



SUSTAINABLE BIOSIMILAR COMPETITION

Liese
Barbier

clinical,
regulatory and
policy insights

Colophon

The research presented in this thesis was performed at the Unit of Clinical Pharmacology and Pharmacotherapy of the Department of Pharmaceutical and Pharmacological Sciences, Faculty of Pharmaceutical Sciences, KU Leuven, Leuven, Belgium as part of the research of the Market Analysis of Biologicals including Biosimilars After Loss of Exclusivity (MABEL) Fund, a collaboration between KU Leuven and Erasmus MC Rotterdam.

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Cover design: Elise Buntinx – *Reflections*

The image explores the multidisciplinary reflections of the various stakeholders in the drug lifecycle and those generated through this PhD research from different angles. This is set against the backdrop of the literally and figuratively changing landscape of off-patent biologicals and biosimilars as embodied by reflections of (bio)similar copies.

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Jury:

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Liese

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LIST OF ABBREVIATIONS

ADA(s)	Anti-drug antibody(-ies)
ADR	Adverse drug reactions
AE	Adverse event
Anti-TNF	Anti-tumor necrosis factor
AUC	Area under the curve
BAFO	Best and final offer
BWP	Biologics Working Party
BMWP	Biosimilar Medicinal Products Working Party
BPCI	Biologics Price Competition and Innovation
bpCR	Breast pathological complete response
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CQA	Critical quality attribute
CRM	Commission for Reimbursement of Medicinal Products
DMARDs	Disease modifying anti rheumatic drugs
EAHP	European Association of Hospital Pharmacists
EBC	Early breast cancer
EC	European Commission
ECCO	European Crohn's and Colitis Organisation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European public assessment report
ESNO	European Specialist Nurses Organisations
EU	European Union
FAMHP	Federal Agency of Medicines and Health Products
FDA	US Food and Drug Administration
FIMEA	Finnish Medicines Agency
FSH	Follicle-stimulating hormone
G-BA	German Statutory Health Insurance
G-CSF	Granulocyte colony-stimulating factor
GPP	Green public procurement
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung
HCP	Healthcare professional
HER2	Human epidermal growth factor receptor 2
HMA	Heads of Medicines Agencies
HSE	Health Service Executive
HV	Healthy volunteer
IBD	Inflammatory bowel disease
IMCRA	International Coalition of Medicines Regulatory Authorities
INN	International non-proprietary name
IV	Intravenous
LMWH	Low molecular weight heparin
LoA	Level of agreement
LOE	Loss of efficacy
LOE	Loss of exclusivity
LVEF	Left ventricular ejection fraction

LIST OF ABBREVIATIONS

LVSD	Left ventricular systolic dysfunction
mAb(s)	Monoclonal antibody/-ies
MA	Marketing authorization
MAA	Marketing authorization application
MBC	Metastatic breast cancer
MCDA	Multi-criteria decision analysis
MEA	Managed entry agreement
MEAT	Economically most advantageous tender
MEB	Dutch Medicines Evaluation Board
MNP	Medical need programs
N	Number
NA	Not applicable
NCA	National Competent Authority
NGT	Nominal group technique
NHS	National Health Service
NI	Non-inferiority
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
NPA	Not publicly available
NR	Not reported
NVZA	Dutch Association of Hospital Pharmacists
ORR	Overall response rate
OS	Overall survival
pCR	Pathological complete response
PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PFP	Pre-filled pens
PFS	Progression free survival
PFS	Pre-filled syringe
PK	Pharmacokinetic
P&R	Pricing & reimbursement
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	Patient support programs
RD	Risk difference
RR	Risk ratio
ROW	Rest of the world
RP	Reference product
RWE	Real world evidence
SAE	Serious adverse event
SC	Subcutaneous
SOJA	System of objectified judgement analysis
TEAE	Treatment emergent serious adverse event
TL	Trough levels
TNF- α	Tumor necrosis factor alpha
tpCR	Total pathological complete response
US	United States of America
VAS	Value-added services

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PART 1
GENERAL INTRODUCTION &
OBJECTIVES

1. NEED FOR AFFORDABLE AND SUSTAINABLE ACCESS TO MEDICINES

Access to safe, effective and affordable medicines is a fundamental pillar of healthcare in our society (1). However, the advent of innovative, yet often high-cost medicines and the growing prevalence of chronic diseases associated with ageing demographics are – among other factors – weighing on healthcare budgets and are making it increasingly challenging to ensure sustainable patient access to these new treatment options (1),(2),(3). This trend is expected to persist, with global pharmaceutical expenditure projected to continue to grow by 3-6% per annum to reach around USD 1.6 trillion by 2025 (4).

