders or even continentally or globally [164]. The size of the group that shares an imaginary is essential to the power of the imaginary [164]. Several imaginaries can coexist in society, and they will either support or oppose each other [164]. Imaginaries can be communicated and promoted by, for example, organizations or professional societies [164]. However, some imaginaries are elevated over others to a dominant position by regulators, courts, the media or other powerful institutions to shape policy [164]. Politics and policy is a place where sociotechnical imaginaries are created and expanded [166]. However, imaginaries are not the same as, for example, discourses that focus primarily on language [164].

It is beyond the scope of this thesis to go in-depth with the complete picture and use of the theory of sociotechnical imaginaries and vanguard visions, but numerous scholars have used this theory to investigate futures of autonomous driving [167], personalized medicines [168] and corporate

imaginaries of biotechnological agriculture [169]. Jasanoff herself has applied sociotechnical imaginaries to the field of policy and biotechnology, where she distinguishes between 'green' (agricultural) and 'red' (pharmaceutical) biotechnology [162], the latter being the focus here. As a response to the biotechnological development, regulators have had to put systems in place for creating a market for biotechnological products, monitoring the development and hazards [162]. Both private and public stakeholders and their *"claims, beliefs, discourses, and actions of all these institutions, and the strategies by which they acquire and maintain legitimacy" (p.28)* are, according to Jasanoff, important to take into consideration when evaluating the field [162]. However, the changes that most influence and create meaning in society originate from decisions made in the courts, or by expert bodies or professional classes [162]. Policy documents can be used as a lens to see how desirable futures are envisioned [164].

To view the field of biosimilars, within the context of sociotechnical imaginaries theory, it is essential to focus on how the future of these products is imagined. To trace and contextualize vanguard visions, it is necessary to look at the means that the vanguard vision holders use, but also to look at images, texts and the language used [164]. In hindsight, it is evident that the once vanguard vision of biosimilarity has become a sociotechnical reality as several biosimilars have been approved and are on the market. This reality appears to originate from both technical and societal developments. On the one hand, the societal drive for these products was built on an imaginary of generic follow-on products for biotechnological medicines [10,170], where this was imagined as a desirable future for society as a means to lower prices for biological medicines, to relieve healthcare budgets and increase access to medicines [10]. On the other hand, the scientific concept of biosimilarity was envisioned in 1998 as a possible future in a policy document from the EMA [30], which can be seen as the beginning of the transformation of a vanguard vision of biosimilarity to a sociotechnical imaginary. This was initially contested by some from the pharmaceutical industry who described it as impossible to make follow-on products for biological medicines due to the molecular complexity and without compromising safety or violating IPRs [171]. Nonetheless, the concept became a reality, as previously mentioned, when it was written into the EU legislation in 2003 [86]. This initially shows that sociotechnical imaginaries can be a useful and thought-provoking approach to understand the development of the field of biosimilars.

On the basis of the above, it is relevant to apply the theory to the results of this research on the views of EU national medicines agency regulators and the pharmaceutical industry as they are in a powerful position for converting vanguard visions into more established imaginaries. The theory is useful because it highlights the participants' views, which, according to Jasanoff, are relevant in that norms,

meanings and ideas are created by institutions involved in regulation of biotechnology [162]. Applying this theoretical perspective can thus provide explanations for policy development and visions for future policy. As the West can be considered a usual place for pharmaceutical knowledge making [172], it is pertinent to apply the theory of sociotechnical imaginaries in this part of the world. In addition, it is essential to use a cross-disciplinary approach to obtain a more nuanced and sufficient description of the reality as it is seen [164]; this approach was applied in the conduct of the thesis research. The interviews allowed access to contemporary 'story-telling', which according to Jasanoff is important in eliciting changes in the regulation of science and technology [162].

The research results of this thesis show that the evolving regulation of biosimilars needs to adapt to emerging products, and the future of the regulation of biosimilars is most likely depends on which vanguard visions and imaginaries mature to reality. For example, once consensus is reached or regulators are certain of how they see the future of biosimilar clinical trial requirements, these are likely to become reality. The exact outcome can be guided by the current imaginaries. The results of this research suggest that there are two imaginaries. The first, a utopic imaginary: a positive outcome that a scientifically sound reduction of biosimilar clinical trial requirements could result in lower development costs which in turn would make more biological active substances attractive for biosimilar development, which could benefit patients. Additionally, this could bring technological advancements, such as initial steps toward deciding the future regulation of the next generation follow-on products, such as biosimilars for orphan drugs. The second is a dystopic imaginary: a negative outcome that the future of reducing or waiving biosimilar clinical trial requirements could lead to unknown, potential risks that could endanger patients and reduce trust in biosimilars and regulatory agencies.

From a societal perspective, a vision of substitution of biologics brings with it a positive vision of increased access to medicines for patients via price-lowering effects from substitution, enabling better use of restricted resources in healthcare systems. This vision builds on the imaginary of the successful competition introduced by generics [10,173]. However, a dystopic vision is that companies would refrain from continuing development of new biosimilars if the current large investments in development were made with an expectation of low prices. In turn, this could reduce access to medicines for patients. The results of this research also suggest a dystopic vision in which the substitution of biologics is seen as risky and unsafe. The findings also show that companies act upon these visions and apparently, at least earlier, spread information that played on the dystopic vision of biosimilars. In the words of Jasanoff, companies thus played on sociotechnical imaginaries and their associated hopes and fears of clients in a way that may cross geopolitical borders [164].

Looking at the results, it appears that industry and regulators largely control the future visions of the regulation of biosimilars. Thus, they also control the options for which futures the regulation can develop. This pertains to how biosimilars are developed, approved, and used. The picture shows that essentially a diverse, but limited group of persons steer the development of the regulation of biosimilars, albeit within a large and complex regulatory system.

Encouraging some visions or imaginaries over others by powerful actors, such as regulators and industry, will have an effect on how society perceives the possible futures.

Consequently, it will also affect how these visions become integrated into policy, and in the end constitute reality. However, it is important to note that, from a theoretical perspective, visions can inspire, but if they divert too much from the existing collective understanding, they may seem unrealistic [165]. Nonetheless, vanguard visions typically compete with each other [165]. If the dystopic vision becomes a dominant sociotechnical imaginary, it appears unlikely that an imaginary of biologics substitution will become reality. Thus, the field of biosimilars is currently at a crucial point in time where conscious decisions are needed regarding whether regulation of biosimilars should move toward the substitution of biologics. The situation can be put in perspective in the following quote, stating the reality of policy is driven by both collective knowledge and political agenda:

"Political culture in contemporary knowledge societies includes the tacit, but nonetheless powerful, routines by which collective knowledge is produced and validated. It embraces institutionalized approaches to reasoning and deliberation. But equally, as we shall see, political culture includes the moves by which a polity, almost by default, takes some issues or questions out of the domain of politics as usual" [162] *(p. 21).*

Discussion of Methods and Theory

The following section assesses the quality of the research using the criteria suggested by Kitto et al. [174] and the concept of information power as described by Malterud [175] to evaluate the sample size. The criteria by Kitto et al. are clarification, justification, procedural rigor, representativeness, interpretative rigor, reflexivity and evaluative rigor as well as transferability [174]. The following sections include a brief description of the criteria/concept including an assessment of the research conducted in this matter.

Clarification and justification

Clarity of the research question is key for evaluating the results and interpretations. Moreover, there must be sufficient justification if the research is informed by specific theoretical approaches and of why the applied methods are appropriate. [174]

In this doctoral work, the research questions are clearly formulated. A theoretical framework has not been used to inform the research design and process but was applied and justified (see below) post-hoc to provide a framework for a wider understanding of the results. However, a cross-disciplinary approach was applied, which is appropriate as it both allows more nuanced and robust research to be conducted as well as providing reliability when multiple persons with different backgrounds and expertise agree on the research results. The authors of Papers I–III are from the fields of pharmaceutical policy (LCD, ABA, MLDB), regulatory science, (LCD, MLDB), law (TM, AS, ASK), medicine (ASK), protein formulation (MvdW), social science (SKS), and a regulatory affairs specialist in a pharmaceutical company (HH). Moreover, qualitative methods are most suitable for obtaining rich data via in-depth interviews [176] and are recommended for accessing expert knowledge [124].

Further, the relatively small total population of eligible participants makes quantitative studies inappropriate.

Procedural rigor

Procedural rigor involves allowing the reader access to how the participants were accessed, how the data were collected and analyzed, and how non-participation was dealt with. [174]

Only the overall sampling strategies, networking and snowballing, and not full details of the recruitment, have been reported to protect the anonymity and confidentiality of the participants. The research has been described regarding when and how long the interviews were and what questions were asked. Further, it has also been describes how the analyses were carried out. The data collection itself occurred as interviews that were calm and pleasant conversations between the interviewer and participants, and participants showed a great willingness to take part in the research. It was a strength of the research that the same data collection instrument was used to collect knowledge from both regulators and company participants with different types of products. However, the data collection can have been influenced by the participants' perceptions of the interviewer's competence and status [124]. The participants may have given the interviewer "credit" for being a PhD candidate; however, they may also have been skeptical about the younger age and female gender of the researcher [124]. Both status and gender of the interviewer are reported as influencing expert interviewing [124]. Only

a few times during the interviews did the interviewer detect negative associations due to gender or status, but these did not appear to influence the willingness of the expert to share expertise or the quality of the interview. Further, the use of "going naïve" as interview technique can be beneficial because it can provide in-depth data [177]. An unknown aspect of the data collection is whether the participants have shared their own opinions or the opinions of their workplaces. This is not possible to assess as participants may or may not have the same opinions as their workplace, and their opinions may have been conscious or unconscious. Nevertheless, several participants appear to have provided their own opinion as some stressed that they were willing to participate only because the research focused on their own opinions rather than to participate as formal representatives of their workplace. Non-participation was met openly and an offer to reach out with the results of the research was made and accepted by the eligible participants who declined. Four chose to decline: three due to the in-house policy of the EMA or the FDA and one did not have the time.