An important part of this expenditure growth is coming from biological medicines. Biological medicines, also called biologicals, are molecules produced by or extracted from a biological source such as living cells or organisms and often exert a highly specific set of functions in the body (5),(6),(7). Compared to traditional, small molecules, which are produced through chemical synthesis, biologicals are larger and more complex. The size and structural complexity of biologicals however varies, ranging from relatively simple proteins such as insulin to more complex structures such as monoclonal antibodies (mAbs) (6).

Although biological medicines have shaped and will continue to shape the treatment paradigm of a wide range of complex, chronic and life-threatening diseases including diabetes, autoimmune diseases and cancers, they often have a high price tag (8). Today, biologicals already represent almost one third of the total global pharmaceutical expenditure, and are growing at around double the pace of the overall market, reaching USD 452 billion in 2022 from USD 277 billion in 2017 (4),(9),(10). In Europe, biologicals play an even bigger role, accounting for EUR 90 billion or around 40% of total pharmaceutical expenditure in 2020 (9),(11).

Following their success and high price, biologicals are putting substantial pressure on restricted national healthcare budgets. This budgetary pressure challenges the sustainability of healthcare systems and may limit access to biologicals or other important treatments for patients, especially so in countries with more limited resources (12),(13).

2. THE ARRIVAL OF BIOSIMILAR MEDICINES

Following the expiry of patents and other exclusivity rights on original biological medicines, the market opens up for alternative versions, so-called biosimilar medicines or biosimilars. As defined by the European medicines Agency (EMA), a biosimilar is “*a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established*” (14). Biosimilars offer a key opportunity to introduce competition in the biological medicines market, lowering treatment costs and improving access to these important therapies, providing as such benefits for healthcare budgets and patients (8).

2.1 THE EUROPEAN REGULATORY FRAMEWORK FOR BIOSIMILARS

The European Union (EU) has pioneered biosimilar regulation with the introduction of the first legal and regulatory pathway for biosimilar evaluation and approval in 2004 and the first biosimilar approval in 2006 (6),(15). In 2005, the EMA issued its overarching “*Guideline on similar biological medicinal products*” providing regulatory guidance on data requirements for biosimilar development and licensing. In 2006, this was accompanied by the publication of two other overarching biosimilar guidelines “*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues*” and “*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*” (14),(16),(17),(18). Over the years, more biosimilar guidelines, including product-specific ones, have been published. In addition, revisions have been made to existing guidelines, reflecting the evolving regulatory knowledge based on the accumulated experience with biosimilar evaluation and use and analytical and scientific progress over the past 15 years (6),(18),(19). Figure 1 depicts a schematic overview of important milestones in the European biosimilar regulatory landscape.

The 2004 amended Directive 2001/83/EC provides the legal basis for the licensing of biosimilars (15). Given they mostly use biotechnology for their production¹, biosimilars are generally assessed under the centralised authorisation procedure (i.e. via the EMA), which is an EU-wide procedure involving a single marketing authorisation application, a single evaluation and a single authorisation for use in all EU Member States and EEA countries (6). It is the EMA’s Committee for Medicinal Products for Human Use (CHMP) that carries out a scientific assessment of the marketing authorisation application. This assessment is led by two appointed rapporteurs (rapporteur and co-rapporteur) and their team of assessors. Also, multi-disciplinary EU experts (e.g. members of the Biologics Working Party (BWP), members of the Biosimilar Medicinal Products Working Party (BMWP)) and other EMA scientific committees (e.g. Pharmacovigilance Risk Assessment Committee (PRAC) for the product’s safety assessment) are involved throughout the assessment. At the end of the evaluation, a recommendation (positive or negative opinion) is provided by the CHMP. Subsequently, the European Commission (EC) takes a legally binding decision based on the EMA’s recommendation (20). The evaluation of a biosimilar follows the same time schedule as the evaluation of a medicine with a new active substance, i.e. 210 days of active evaluation time (21).