Representativeness

The sampling strategy must be reported for representativeness. I the strategy supports conceptual generalizability, however, it is equally important that the research is assessed using the participant characteristics. This must include comparisons of participants' responses to reveal similarities and contrasts among participants. [174]

The sampling strategy was reported as purposeful and the responses by participants have been compared in the analysis and subsequently described in the results. The variety and types of participants were chosen to obtain a high conceptual generalizability. The choice to include medicines regulators as well as different types of company participants, all with experience within biologics, and to recruit participants with different expertise was made to obtain many different views on the research question. However, it is a limitation that regulators' opinions on the US system is theoretical rather than based on experiences. It would also have been relevant to include other views such as those of HTA bodies, trade unions, physicians and patients. However, regulators and industry are central stakeholders in the decision-making surrounding marketing authorization of biologics and are key to obtaining a full picture of the current regulatory aspects of biosimilars as well as how this landscape is evolving.

Interpretative rigor

The interpretative rigor of the research pertains to numerous techniques to obtain as full and exhaustive interpretation of the data as possible. Means to do so include interrater reliability,

respondent validation, and triangulation using multiple methods or theories. Further, it is important to look at both the overall pattern in the data as well as distinct responses. [174]

It has been reported how the data were analyzed by two analysts and audited by a third researcher. This was done to obtain interrater reliability of the results to ensure a robust analysis and to capitalize as much as possible on discussions between analysts to develop the coding and understanding of the data. Distinct responses have been evaluated for their role in the findings.

Respondent validation was also used, i.e. each participant approved the respective transcript/notes and was given an opportunity to comment on it. However, triangulation of methods or theories was not applied in the initial design or analysis of the research. The original research was not driven by a specific theory-driven approach due to its explorative nature. However, subsequent to seeing the findings it became evident that a theoretical context could give a wider theoretical understanding of the findings.

Reflexivity and evaluative rigor

Reflexivity is a clear description by the researchers of the effect of any relationship among researchers to the research topic or to the participants. Moreover, reflexivity regarding the social setting and context of the research should be addressed alongside how researchers' values could influence the design, collection and analysis of the data. Evaluative rigor is to report any ethical aspects of the research and whether an ethics approval has been obtained. Further, this includes ensuring that the findings represent the data as a whole. [174]

The participants were willing to take part in the research as they found the research question important. The researcher's preunderstanding of the research has been included in the thesis to address reflexivity; however, this does not address the researcher's views on the methods. The specific choice to use interviews as a method is due to it being a recommended way to access expert knowledge and provide nuanced understandings of a research topic [124,125]. An alternative method could have been a questionnaire-based survey, but this would have elicited officially accepted standards rather than participants' own views [124]. Evaluative rigor has been reported regarding ethics, and substantial efforts have been made to reflect on the coding and interpretation of the data analyses to ensure that the findings represent the data as a whole.

Transferability

Transferability refers to an evaluation of whether, and if so, to what extent the research findings can inform settings other than the specific researched setting. Moreover, it also assesses how the findings relate to policy, practice or other current research. [174]

The transferability has been reported and the findings are deemed to be slightly transferable to other contexts. It is crucial to note that this research has been conducted within the field of recombinant proteins, and that the results of this thesis might not be transferable to biosimilars of other types of products. Another limit to transferability is that not all jurisdictions will have a distinction between a central medicines agency and national medicines agencies in member states, such as the regulatory structures in the EU. However, since the European regulatory framework for biosimilars is in the forefront of the field it is likely that other jurisdictions will consider doing the same if a way is found to reduce or waive the biosimilar clinical comparability trial requirements or member state's implementing substitution of biologics,. Thus, the findings can be used by other jurisdictions as inspiration for their regulatory frameworks for biosimilars.

Information power of sample size

To evaluate the sample size of qualitative research, Malterud et al. state that the following five variables must be assessed: aim, specificity, theory, dialog and analysis [175].

A total of 25 persons were interviewed and this is evaluated as appropriate for the following reasons. A relatively small sample size is argued for because 1) the aim is narrow as it is only select experts in the field who were relevant to recruit, 2) the participants are highly relevant and have specific knowledge for investigating the research aim and 3) the quality of interview dialog was robust and the interviews relatively long. However, the following aspects argue for a relatively large sample size 1) the absence of a theoretical underpinning to the research design and 2) that the analysis is across the participants' views on the research topic and does not focus specifically on a single person's views. However, even though the analysis is across participants, the total population of eligible participants is not large, and considering all five variables overall, 25 participants is deemed appropriate to answer the research question.

Another aspect that was relevant for the sample size is the anonymity of the participants. The number of experts in the field is relatively small, and thus, for example including EU national medicines agency regulators from all EU countries would threaten anonymity of the participating regulators. Therefore, it was purposefully chosen to interview only a part of these.

Discussion of theory

Theory can provide a lens for research and provide a wider conceptual understanding of data [178]. The theory of sociotechnical imaginaries does not currently describe what characterizes power and how it is exerted, neither does it describe how the competition works between various imaginaries and visions. Overall, this theory was chosen because it grasps and provides a framework for

understanding the nuances of the results, unlike the other theories that have been considered, for instance, boundary work by Star [179] and tacit/explicit knowledge by Collins [180]. These theories were not chosen for the following reasons 1) the theory of boundary work is limited to focusing singularly on the different contested issues of biosimilars and, thus, does not offer a framework to see the interplay between different aspects. This is because boundary work deals with the boundaries of an object between persons, thus on the flexible and shared structure and how work around the object is structured for different persons [179]. Further, 2) that the theory of tacit/explicit knowledge would, in the context of this research, deal only with the scientific ability to recreate a biomolecule that is highly similar to another biomolecule, which was found to be a manageable challenge in the results of Study I. For these reasons, the theory of sociotechnical imaginaries was found to offer a wider range of description and explanation of the results than would the other theories.

Future Research

This study points to further research. Some of the areas to investigate in the future are as follows:

1. Regarding the findings and discussion on interchangeability of biosimilars, it is unclear what exactly is needed to gain clarity on the science underlying interchangeability of biosimilars. This is true regardless whether or not this leads towards substitution of biologics. Further, the research should try to establish a framework for how, or under what circumstances, the likeness between biomolecules can be seen as switchable and substitutable, respectively.
2. When it comes to the sociotechnical imaginaries of biosimilars, an in-depth analysis of how various stakeholders interact within the field of biosimilars would be of importance. Further, how such interactions result in policy would shed light on policy development. This would be important knowledge for the field of biosimilars, but it could potentially also be applied to other types of pharmaceuticals.
3. Study of new innovative approaches within drug development. Methodologically, a similar cross-disciplinary approach can be used to explore nuances and several perspectives on the application of innovative approaches to drug development processes, for example, artificial intelligence. It is essential to investigate the influence of such applications regarding both the opportunities and challenges.
4. A qualitative study of prescriber perceptions. It is essential to study how physicians think about the biosimilar clinical trials and how their thoughts affect prescribers' decision-making. Such understanding would enable targeted initiatives to support physicians' trust in biosimilars.

Conclusion

The European regulation of biosimilars is a success, but the participants from EU national medicines agencies and the pharmaceutical industry show a picture of biosimilars as a diverse and complex field that is undergoing rapid changes.

From a scientific perspective, establishing biosimilarity for recombinant proteins tends not to be scientifically challenging providing there is access to biotechnology expertise. Moreover, the biosimilar clinical trial requirements are likely to evolve toward reducing or waiving clinical trials for comparable efficacy due to scientific advancements.

From a legal perspective, trade secrets appear to be a surmountable barrier to recombinant biosimilar development, but patents are legal obstacles because of the patent thickets protecting each biological product. Particularly challenging is the lack of an efficient search mechanism, which leaves biosimilar developers with considerable uncertainty regarding the patent landscape protecting originator biologics.

From a regulatory perspective, the regulation of biosimilars is in place, but will most probably still need to be adapted as new methods and approaches gain acceptance. The European regulation of biosimilars is expected in the future to contain regulation for approval of biosimilars of recombinant orphan drugs; however, changes to the existing framework will probably be needed for the next generation of follow-on products to gene- and cell-based therapies.

From a societal perspective, the use of biosimilars is at a crucial point in time, where there is uncertainty regarding the scientific likeness between biological molecules and the ability to safely substitute biologics. Reassurance of the scientifically sound way forward could be obtained by a scientific definition or official EMA opinion on interchangeability of biosimilars on a product-to-product level.

Currently, a clear regulatory vision is lacking of how far science overall can bring biosimilars and biosimilarity. Further, it would be highly beneficial if a common understanding could be found on substitution of biologics across jurisdictions. Regulatory clarity on interchangeability of biosimilars would be a fruitful next step to ensure scientific reasons for either embarking on or refraining from realizing substitution of biologics in the near future.

Acknowledgements

My PhD research was carried out at the Copenhagen Centre for Regulatory Science (CORS) and Social and Clinical Pharmacy Group at the University of Copenhagen from November 2017 to October 2020. Many have followed me on this journey and contributed to this thesis becoming a reality as well as forming me as a researcher. For this I would like to express my appreciation! In particular, I would like to sincerely thank:

My main supervisor **Prof. Anna Birna Almarsdóttir** for your endless encouragement and your belief in me especially when I faced the challenges of understanding and maneuvering across disciplines and venturing into the political and complex field of biosimilars.