¹ The centralised procedure of marketing authorization is mandatory for certain medicines, such as medicines containing a new active substance to treat diseases such as cancer and auto-immune disorders, and medicines that are developed by means of biotechnology (6),(500). Biosimilars of low-molecular weight heparins that are purified from their native source (porcine intestinal mucosa) fall outside of the mandatory scope and as such national approval may be sought (6),(44).

2.2 BIOSIMILARS: A NEW DEVELOPMENT AND EVALUATION PARADIGM

Whereas for a medicine with a new active substance, *de novo* safety and efficacy needs to be shown, biosimilar development aims to convincingly demonstrate biosimilarity, i.e. a high level of similarity in terms of structure, biological activity and efficacy, safety and immunogenicity compared to its original biological medicine (the so-called reference product) (14),(22).

Because of the intrinsic minor variability of biological medicines, and their complex manufacturing process, minor structural differences may exist between the biosimilar and its reference product (5), (6). This natural variability (also called ‘microheterogeneity’) is inherent to all biological medicines, and is also present between different batches of the same biological product (6),(23),(24). The applicant needs to demonstrate that these structural differences between the biosimilar and its reference product are not clinically meaningful, i.e. do not have an effect on the product’s safety and efficacy (14).

By demonstrating high similarity, biosimilars can rely on the knowledge and experience gained with the reference product. Consequently, the data requirements for approval of a biosimilar are different from those for the reference product, and are scientifically tailored to meet the aim of demonstrating biosimilarity (24).

Biosimilarity demonstration is based on a comprehensive comparability exercise which consists of a series of comparative head-to-head studies between the biosimilar and its reference product (14),(19). The comparability exercise is conceived as a step-wise process in which the knowledge and evidence gathered from the first step (consisting of comparative quality studies), together with the nature and complexity of the reference product, informs the extent and type of non-clinical and clinical studies required in the next step of development (14),(17).

The scientific concept of the comparability exercise is a well-established scientific principle of regulatory science which is routinely applied for evaluating the impact of changes to the manufacturing process of a biological medicine (6),(14),(23),(24). Biological medicines typically undergo several changes to their manufacturing process during their commercial life cycle, e.g. to improve the process or increase product scale (6),(23),(25). These require comparability studies between batches pre and post manufacturing change to ensure consistent quality, safety, and efficacy. While the extent of the comparability studies required following a manufacturing change depends on the type of change and its expected impact, analytical and functional comparability testing is generally considered sufficient (6),(19). For biosimilars however, a more extensive comparability exercise including clinical testing is usually required (19),(24).

The foundation of biosimilarity demonstration is the extensive physicochemical and functional characterization of the biosimilar compared to the reference product. Once a high level of physicochemical and functional similarity has been established, the nature and extent of non-clinical and clinical studies is determined. This in order to further establish biosimilarity and evaluate the clinical relevance of minor structural differences that may have been observed between the