My co-supervisors **Assoc. Prof. Marco van de Weert, Prof. Marie Louise De Bruin**, **Dr. Hans Hoogland** and **Prof. Timo Minssen** - you have all been there for me, sharing your expertise, encouragement and constructive critiques in all phases of the research.

Prof. Sofia Kälvemark Sporrong and **Clas Sporrong** for your never-ending support and tips in many facets of both life and PhD life, whether it was challenging my research world view, giving me insight into biologic manufacturing or offering tasty cooking tips.

Ass. Prof. Ameet Sarpatwari and **Prof. Aaron S. Kesselheim** for providing valuable learning experiences throughout our collaboration both remotely and especially during my research stay at PORTAL in Boston. Your input and warm welcome into the group had a big influence on my wonderful stay abroad and helped me to reach the next level as a researcher. My time in Boston has a very special place in my heart.

Dr. Janine M. Traulsen for always being there and your much appreciated inputs on minor and major aspects of research as well as the valuable lessons on interdisciplinarity and research cultures.

All my colleagues at Social and Clinical Pharmacy, **the Copenhagen Centre for Regulatory Science (CORS)**, and **the Centre for Advanced Studies in Biomedical Innovation Law (CeBIL)** at the University of Copenhagen for your encouragements and support. Thank you in particular to my fellow PhD candidates, especially Joo Hanne Poulsen for all our chats about the joys and frustrations of the PhD journey.

Nobel Laureates and my fellow young researchers for the enlightening scientific experience at the Lindau Nobel Laureate Meeting 2020.

My professional network for your help and contributions to make me wiser on the field of biosimilars and aiding my data collection.

All the participants who took your time to discuss with me and share your knowledge and expertise, without your valuable contributions this research would not have been possible.

Copenhagen Center for Regulatory Science (CORS) for funding the project and under which this research was conducted. CORS is a cross-faculty university-anchored center involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring Pharmaceuticals, LEO Pharma) as well as patient organizations (Rare Diseases Denmark). The center is devoted solely purely devoted to the regulatory scientific aspects of the regulatory field and with a patient-oriented focus. CORS's and the research is neither focused on company-specific products or directly company related to a specific company. **LEO Pharma A/S** for the grant to CORS that constitute the financial foundation for this PhD scholarship.

All the funding bodies and grants that supported and enabled my research stay abroad to PORTAL at Harvard Medical School and Brigham and Women's Hospital as well as my attendances at conferences to learn from other researchers and to disseminate my research: EliteResearch Travel Grant by the Danish Ministry for Higher Education and Science; Jørgen Kejser Memorial Grant from Muskelsvindfonden; the Graduate School at Faculty of Health and Medical Sciences at the University of Copenhagen; Augustinus Fonden; Christian and Ottilia Brorson Travel Grant; Dansk Kvindesamfunds Fællesfond; and Lundbeckfonden.

Family and **friends** for the joy you bring to my life and for your love and support during my pursuit of a PhD degree. Especially **Kasper Druedahl**, **Matilde S. Karlsen** and **Nelleke Duijm**.

Last but not least there are no words for my appreciation for **my parents** who are always there for me, in Denmark or abroad, and for your endless love and support.

References

1. Martin LH. Truth, Power, Self: An Interview with Michel Foucault - October 25th, 1982. In: Martin LH, Gutman H, Hutton PH, editors. Technologies of the self: a seminar with Michel Foucault. Amherst: The University of Massachusetts Press; 1988. p. 9–15.

2. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov. 2008;7(1):21–39. Doi:10.1038/nrd2399

3. Ingrasciotta Y, Cutroneo PM, Marciano I, Giezen T, Atzeni F, Trifiro G. Safety of biologics, including biosimilars: perspectives on current status and future direction. Drug Saf. 2018;41(11):1013–22. Doi:10.1007/s40264-018-0684-9

4. Walsh G. Biopharmaceutical benchmarks. Nat Biotechnol. 2018;36(12):1136–45. Doi:10.1038/nbt.4305

5. Miller KL, Lanthier M. Regulatory watch: innovation in biologic new molecular entities: 1986- 2014. Nat Rev Drug Discov. 2015;14(2):83. Doi:10.1038/nrd4535

6. Roy A. Biologic medicines: the biggest driver of rising drug prices [Internet]. Forbes. 2019 Mar 8 [accessed 2020 Oct 29]. Available from: https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest- driver-of-rising-drug-prices/

7. IQVIA Institute. Advancing biosimilar sustainability in Europe - a multi-stakeholder assessment [Internet]. 2018 Sep [accessed 2020 Oct 29]. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-biosimilar- sustainability-in-europe

8. Olech E. Biosimilars: rationale and current regulatory landscape. Semin Arthritis Rheum. 2016;45(5 Suppl):S1-10. Doi:10.1016/j.semarthrit.2016.01.001

9. Tsiftsoglou AS, Ruiz S, Schneider CK. Development and regulation of biosimilars: current status and future challenges. BioDrugs. 2013;27(3):203–11. Doi:10.1007/s40259-013-0020-y

10. Tsiftsoglou AS, Trouvin JH, Calvo G, Ruiz S. Demonstration of biosimilarity, extrapolation of indications and other challenges related to biosimilars in Europe. BioDrugs. 2014;28(6):479– 86. Doi:10.1007/s40259-014-0109-y

11. European Medicines Agency. Guideline on similar biological medicinal products. CHMP/437/04 Rev 1 [Internet]. 2014 Oct 23 [accessed 2020 Oct 29]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC 500176768.pdf

12. European Medicines Agency. Medicine data [Internet]. 2020 Oct 18 [accessed 2020 Oct 18]. Available from: https://www.ema.europa.eu/en/medicines/download-medicine- data#european-public-assessment-reports-(epar)-section

13. U.S. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product [Internet]. 2015 Apr [accessed 2020 Oct 29]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc es/UCM291128.pdf

14. Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983-2018. JAMA. 2020;323(2):164–76. Doi:10.1001/jama.2019.20288

15. IQVIA Institute. The impact of biosimilar competition in Europe [Internet]. 2019 Oct [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/docsroom/documents/38461/attachments/1/translations/en/renditions/native

16. IQVIA Institute. The impact of biosimilar competition in Europe [Internet]. 2018 Sep [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/docsroom/documents/31642/attachments/1/translations/en/renditions/native

17. Price WN, Rai AK. Are trade secrets delaying biosimilars? Science. 2015;348(6231):188–9. Doi:10.1126/science.aab1684

18. Moorkens E, Jonker-Exler C, Huys I, Declerck P, Simoens S, Vulto AG.

Overcoming barriers to the market access of biosimilars in the European Union: the case of biosimilar monoclonal antibodies. Front Pharmacol. 2016;7:193. Doi:10.3389/fphar.2016.00193

19. Aladul MI, Fitzpatrick RW, Chapman SR. Differences in UK healthcare professionals' knowledge, attitude and practice towards infliximab and insulin glargine biosimilars. Int J Pharm Prac. 2019;27(2):214–7. Doi:10.1111/ijpp.12485

20. Peyrin-Biroulet L, Lönnfors S, Roblin X, Danese S, Avedano L. Patient perspectives on biosimilars: a survey by the European federation of crohn's and ulcerative colitis associations. J Crohns Colitis. 2017;11(1):128–33. Doi:10.1093/ecco-jcc/jjw138

21. van Overbeeke E, De Beleyr B, de Hoon J, Westhovens R, Huys I. Perception of originator biologics and biosimilars: a survey among Belgian rheumatoid arthritis patients and rheumatologists. BioDrugs. 2017;31(5):447–59. Doi:10.1007/s40259-017-0244-3

22. Gasteiger C, Lobo M, Dalbeth N, Petrie KJ. Patients' beliefs and behaviours are associated with perceptions of safety and concerns in a hypothetical biosimilar switch. Rheumatol Int. 2020;online ahead of print. Doi:10.1007/s00296-020-04576-7

23. Giuliani R, Tabernero J, Cardoso F, McGregor KH, Vyas M, De Vries EGE. Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. ESMO Open. 2019;4(2):e000460. Doi:10.1136/esmoopen-2018-000460

24. Chapman SR, Fitzpatrick RW, Aladul MI. Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: result of a UK web-based survey. BMJ Open. 2017;7(6):e016730. Doi:10.1136/bmjopen-2017-016730

25. Danese S, Fiorino G, Michetti P. Changes in biosimilar knowledge among European Crohn's Colitis Organization [ECCO] members: An updated survey. J Crohns Colitis. 2016;10(11):1362– 5. Doi:10.1093/ecco-jcc/jjw090

26. Kurki P, Ekman N. Biosimilar regulation in the EU. Exp Rev Clin Pharmacol. 2015;8(5):649–59. Doi:10.1586/17512433.2015.1071188

27. European Medicines Agency. Biosimilar medicines: overview [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview#biosimilar-development-and-approval- in-the-eu-section

28. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars - why terminology matters. Nat Biotechnol. 2011;29(8):690–3. Doi:10.1038/nbt.1936

29. U.S. Food and Drug Administration. Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products [Internet]. 1996 Apr [accessed 2020 Oct 29]. Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm1228 79.htm

30. European Agency for the Evaluation of Medicinal Products (now European Medicines Agency). Concept paper on the development of a committee for proprietary medicinal products (CPMP) guideline on comparability of biotechnology-derived products. CPMP/BWP/1113/98 [Internet]. 1998 Jun 24 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/documents/scientific-guideline/concept-paper-development- committee-proprietary-products-cpmp-guideline-comparability-biotechnology_en.pdf

31. Berkowitz SA, Engen JR, Mazzeo JR, Jones GB. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov. 2012;11(7):527– 40. Doi:10.1038/nrd3746

32. Vulto AG, Jaquez OA. The process defines the product: what really matters in biosimilar design and production? Rheumatology. 2017;56(suppl_4):iv14–29. Doi:10.1093/rheumatology/kex278

33. Schiestl M, Stangler T, Torella C, Čepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011;29(4):310–2. Doi:10.1038/nbt.1839

34. Liu L. Antibody glycosylation and its impact on the pharmacokinetics and pharmacodynamics of monoclonal antibodies and Fc-fusion proteins. Journal of

Pharmaceutical Sciences. 2015. Doi:10.1002/jps.24444

35. Pineda C, Castañeda Hernández G, Jacobs IA, Alvarez DF, Carini C. Assessing the immunogenicity of biopharmaceuticals. BioDrugs. 2016;30(3):195–206. Doi:10.1007/s40259-016-0174-5

36. Halim LA, Brinks V, Jiskoot W, Romeijn S, Haselberg R, Burns C, et al. Quality and batch-to-batch consistency of original and biosimilar epoetin products. J Pharm Sci. 2016;105(2):542–50. Doi:10.1016/j.xphs.2015.10.019

37. van de Weert M, Randolph TW. Physical instability of peptides and proteins. In: van de Weert M, Frøkjær S, Hovgaard L, editors. Pharmaceutical formulation development of peptides and proteins. Boca Raton, FL, USA: CRC Press; 2013. p. 107–29.