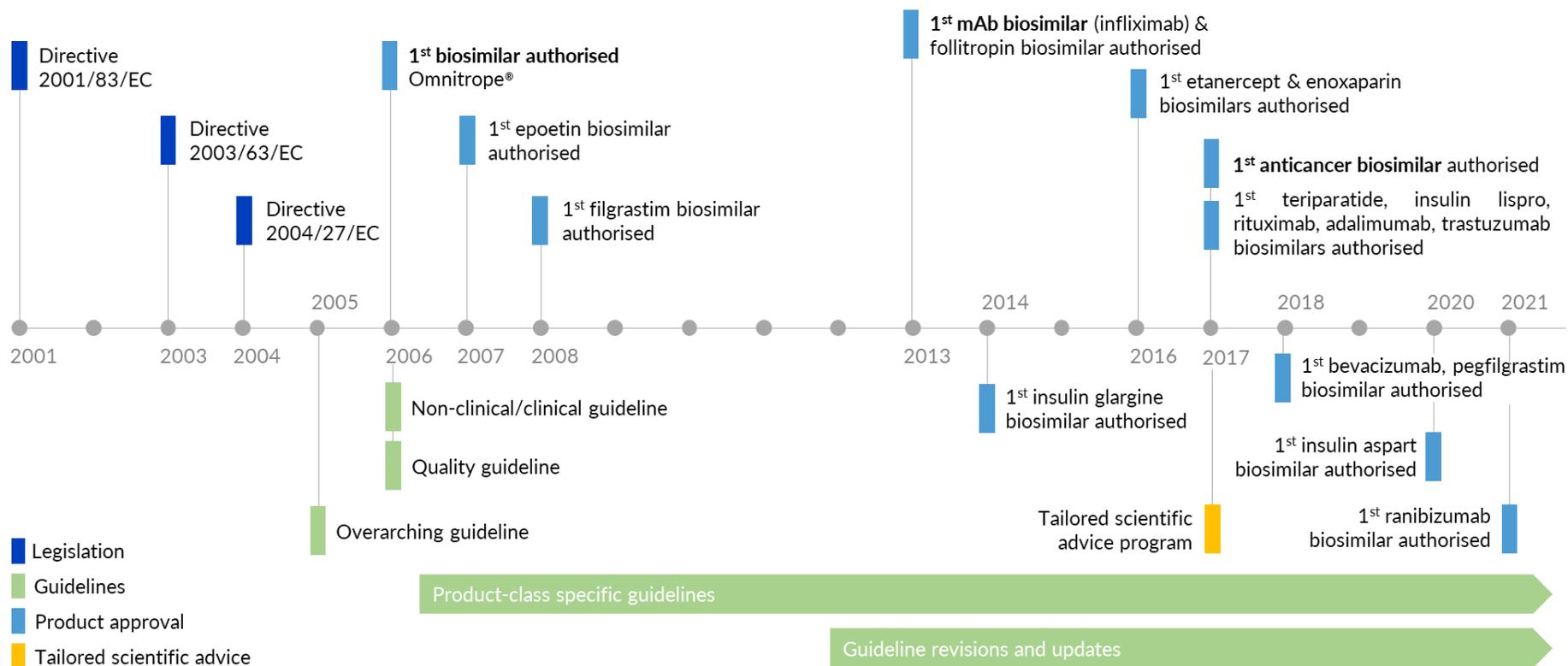
biosimilar and the reference product (14). First, relevant non-clinical studies should be performed, which may include comparative *in vitro* and *in vivo* studies. The latter are not conducted by default and should be obviated when the evidence from preceding steps allows for this (17),(26). The subsequent clinical development package generally consists of a PK/PD study and a comparative efficacy and safety clinical trial in an approved indication of the reference product (17). In cases where a suitable PD endpoint and clear mechanism of action is available, a PK/PD study may be sufficient to demonstrate clinical comparability (17). When this is not the case and for complex and multifunctional biologicals such as mAbs, a randomised, parallel group comparative efficacy and safety clinical trial is generally considered necessary (5),(17),(19).

With the accumulated experience with biosimilar evaluation and the analytical and scientific progress made over the past years, a further tailoring of clinical data for biosimilars may be considered by EU regulators (19). Since 2017, the EMA offers the possibility for applicants to seek tailored scientific advice on the proposed development strategy for their biosimilar candidate with the aim to further assist them with the step-wise development (26).

Ultimately, regulators evaluate a biosimilar marketing authorization application by examining the total body of evidence for biosimilarity. This is also called the totality of evidence approach. When a biosimilar has demonstrated to be highly similar to its reference product, extrapolation of safety and efficacy data to other indications for which the reference product is approved may be considered based on the total body of evidence for biosimilarity (14),(17),(27). The scientific principle of extrapolation of indication allows to avoid the unnecessary repetition of costly clinical studies, in turn contributing to the lower development cost of biosimilars. Importantly, extrapolation is not granted by default, but requires a sound scientific justification and is a matter of case-by-case assessment (24),(27).

FIGURE 1. SCHEMATIC OVERVIEW OF THE EVOLUTION OF THE BIOSIMILAR REGULATORY LANDSCAPE IN EUROPE.