38. Parr MK, Montacir O, Montacir H. Physicochemical characterization of biopharmaceuticals. J Pharm Biomed Anal. 2016;130:366–89. Doi:10.1016/j.jpba.2016.05.028

39. Shire SJ. Formulation and manufacturability of biologics. Curr Opin Biotechnol. 2009;20(6):708–14. Doi:10.1016/j.copbio.2009.10.006

40. Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and european experience on the regulatory trajectory in the United States. Clin Ther. 2012;34(2):400–19. Doi:10.1016/j.clinthera.2011.12.005

41. Walsh G, Jefferis R. Post-translational modifications in the context of therapeutic proteins. Nat Biotechnol. 2006;24(10):1241–52. Doi:10.1038/nbt1252

42. Kim S, Song J, Park S, Ham S, Paek K, Kang M, et al. Drifts in ADCC-related quality attributes of Herceptin®: impact on development of a trastuzumab biosimilar. mAbs. 2017;9(4):704–14. Doi:10.1080/19420862.2017.1305530

43. Krause ME, Sahin E. Chemical and physical instabilities in manufacturing and storage of therapeutic proteins. Curr Opin Biotechnol. 2019;60:159–67. Doi:10.1016/j.copbio.2019.01.014

44. Chi EY, Krishnan S, Randolph TW, Carpenter JF. Physical stability of

proteins in aqueous solution: mechanism and driving forces in nonnative protein aggregation. Pharm Res. 2003;20(9):1325–36. Doi:10.1023/A:1025771421906

45. European Medicines Agency. Guideline on immunogenicity assessment of therapeutic proteins. EMEA/CHMP/BMWP/14327/2006 Rev 1 [Internet]. 2017 May 17 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf

46. Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. BioDrugs. 2014;28(4):363–72. Doi:10.1007/s40259-014-0088-z

47. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol. 2009;27(1):26–34. Doi:10.1038/nbt0109-26

48. Luciani F, Galluzzo S, Gaggioli A, Kruse NA, Venneugues P, Schneider CK, et al. Implementing quality by design for biotech products: are regulators on track? mAbs. 2015;7(3):451–5. Doi:10.1080/19420862.2015.1023058

49. ICH (International Conference on Harmonisation). Guideline: pharmaceutical development Q8(R2) [Internet]. 2009 Aug 4 [accessed 2020 Oct 29]. Available from: https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf

50. Cho IH, Lee N, Song D, Jung SY, Bou-Assaf G, Sosic Z, et al. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. mAbs. 2016;8(6):1136–55. Doi:10.1080/19420862.2016.1193659

51. Price WN, Rai AK. Manufacturing barriers to biologics competition and innovation. Iowa Law Rev. 2016;101(3):1023–63.

52. European Union. Trade marks [Internet]. 2020 Sep 7 [accessed 2020 Oct 29]. Available from: https://europa.eu/youreurope/business/running-business/intellectual-property/trade-marks/index_en.htm

53. European Union. Copyright [Internet]. 2020 Aug 5 [accessed 2020 Oct 29]. Available from: https://europa.eu/youreurope/business/running-

business/intellectual- property/copyright/index_en.htm

54. Grammel M, Walsh R, Crawford R. Protecting data in the medtech industry [Internet]. 2019 Aug 12 [accessed 2020 Oct 29]. Available from: https://www.medtechintelligence.com/feature_article/protecting-data-in-the-medtech- industry/

55. Sherkow JS. Protecting products versus platforms. Nat Biotechnol. 2016;34(5):462–5. Doi:10.1038/nbt.3553

56. European Patent Office. How to apply for a European patent [Internet]. 2018 [accessed 2020 Oct 29]. Available from: https://www.epo.org/applying/basics.html

57. World Intellectual Property Organization. What is a patent [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://www.wipo.int/patents/en/

58. European Patent Office. The European Patent Convention. Article 83. Disclosure of the invention [Internet]. [accessed 2020 Oct 29]. Available from: https://www.epo.org/law- practice/legal-texts/html/epc/2016/e/ar83.html

59. European Patent Office. European Patent Convention. Article 63. Term of the European patent [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://www.epo.org/law- practice/legal-texts/html/epc/2016/e/ar63.html

60. European Patent Office. FAQ - applying for a patent [Internet]. 2018 [accessed 2020 Oct 29]. Available from: https://www.epo.org/service-support/faq/own-file.html#faq-274

61. Regulation (EC) No 469/2009 of the European parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (codified version) [Internet]. 2009 [accessed 2020 Oct 29]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1548929626652&uri=CELEX:32009R0469

62. European Commission. Supplementary protection certificates for pharmaceutical and plant protection products [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/growth/industry/policy/intellectual-

property/patents/supplementary- protection-certificates_en

63. Cepl P, de Morpurgo M, Perotti C. EU SPC manufacturing waiver becomes effective: what can industry expect? Eur Pharm Law Rev. 2019;3(3):116–20. Doi:10.21552/eplr/2019/3/5

64. Kupecz A, Roox K, Dekoninck C, Schertenleib D, Stief M, Sanna F, et al. Safe harbors in Europe: An update on the research and Bolar exemptions to patent infringement. Nat Biotechnol. 2015;33(710–5). Doi:10.1038/nbt.3273

65. Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Internet]. Official Journal of the European Union, L311. 2012 [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

66. Directive 2004/27/EC of the European parliament and of the Council of 31 March 2004 [Internet]. Official Journal of the European Union, L136. 2004 [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf

67. Kretzschmar MD. Drug safe harbour provisions in the USA and Europe: implications for the emerging biosimilars industry. J Int Property Law Prac. 2014;9(4):298–311. Doi:10.1093/jiplp/jpt262

68. Wested J, Minssen T. An update on research- & Bolar exemptions in the U.S. and Europe: unsolved questions and new developments in an increasingly important area of law [Internet]. NIR: Nordiskt Immateriellt Rättsskydd. 2019;2:168-183. 2019 Apr 15 [accessed 2020 Oct 29]. Available from: https://ssrn.com/abstract=3360277

69. Bertram V, Lunze A. SPC manufacturing waiver (Part 2): the fairy tale of day-1 entry under the manufacturing and stockpiling waiver – a German view [Internet]. 2019 Dec [accessed 2020 Oct 29]. Available from: https://www.taylorwessing.com/synapse/ti-spc-day-1.html

70. Nicholson Price W, Rai AK, Minssen T. Knowledge transfer for

large-scale vaccine manufacturing. Science. 2020;369(6506):912–4. Doi:10.1126/science.abc9588

71. European Commission. Frequently asked questions: protection against the unlawful acquisition of undisclosed know-how and business information (trade secrets) [Internet]. 2018 [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/growth/industry/intellectual- property/trade-secrets/faq_en

72. Directive (EU) 2016/943 of the European parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure [Internet]. Official Journal of the European Union, L157. 2016 Jun 15 [accessed 2020 Oct 29]. p. 1–18. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016L0943&from=EN

73. GROW. Report for the European Commission. Study on trade secrets and confidential business information in the internal market. Final study report [Internet]. 2018 Feb 6 [accessed 2020 Oct 29]. Available from: http://ec.europa.eu/DocsRoom/documents/27703

74. Sigareva MA., O'Donnell RW. Global strategies for protecting inventions in the biotechnology sector. New Jersey Lawyer. 2017;August:60–4. Available from: www.law.nyu.edu/sites/default/files/upload_documents/Global-Strategies-for-Protecting- Inventions-in-the-Biotechnology-Sector.pdf

75. Jones N, Dean AB. Current patenting trends for biologics versus small molecules. Pharm Pat Anal. 2012;1(3):225–7. Doi:10.4155/ppa.12.34

76. Price WN, Rai AK. How logically impossible patents block biosimilars. Nat Biotechnol. 2019;37(8):862–3. Doi:10.1038/s41587-019-0196-x

77. Storz U. Of patents and patent disputes: The TNFalpha patent files. Part 1: Humira. Hum Antibodies. 2017;25(1–2):1–16. Doi:10.3233/hab-160300

78. Koons C. This shield of patents protects the world's best-selling drug [Internet]. Bloomberg Businessweek; 2017 Sep 7 [accessed 2020 Oct 29]. Available from: https://www.bloomberg.com/news/articles/2017-09-07/this-shield-of-patents-protects-the- world-s-best-selling-drug

79. Staines R. Boehringer Ingelheim axes biosimilars development outside US [Internet]. PharmaPhorum; 2018 Dec 5 [accessed 2020 Oct 29]. Available from: https://pharmaphorum.com/news/boehringer-ingelheim-axes-biosimilars-development- outside-us/

80. Rolfe D, Parker J, Morgan M. Are biosimilars patentable? Expert Opin Ther Pat. 2016;26(8):871– 5. Doi:10.1080/13543776.2016.1193156

81. Rajam N, Timo M. What lurks in the shadows of the openness hyperbole for biopharmaceuticals? Drug Dev Res. 2019;80:282–4. Doi:10.1002/ddr.21526

82. European Medicines Agency. The European regulatory system for medicines: a consistent approach to medicines regulation across the European Union. EMA/716925/2016[Internet] 2016 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines- european-medicines-agency-consistent-approach-medicines_en.pdf

83. Regulation (EC) No 726/2004 of the European Parliament and of the Council. Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Article 57 [Internet]. Official Journal of the European Union, L136. 2013 [accessed 2020 Oct 29]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

84. European Medicines Agency. CHMP Members [Internet]. 2020 Oct [accessed 2020 Oct 27]. Available from: https://www.ema.europa.eu/en/committees/chmp/members#MNMS

85. European Medicines Agency. Authorisation of medicines [Internet]. [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation- medicines

86. Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use [Internet]. Official Journal of the European Union, L159. 2003 [accessed 2020 Oct 29]. Available from:

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

87. European Medicines Agency. Guideline on similar biological medicinal products. CHMP/437/04 [Internet]. 2005 Oct 30 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological- medicinal-products_en.pdf

88. Horton LR, Manning M, Wright E, Gallimore J. All eyes on Omnitrope [Internet]. Scrip Magazine. 2006 May 1 [accessed 2020 Oct 29]. Available from: https://www.hoganlovells.com/~/media/hogan-lovells/pdf/publication/scrip-magazinemay- 06_pdf.pdf

89. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMA/CHMP/BWP/247713/2012 [Internet]. 2014 May 22 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar- biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf

90. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 [Internet]. 2014 Dec 18 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf

91. European Medicines Agency. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. EMEA/CHMP/BMWP/31329/2005 [Internet]. 2006 Feb 22 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/annex-guideline-similar- biological-medicinal-products-containing-biotechnology-derived-proteins_en.pdf

92. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing lowmolecular-weight-heparins.

EMEA/CHMP/BMWP/118264/2007 Rev. 1 [Internet]. 2016 Nov 10 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline- non-clinical-clinical-development-similar-biological-medicinal-products-containing-low_en.pdf

93. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005_Rev. 1 [Internet]. 2015 Feb 26 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline- non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-0.pdf

94. European Medicines Agency. Guideline on similar biological medicinal products containing interferon beta. EMA/CHMP/BMWP/652000/2010 [Internet]. 2013 Feb 21 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific- guideline/guideline-similar-biological-medicinal-products-containing-interferon-beta_en.pdf

95. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010 [Internet]. 2012 May 30 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological- medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf

96. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins. EMEA/CHMP/BMWP/301636/2008 Rev. 1 [Internet]. 2018 Jun 28 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline- non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-1.pdf

97. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle

stimulating hormone (r- hFSH). EMA/CHMP/BMWP/671292/2010 [Internet]. 2013. 2013 Feb 21 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific- guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en.pdf

98. European Medicines Agency. Guideline on similar medicinal products containing somatropin. EMEA/CHMP/BMWP/94528/2005 Rev. 1 [Internet]. 2018 Jun 28 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/annex- guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins_en-1.pdf

99. Cilia M, Ruiz S, Richardson P, Salmonson T, Serracino-Inglott A, Wirth F, et al. Quality issues identified during the evaluation of biosimilars by the European Medicines Agency's Committee for Medicinal Products for Human Use. AAPS PharmSciTech. 2018;19(2):489–511. Doi:10.1208/s12249-017-0892-0

100. Boven K, Stryker S, Knight J, Thomas A, Van Regenmortel M, Kemeny DM, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int. 2005;67(6):2346–53. Doi:10.1111/j.1523-1755.2005.00340.x

101. Casadevall N, Rossert J. Importance of biologic follow-ons: experience with EPO. Best Prac Res Clin Haematol. 2005;18(3):381–7. Doi:10.1016/j.beha.2005.01.014

102. European Medicines Agency, European Commission. Biosimilars in the EU information guide for healthcare professionals [Internet]. 2019 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide- healthcare-professionals_en.pdf

103. Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, et al. Policies for biosimilar uptake in Europe: an overview. PLoS One. 2017;12(12):e0190147. Doi:10.1371/journal.pone.0190147

104. European Medicines Agency. European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products

applications. EMA/940451/2011 [Internet]. 2019 Aug 19 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european- medicines-agency-procedural-advice-users-centralised-procedure-similar-biological- medicinal_en.pdf

105. Medicines for Europe. Positioning statements on physician-led switching for biosimilar medicines [Internet]. 2019 Sep [accessed 2020 Oct 29]. Available from: https://www.medicinesforeurope.com/wp-content/uploads/2017/03/M-Biosimilars- Overview-of-positions-on-physician-led-switching.pdf

106. The Finnish Medicines Agency. Interchangeability of biosimilars – position of Finnish Medicines Agency Fimea [Internet]. 2015 May 22 [accessed 2020 Oct 29]. Available from: https://www.fimea.fi/documents/542809/838272/29197_Biosimilaarien_vaihtokelpoisuus_E N.pdf

107. Danish Medicines Agency. Frequently asked questions about biological and biosimilar medicinal products [Internet]. 2016 Jan 29 [accessed 2020 Oct 29]. Available from: https://laegemiddelstyrelsen.dk/en/sideeffects/biological-and-biosimilar-medicinal- products/frequently-asked-questions

108. The Finnish Medicines Agency. Automatic substitution of biological medicines would be possible if carefully planned and gradually implemented [Internet]. 2019 Jun 10 [accessed 2020 Oct 29]. Available from: https://www.fimea.fi/web/en/-/automatic-substitution-of-biological- medicines-would-be-possible-if-carefully-planned-and-gradually-implemented

109. Health Products Regulatory Authority (HPRA). Guide to biosimilars for healthcare professionals [Internet]. 2020 Aug 5 [accessed 2020 Oct 29]. Available from: www.hpra.ie/docs/default- source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare- professionals-v3.pdf?sfvrsn=27

110. Federal Agency for Medicines and Health Products. Biosimilars [Internet]. 2018 Dec 4 [accessed 2020 Oct 29]. Available from: https://www.famhp.be/en/human_use/medicines/medicines/MA_procedures/types/Biosimil ars

111. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31(2):83–91. Doi:10.1007/s40259-017- 0210-0

112. U.S. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product [Internet]. 2019 May [accessed 2020 Oct 29]. Available from: https://www.fda.gov/media/124907/download

113. U.S. Food and Drug Administration. Clinical immunogenicity considerations for biosimilar and interchangeable insulin products. Draft guidance [Internet]. 2019 Nov [accessed 2020 Oct 29]. Available from: https://www.fda.gov/media/133014/download

114. Gabay M. Biosimilar substitution laws. Hosp Pharm. 2017;52(8):544–5. Doi:10.1177/0018578717726995

115. Sacks CA, Van de Wiele VL, Fulchino LA, Patel L, Kesselheim AS, Sarpatwari A. Assessment of variation in state regulation of generic drug and interchangeable biologic substitutions. JAMA Intern Med. 2020;e203588. Doi:10.1001/jamainternmed.2020.3588

116. Cohen HP. The Sandoz perspective on biosimilar interchangeability: a designation unique to the United States [Internet]. Center for Biosimilars. 2019 Jul 11 [accessed 2020 Oct 29]. Available from: https://www.centerforbiosimilars.com/contributor/hillel-p-cohen/2019/07/the-sandoz-perspective-on-biosimilar-interchangeability-a-designation-unique-to-the-united-states

117. Pfizer. Pfizer's position on interchangeability and substitution [Internet]. 2020 Jul [accessed 2020 Oct 29]. Available from: https://www.pfizerbiosimilars.com/biosimilars-regulatory- considerations

118. European Federation of Pharmaceutical Industries and Associations LoE Biologics WG. EFPIA policy principles for off-patent biologic medicines in Europe [Internet]. 2015 Sep 28 [accessed 2020 Oct 29]. Available from: https://www.efpia.eu/media/25877/efpia-principles-for-off- patent-biologic-medicines-in-europe-30092015.pdf

119. Medicines for Europe – Biosimilar Medicines Group. Position on physician-led

switching and pharmacy substitution of biosimilar medicines [Internet]. 2015 Jul [accessed 2020 Oct 29]. Available from: https://www.medicinesforeurope.com/wp- content/uploads/2015/07/position-on-physician-led-switching-of-biosimilar-medicines.pdf

120. Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. Clin Pharmacol Ther. 2020;108(4):734–55. Doi:10.1002/cpt.1836

121. Kay J. A 'wind of change' to biosimilars: The NOR-SWITCH trial and its extension. J Intern Med. 2019;285(6):693–5. Doi:10.1111/joim.12896

122. Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. Clin Ther. 2002;24(11):1720–40. Doi:10.1016/S0149-2918(02)80075-3

123. Dörner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol. 2015;11(12):713–24. Doi:10.1038/nrrheum.2015.110

124. Meuser M, Nagel U. The expert interview and changes in knowledge production. In: Bogner A, Littig B, Menz W, editors. Interviewing Experts. Basingstoke: Palgrave McMillan; 2009. p. 17–42. Doi:10.1057/9780230244276_2

125. Van Audenhove L, Donders K. Talking to People III: Expert Interviews and Elite Interviews. In: Van den Bulck H, Puppis M, Donders K, Van Audenhove L, editors. The Palgrave Handbook of Methods for Media Policy Research. Cham: Palgrave Macmillan; 2019. p. 179–97. Doi:10.1007/978-3-030-16065-4_10

126. Pope C, Mays N. Qualitative Methods in Health Research. In: Pope C, Mays N, editors. Qualitative Research in Health Care. 4th ed. Hoboken: Wiley-Blackwell; 2020. p. 1–13. Doi:10.1002/9780470750841.ch1

127. Copenhagen Centre for Regulatory Science (CORS). About Regulatory Science [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://cors.ku.dk/about

128. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ. 1995;311(6996):42–5. Doi:10.1136/bmj.311.6996.42

129. Hoekman J, Boon WP, Bouvy JC, Ebbers HC, de Jong JP, De Bruin ML. Use of the conditional marketing authorization pathway for oncology medicines in Europe. Clin Pharmacol Ther. 2015;98(5):534–41. Doi:10.1002/cpt.174

130. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277–88. Doi:10.1177/1049732305276687

131. National Committee on Health Ethics. Act on research ethics review of health research projects [Internet]. 2018 Nov 13 [accessed 2020 Oct 29]. Available from: https://en.nvk.dk/rules-and- guidelines/act-on-research-ethics-review-of-health-research-projects

132. Rai AK, Sherkow JS. The changing life science patent landscape. Nat Biotechnol. 2016;34(3):292–4. Doi:10.1038/nbt.3504

133. Moorkens E, Vulto AG, Huys I. An overview of patents on therapeutic monoclonal antibodies in Europe: are they a hurdle to biosimilar market entry? mAbs. 2020;12(1):1743517. Doi:10.1080/19420862.2020.1743517

134. Webster CJ, Wong AC, Woollett GR. An efficient development paradigm for biosimilars. BioDrugs. 2019;33(6):603–11. Doi:10.1007/s40259-019-00371-4

135. Frapaise FX. The end of phase 3 clinical trials in biosimilars development? BioDrugs. 2018;32(4):319–24. Doi:10.1007/s40259-018-0287-0

136. Allocati E, Bertele' V, Gerardi C, Garattini S, Banzi R. Clinical evidence supporting the marketing authorization of biosimilars in Europe. Eur J Clin Pharmacol. 2020;76(4):557–66. Doi:10.1007/s00228-019-02805-y

137. European Medicines Agency. EMA regulatory science to 2025: strategic reflection. EMA/110706/2020 [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory- science-2025-strategic-reflection_en.pdf

138. Lee CWC, Kesselheim AS, Sarpatwari A. Clinical development times for biosimilars in the United States. Mayo Clin Proc. 2020;95(10):2152–4.

Doi:10.1016/j.mayocp.2020.06.039

139. Teeple A, Ellis LA, Huff L, Reynolds C, Ginsburg S, Howard L, et al. Physician attitudes about non- medical switching to biosimilars: results from an online physician survey in the United States. Curr Med Res Opin. 2019;35(4):611–7. Doi:10.1080/03007995.2019.1571296

140. O'Callaghan J, Bermingham M, Leonard M, Hallinan F, Morris JM, Moore U, et al. Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland. Regul Toxicol Pharmacol. 2017;88:252–61. Doi:10.1016/j.yrtph.2017.06.013

141. Heikkilä R, Mäntyselkä P, Hartikainen-Herranen K, Ahonen R. Customers' and physicians' opinions of and experiences with generic substitution during the first year in Finland. Health Policy. 2007;82(3):366–74. Doi:10.1016/j.healthpol.2006.10.006

142. Toverud EL, Hartmann K, Håkonsen H. A systematic review of physicians' and pharmacists' perspectives on generic drug use: what are the global challenges? Appl Health Econ Health Policy. 2015;13(Suppl 1):S35-45. Doi:10.1007/s40258-014-0145-2

143. Kesselheim AS, Gagne JJ, Eddings W, Franklin JM, Ross KM, Fulchino LA, et al. Prevalence and predictors of generic drug skepticism among physicians: results of a national survey. JAMA Intern Med. 2016;176(6):845–7. Doi:10.1001/jamainternmed.2016.1688

144. Dylst P, Vulto A, Simoens S. Demand-side policies to encourage the use of generic medicines: an overview. Expert Rev Pharmacoecon Outcomes Res. 2013;13(1):59–72. Doi:10.1586/erp.12.83

145. Olsson E, Svensberg K, Wallach-Kildemoes H, Carlsson E, Hällkvist C, Kaae S, et al. Swedish patients' trust in the bioequivalence of interchangeable generics: what factors are important for low trust? Pharm Prac. 2018;16(4):1298. Doi:10.18549/PharmPract.2018.04.1298

146. Weißenfeld J, Stock S, Lüngen M, Gerber A. The nocebo effect: a reason for patients' non- adherence to generic substitution? Pharmazie. 2010;65(7):451–6. Doi:10.1691/ph.2010.9749

147. Ebbers HC, Schellekens H. Are we ready to close the discussion on the interchangeability of biosimilars? Drug Discov Today. 2019;24(10):1963–7. Doi:10.1016/j.drudis.2019.06.016

148. Pouillon L, Socha M, Demore B, Thilly N, Abitbol V, Danese S, et al. The nocebo effect: a clinical challenge in the era of biosimilars. Expert Rev Clin Immunol. 2018;14(9):739–49. Doi:10.1080/1744666X.2018.1512406

149. Greene JA. When is a medicine good enough? science, similarity, and the history of generic drugs. Clin Pharmacol Ther. 2019;105(2):290–1. Doi:10.1002/cpt.1316

150. Diaz JI. How will COVID-19 impact biosimilar trends in the top 5 European markets? [Internet]. 2020 May 5 [accessed 2020 Oct 29]. Available from: https://www.biosimilardevelopment.com/doc/how-will-covid-impact-biosimilar-trends-in- the-top-european-markets-0001

151. Druedahl LC, Lebret A, Minssen T. ELSI Implications of Prioritizing Biological Therapies in Times of COVID-19. Journal of Law, Medicine & Ethics. 2020;48:579–82. Doi:10.1177/1073110520958884

152. Glintborg B, Ibsen R, Bilbo REQ, Lund Hetland M, Kjellberg J. Does a mandatory non-medical switch from originator to biosimilar etanercept lead to increase in healthcare use and costs? A Danish register-based study of patients with inflammatory arthritis. RMD Open. 2019;5(2):e001016. Doi:10.1136/rmdopen-2019-001016

153. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 5th ed. New York, NY: Oxford University Press, Inc; 2001.

154. Traulsen JM, Bissell P. (7) The risk society. Int J Pharm Prac. 2005;11(4):251–8. Doi:10.1211/0022357022638

155. IQVIA. The Prospects for Biosimilars of Orphan Drugs in Europe: Current landscape and challenges ahead [Internet]. 2020 Jul 21 [accessed 2020 Oct 29]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-prospects-for-biosimilars- of-orphan-drugs-in-europe.pdf?_=1602317947057

156. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA. 2011;305(22):2320–6.

Doi:10.1001/jama.2011.769

157. Buckley BM. Clinical trials of orphan medicines. Lancet. 2008;371(9629):2051–5. Doi:10.1016/S0140-6736(08)60876-4

158. Dowlat HA. The opportunities and challenges of biosimilar orphans. Expert Opin Orphan Drugs. 2016;4(6):563–6. Doi:10.1517/21678707.2016.1171142

159. Mestre-Ferrandiz J, Palaska C, Kelly T, Hutchings A, Parnaby A. An analysis of orphan medicine expenditure in Europe: Is it sustainable? Orphanet J Rare Dis. 2019;14(1):287. Doi:10.1186/s13023-019-1246-7

160. Bashaw ED, Huang SM, Coté TR, Pariser AR, Garnett CE, Burckart G, et al. Clinical pharmacology as a cornerstone of orphan drug development. Nat Rev Drug Discov. 2011;10(11):795–6. Doi:10.1038/nrd3595

161. Luzzatto L, Hyry HI, Schieppati A, Costa E, Simoens S, Schaefer F, et al. Outrageous prices of orphan drugs: a call for collaboration. Lancet. 2018;392(10149):791–4. Doi:10.1016/S0140- 6736(18)31069-9

162. Jasanoff S. Why Compare? In: Designs on nature: science and democracy in Europe and the United States. Princeton, NY: Princeton University Press; 2005. p. 13–41. Doi:10.1515/9781400837311

163. Borup M, Brown N, Konrad K, Van Lente H. The sociology of expectations in science and technology. Technol Anal Strategic Manag. 2006;18(3/4):285–98. Doi:10.1080/09537320600777002

164. Jasanoff S. Future imperfect: science, technology, and the imaginations of modernity. In: Jasanoff S, Kim S-H, editors. Dreamscapes of modernity: sociotechnical imaginaries and the fabrication of power. Chicago: University of Chicago Press; 2015. p. 1–33. Doi:10.7208/chicago/9780226276663.001.0001

165. Hilgartner S. Capturing the imaginary: vanguards, visions and the synthetic biology revolution. In: Hilgartner S, Miller C, Hagendijk R, editors. Science and democracy: making knowledge and making power in the biosciences and beyond. London: Routledge; 2015. p. 33–55. Doi:10.4324/9780203564370

166. Jasanoff S, Kim S-H. Imagined and Invented Worlds. In: Jasanoff S, Kim S-H, editors. Dreamscapes of modernity: sociotechnical imaginaries and the

fabrication of power. Chicago: University of Chicago Press; 2015. p. 321–41. Doi:10.7208/chicago/9780226276663.003.0015

167. Graf A, Sonnberger M. Responsibility, rationality, and acceptance: how future users of autonomous driving are constructed in stakeholders' sociotechnical imaginaries. Public Underst Sci. 2020;29(1):61–75. Doi:10.1177/0963662519885550

168. Tarkkala H, Helén I, Snell K. From health to wealth: the future of personalized medicine in the making. Futures. 2019;109:142–52. Doi:10.1016/j.futures.2018.06.004

169. Smith E. Corporate Imaginaries of Biotechnology and Global Governance: Syngenta, Golden Rice, and Corporate Social Responsibility. In: Jasanoff S, Kim S-H, editors. Dreamscapes of modernity: sociotechnical imaginaries and the fabrication of power. Chicago: University of Chicago Press; 2015. p. 254–76.

170. Blackstone EA, Fuhr JP. Generic biopharmaceutical drugs: an economic and policy analysis. Biotechnol healthc. 2007;4(1):43–8.

171. Herrera S. Biogenerics standoff. Nat Biotechnol. 2004;22(11):1343–6. Doi:10.1038/nbt1104- 1343

172. Pollock A. Places of pharmaceutical knowledge-making: global health, postcolonial science, and hope in South African drug discovery. Soc Stud Sci. 2014;44(6):848–73. Doi:10.1177/0306312714543285

173. IQVIA. The role of generic medicines in sustaining healthcare systems: a european perspective [Internet]. 2015 Jun [accessed 2020 Oct 29]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-role-of-generic-medicines-in-sustaining-healthcare-systems.pdf?la=en&hash=4C089164240AFAD4F3B4C65606693CC9

174. Kitto SC, Chesters J, Grbich C. Qualiy in qualitative research. Med J Aust. 2008;188(4):243–6. Doi:10.5694/j.1326-5377.2008.tb01595.x

175. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res. 2016;26(13):1753–60. Doi:10.1177/1049732315617444

176. DiCicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ. 2006;40:314–21. Doi:10.1111/j.1365-2929.2006.02418.x

177. Morgall JM, Almarsdóttir AB. No struggle, no strength: how pharmacists lost their monopoly. Soc Sci Med. 1999;48(9):1247–58. Doi:10.1016/S0277-9536(98)00424-9

178. Reeves S, Albert M, Kuper A, Hodges BD. Qualitative research: why use theories in qualitative research? BMJ. 2008;337:a949. Doi:10.1136/bmj.a949

179. Star SL. This is not a boundary object: Reflections on the origin of a concept. Sci Technol Human Values. 2010;35(5):601–17. Doi:10.1177/0162243910377624

180. Collins HM. Tacit knowledge, trust and the Q of sapphire. Soc Stud Sci. 2001;31(1):71–85. Doi:10.1177/030631201031001004

181. European Medicines Agency. Biosimilar medicines: marketing authorisation [Internet]. 2020 [accessed 2020 Oct 29]. Available from: https://www.ema.europa.eu/en/human- regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation

Appendix I – Study I – Interview Guide I

Interview guide – medicines authority regulators

- Interview introduction
- Introduction to the interviewer and the project; the context of the study (PhD project); objective of the study; the topics of the interview. Information about anonymity and confidentiality.
- Interviewer ask the interviewee to introduce their experience with biosimilars.
- Interviewer ask for permission to audio-record and for written informed consent. Asking if any questions before the interview.

INTERVIEW TOPIC 1. Establishing biosimilarity

- What aspects do you experience as challenging for companies regarding establishing biosimilarity? (e.g., quality, nonclinical, clinical, specific parts of these?)
    - Are these challenges similar for both recombinant protein products and other types of biological products? (e.g., derived from natural sources such as intestines, blood, etc.)
    - What aspect of establishing biosimilarity do you think is the most difficult?
- What aspects do you perceive as challenging for companies regarding the biosimilar manufacturing process development? (e.g., specific parts of upstream or downstream processes)
- When initiating biosimilar development, what do you think are the main pros and cons about choosing the same excipients as the originator product?
- Do you evaluate the manufacturing methods and their order when evaluating biosimilarity between the proposed biosimilar and originator products?
- For evaluating biosimilars:
    - Are the same clinical endpoints as the originator clinical trials needed for the clinical comparability exercise for biosimilars?
    - Do you prefer some analytical methods over others?

- Do you think the analytical methods need to be the same for the biosimilar application as for the full application of the reference product?

INTERVIEW TOPIC 2. Usefulness of limited disclosure to an aggregated analysis of the Quality by Design (QbD) space of the originator product.

The interviewer introduces the QbD topic, and questions follow:

- What manufacturing process parameters and their operational ranges for the originator process do you think would be useful for biosimilar developers? (parts of QbD space)
    - Which would be more helpful and why?
        - (for example, excipients variation ranges, specific process parameters ranges, critical quality attributes for the product, etc.)
    - Are there combinations of some parts that would be more useful than others?
- Are QbD usually a part of the market authorization application for originator biologics?
- Are QbD usually a part of the market authorization application for biosimilars?
- What are the regulatory advantages for a company to submit a QbD space as part of the product approval?
- If introducing a regulatory requirement for limited disclosure to part of the originator QbD space, how do you think this would affect the innovation incentives for new biologics?

INTERVIEW TOPIC 3. Comparing the EU and the US

- Why do you think that there is a difference in number of approved biosimilars comparing EU and US? Other than the difference in year of introduction?
- Do the regulatory differences for biosimilars between EU and US affect the biosimilar development?
    - If yes, what parts get affected?
    - If no, why not? Outro
- What do you think is the most important that we have talked about?
- Are there other relevant aspects that we have not talked about?
- Are there any potential “landmines”/controversial aspects I need to be aware of?

Thank you so much for your participation this has been of great help! If I at a later point have more questions, can I reach out to you for an additional interview?

Interview guide – pharmaceutical company representatives

- Interview introduction
- Introduction to the interviewer and the project; the context of the study (PhD project); objective of the study; the topics of the interview. Information about anonymity and confidentiality.
- Interviewer ask the interviewee to introduce their experience with biosimilars.
- Interviewer ask for permission to audio-record and for written informed consent. Asking if any questions before the interview.
- Start-questions for pharmaceutical company representatives:
- Does *company X* currently market biosimilars?
    - Is *product Z* a recombinant protein product or another type?
- Does *company X* have biosimilars in the pipeline or plan to have?
- Does *company X* market so-called originator-biologics?
- Would you say that *company X* is mostly an 'originator' or a 'biosimilar' company?

INTERVIEW TOPIC 1. Establishing biosimilarity

- What aspects did you experience as challenging regarding establishing biosimilarity for *product Z*? (e.g., quality, nonclinical, clinical, specific parts of these?)
    - Do you think these challenges are specific for recombinant protein products?
    - What was the most difficult?
- What aspects of the manufacturing process development for *product Z* were challenging? (e.g., specific parts of upstream or downstream processes)
- When initiating biosimilar development, what do you think are the main pros and cons about choosing the same excipients as the originator product?

INTERVIEW TOPIC 2. Usefulness of limited disclosure to an aggregated analysis of the Quality by Design (QbD) space of an approved biological.

The interviewer introduces the QbD topic, and questions follow:

- What manufacturing process parameters and their operational ranges for the originator process would have been of use for the process development for *product Z*? (e.g., parts of QbD space)
    - Which would be more helpful and why?
        - (for example, excipients variation ranges, specific process parameters ranges, critical quality attributes for the product, etc.)
    - Are there combinations of some parts that would be more useful than others?
- Would you be willing to limited disclose information about your QbD space if you achieved such information about the originator/biosimilar product process? (Knowledge eco-system)
- If introducing a regulatory requirement for limited disclosure to part of the originator QbD space, how do you think this would affect the innovation incentives for new biologics?

INTERVIEW TOPIC 3. Comparison between the EU and the US

- Have you for *product* Z applied different approaches to biosimilar development depending on which of the EU/US jurisdictions you aim to apply for marketing authorization in?
    - If yes, what parts get affected?
    - If no, why not?
- What do you think are the main consequences of the regulatory differences between the EU and the US?
- How would you explain the difference in numbers of biosimilars in the EU compared to the US besides from the difference in year of regulatory introduction?

Outro

- What do you think is the most important that we have talked about?
- Are there other relevant aspects that we have not talked about?
- Are there any potential “landmines”/controversial aspects I need to be aware of?

Thank you so much for your participation this has been of great help! If I at a later point have more questions, can I reach out to you for an additional interview?

Appendix II – Study II and III – Interview Guide II

Interview guide – medicines authority regulators

- Interview introduction
- Introduction to the interviewer and the project; the context of the study (PhD project); objective of the study; the topics of the interview. Information about anonymity and confidentiality.
- Interviewer ask the interviewee to introduce their experience with biosimilars.
- Interviewer ask for permission to tape-record and for written informed consent. Asking if any questions before the interview.

INTERVIEW TOPIC 1. The incentives for the EU regulation of biosimilars:

- What do you think are the 3 main incentives for the introduction of the regulation of biosimilars in the EU?
    - Do you think one was more important than the others?
- Wherefrom did the initiative for the legislation for introducing biosimilars come?
- Do you think the current structure of this regulation fulfils these incentives?
- Do you think the current structure of the regulation of biosimilars is adequate?
- How do you think that the step-wise approach is functioning in practice?

INTERVIEW TOPIC 2. Innovation

- Do you think that the biosimilar regulation has influenced the incentive for innovation in new biologics? Why/Why not?
- What is the incentive for companies to develop their first biosimilar?
- What is the incentive for companies to develop their second or following biosimilar?
- Do you consider biosimilars (developing new process and new product) to be re-producing the science made in the invention of the originator product or to be 'new science'?
    - Is it new knowledge if a company builds a new factory to make the same product?

- How do you see your organization to play a part in transmission of "know-how" knowledge?

INTERVIEW TOPIC 3. Competition in the EU

- How do you think that the competition in the biologics market is after introducing biosimilars?
  - What would you like to change about it if you could?
  - How do you think it could be changed?
- Do you think that public health has benefitted from biosimilars? If so, why?

INTERVIEW TOPIC 4. Comparability exercise vs. establishing biosimilarity

- Do you see a scientific difference between the comparability exercise in relation to manufacturing changes compared to establishing biosimilarity for a proposed biosimilar?
- Do you think that there are differences between requirements for establishing biosimilarity and approving manufacturing changes?
- Do you think that the two types of procedures are handled similarly by medicines agencies?
  - Is that handling adequate according to you?

INTERVIEW TOPIC 5. Interchangeability of biosimilars

- How do you see interchangeability of biosimilars in the EU?
- How do you see interchangeability of biosimilars in the US?
- Do you think that there is a scientific difference in interchangeability between EU and US?
- How do you think that the interchangeability designation should be?

INTERVIEW TOPIC 6. Comparison to the US

- What do you think are the incentives of the biosimilar regulation in the US?
- How do you think the current structure of this regulation fulfils this incentive?

Interview outro

- Do you see upcoming technological evolution/trends that would allow biosimilars to be identical to the originator biological?
- Are there other consequences of the introduction of the biosimilar regulation that you find important and that we have not talked about?
- What do you think is the most important that we have talked about?
- Are there other relevant aspects that we have not talked about?
- Are there any potential "landmines"/controversial aspects I need to be aware of?

Thank you so much for your participation this has been of great help! If I at a later point have more questions, can I reach out to you for an additional interview?

Interview guide – pharmaceutical company representatives

- Interview introduction
- Introduction to the interviewer and the project; the context of the study (PhD project); objective of the study; the topics of the interview. Information about anonymity and confidentiality.
- Interviewer ask the interviewee to introduce their experience with biosimilars
- Interviewer ask for permission to tape-record and for written informed consent. Asking if any questions before the interview.
- If the interviewee is from a company, the following interview-start will be used:
- Does company X currently market biosimilars?
- Does company X have biosimilars in the pipeline or plan to have?
- Does company X market so-called innovator-biologics?
- Would you mostly say that company X is an 'originator' or a 'biosimilar' company?
    - Does company X have other business units that are also producing biosimilars?

INTERVIEW TOPIC 1. The incentives for the EU biosimilar regulation:

- What do you think are the 3 main incentives for the introduction of the biosimilar regulation in EU?
    - Do you think one was more important than the others?

- Wherefrom did the initiative for the legislation for introducing biosimilars come?
- Do you think the current structure of this regulation fulfils these incentives?
- Do you think the current structure of the biosimilar regulation is adequate?
- Companies with marketed biosimilars specific questions:
- Have you undertaken a step-wise biosimilar development?
    - Is this the general picture?
- Did your view on the biosimilar approval pathway change after the decision on the biosimilar approval of *Product Z*, and if so how?
- On basis of your experience with biosimilars, has company X had a change in incentive for continuing to develop biosimilars? If so, what caused this change?
- Having the experience with successful biosimilar development and manufacturing, do you feel more or less incentivized to try developing a second? Why/Why not?
- Companies only with marketed originator products specific questions:
- Do the biosimilar regulation make company X consider developing biosimilars, why/why not?

INTERVIEW TOPIC 2. Innovation

- Do you think that the biosimilar regulation has influenced the incentive for innovation in new biologics? Why/Why not?
- How is the incentive for companies to develop their first biosimilar?
- How is the incentive for companies to develop their second or following biosimilar?
- Do you consider biosimilars (developing new process and new product) to be re-producing the science made in the invention of the originator product or to be 'new science'?
    - Is it new knowledge if a company builds a new factory to make the same product?
    - How do you see your organization to play a part in transmission of "know-how" knowledge?
- Companies only with marketed originator products specific questions:

- Have you considered to change your innovation focus from traditional biologic development to using new emerging technologies to avoid biosimilars being developed for your product?

INTERVIEW TOPIC 3. Competition in the EU

- How do you think that the competition in the biologics market is after introducing biosimilars?
    - What would you like to change about it if you could?
    - How do you think it could be changed?
- Do you think that public health has benefitted from biosimilars? If so, why?

INTERVIEW TOPIC 4. Comparability exercise vs. establishing biosimilarity

- Do you see a scientific difference between the comparability exercise in relation to manufacturing changes compared to establishing biosimilarity for a proposed biosimilar?
- Do you think that there is alignment between requirements for establishing biosimilarity and approving manufacturing changes?
- Do you think that the two types of procedures are handled similarly by medicines agencies?
    - Is that handling adequate according to you?

INTERVIEW TOPIC 5. Interchangeability of biosimilars

- How do you see interchangeability of biosimilars in the EU?
- How do you see interchangeability of biosimilars in the US?
- Do you think that there is a scientific difference in interchangeability between EU and US?
- How do you think that the interchangeability designation should be?

INTERVIEW TOPIC 6. Comparison to the US

- What do you think are the incentives of the biosimilar regulation in the US?
- How do you think the current structure of this regulation fulfils this incentive?
- Companies with marketed biosimilars specific questions:

- Did you experience differences in the step-wise approach for approval in the two jurisdictions?
- Have you received scientific advice from both EMA and FDA during development, where these identical?
    - If not, how did they differ?

Interview outro

- Do you see upcoming technological evolution/trends that would allow biosimilars to be identical to the originator biological?
- Are there other consequences of the introduction of the biosimilar regulation that you find important and that we have not talked about?
- What do you think is the most important that we have talked about?
- Are there other relevant aspects that we have not talked about?
- Are there any potential "landmines"/controversial aspects I need to be aware of?

Thank you so much for your participation this has been of great help! If I at a later point have more questions, can I reach out to you for an additional interview?

Appendix III – Study II and III – Interview Guide III

Interview guide

- Interview introduction
- Introduction to the interviewer and the project; the context of the study (PhD project); objective of the study; the topics of the interview. Information about anonymity and confidentiality.
- Interviewer ask the interviewee to introduce their experience with biosimilars
- Interviewer ask for permission to tape-record and for written informed consent. Asking if any questions before the interview.
- If the interviewee is from a company, the following interview-start will be used:
- Does company X currently market biosimilars?
- Does company X have biosimilars in the pipeline or plan to have?
- Does company X market so-called originator-biologics?
- Would you say that company X is mostly an 'originator' or a 'biosimilar' company?

INTERVIEW TOPIC 1. Exploring legal/regulatory challenges with biosimilar regulation

- What do you think is the main legal/regulatory challenge with biosimilar regulation?
    - What do you think are the main challenges pre-MA? (during research and IPR prosecution stage)
    - What do you think are the main challenges during MA procedure?
    - What do you think are the main challenges post-MA? (e.g., Post IP grant and post MA challenges such a marketing, competition, pharmacovigilance and reimbursement, parallel trade, IP litigation in courts etc.)
- Do you think that there are parts of the regulatory system regarding biosimilars that are unclear?
    - Is a lack of clarity sometimes preferable- and if so for what reasons?
- What part of the biosimilar regulation (/legislation) do you think should be improved?

    - How do you think it should be instead?
- Have you observed differences in the case law for biologics compared to for small molecule drugs?
- Regulator specific questions:
- When do you know it is time for a new guideline/product specific guideline?
- Bridging studies:
    - What do you think of the usefulness of these as they are?
    - What would you like the future to bring for these?
- Do you think that there are the necessary legislative tools for assessing proposed biosimilars?
- Is it possible to develop a synthetic peptide that mimics a biological product and thus with a biological product as a reference product?
- Companies with an originator biologic product specific questions:
- What is the consequence of the current market exclusivity rights gained for developing further indications for biologics compared to the incentive to develop new biologics?

INTERVIEW TOPIC 2. Switching (comparing EU and US)

- How do you see the requirement for switching studies in the US?
- What influence has the difference in demand of switching studies between US and EU?

INTERVIEW TOPIC 3. Miscellaneous

- Do you think sufficient incentives are in place for promoting and encouraging the development of so- called biobetters?
- What do you think is the balance for price reduction for biosimilars vs. the incentive to develop them? (If too low cost, it will be difficult to earn enough to profit from the investment)
- Do you think it might be a good idea to consider new incentives not only on the “offering side” but also on the “demand side”?
- Are the guidelines a praxis or can one divert from the guideline and still expect to be granted a biosimilar marketing authorization?

INTERVIEW TOPIC 4. Litigation (only for companies)

- Companies with a marketed biosimilars **or** an originator biologic product specific questions:
- When is the process deemed too close to or too far away from the originator product?
- Which product-related factors are regarded most important in this delineation?
- What are your concerns regarding IPR and trade secrets for the reference product? And the biosimilar?
- Considering biosimilars not being identical to the originator product, how do you see the risk of product patent litigation?

INTERVIEW TOPIC 5. Decision making for drug candidate as biosimilar or new product (only for companies)

- Companies with a marketed biosimilar specific questions:
- Have you previously considered applying for other market authorization pathways for your biosimilar?
    - What regulatory pathway(s) did you consider otherwise?
    - When did you consider this? (Companies with an originator biologic product specific questions:
- Have you had a product approved as a new product that you initially intended as a biosimilar?

Outro

- Which do you consider the key legal and regulatory challenges?
- What do you think is the most important that we have talked about?
- Are there other relevant aspects that we have not talked about?
- Are there any potential “landmines”/controversial aspects I need to be aware of?

Thank you so much for your participation this has been of great help! If I at a later point have more questions, can I reach out to you for an additional interview?