Figure adapted from Hidalgo-Simon, A (2021) *Translating experience into regulation: view from the European Medicines Agency* (276)



2.3 BIOSIMILAR APPROVALS IN THE EU

To date (July 2021), 70 biosimilars covering 17 distinct reference biologicals have a valid marketing authorization for use in Europe or a positive CHMP opinion pending EC decision (28). This number includes duplicate marketing authorizations since in certain cases (e.g. for co-marketing reasons) a company may apply for more than one marketing authorisation for the same medicinal product (19),(29). Biosimilars are available across different therapeutic areas, including haematology, auto-immune diseases, endocrinology and oncology. The very first biosimilar approval was of a growth hormone, somatropin (Omnitrope®) in 2006. The early approved biosimilars ('first wave') consisted mainly of products that replace a protein that is deficient in the body (e.g. such as growth hormone) or enhance an existing pathway (e.g. growth factors epoetin or filgrastim). In 2013, the first mAb biosimilar (infliximab Remsima®/Inflectra®) was approved, soon followed by more approvals of biosimilars targeting tumor necrosis factor alpha (TNF- α) (e.g. etanercept and adalimumab). A third wave of biosimilar approvals, starting in 2017, included the first mAb biosimilars used in haematology and oncology (e.g. trastuzumab, rituximab, bevacizumab) (30),(31). At present, more than 30 biosimilar mAbs have been approved for use in the EU market. An overview of all EU-approved biosimilars is provided in Table 1. It is important to note that approval does not necessarily equate to product availability on a national level. Differences in availability of the approved biosimilars may be present between EU markets (32) as it is up to the marketing authorization holder to organize the product launches in the different countries.

The number of approved biosimilars is expected to continue to grow in the near future, with currently 12 biosimilar candidates under evaluation by the CHMP (33). Moreover, there is a large long term opportunity for biosimilar development and market entry, given another major wave of expiries of exclusivities is forecasted over the next ten years (9),(34).

TABLE 1. OVERVIEW OF EU-APPROVED BIOSIMILARS

Valid marketing authorization or pending EC decision, in chronological order of first biosimilar approval (July 2021) (28)

	Molecule	Reference product	Date of first biosimilar approval	N approved biosimilars	Brand names°
1	Somatropin	Genotropin®	12/04/2006	1	Omnitrope®
2	Epoetin	Eprex®	27/08/2007	5	Abseamed®/Binocrit®/Epoetin Alfa Hexal®, Retacrit®, Silapo®
3	Filgrastim	Neupogen®	15/09/2008	7	Accofil®/Grastofil®, Filgrastim Hexal®/Zarzio®, Nivestim®, Ratiograstim®/Tevagrastim®
4	Infliximab	Remicade®	10/09/2013	4	Flixabi®, Inflectra®/Remsima®, Zessly®
5	Follitropin alfa	Gonal-f®	27/09/2013	2	Bemfola®, Ovaleap®
6	Insulin glargine	Lantus®	09/09/2014	2	Abasaglar®, Semglee®
7	Etanercept	Enbrel®	13/01/2016	3	Benepali®, Erelzi®, Nepexto®
8	Enoxaparine	Clexane®	15/09/2016	1	Inhixa®
9	Teriparatide	Forsteo®	04/01/2017	3	Livogiva®, Movymia®, Terrosa®
10	Rituximab	Mabthera® IV	17/02/2017	6	Blitzima®/Ritemvia®, Rixathon®/Riximyo®, Ruxience®, Truxima®
11	Adalimumab	Humira®	21/03/2017	9	Amgevita®, Amsparity®, Halimatoz®/Hefiya®/Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflyma®
12	Insulin lispro	Humalog®	18/07/2017	1	Insulin lispro Sanofi®
13	Trastuzumab	Herceptin® IV	15/11/2017	6	Herzuma®, Kanjinti®, Ogivri®, Ontruzant®, Trazimera®, Zercepac®
14	Bevacizumab	Avastin®	15/01/2018	9	Abevmy®+, Alymsys®, Aybintio®, Equidacent®, Lextemy®+, Mvasi®, Onbevzi®, Oyavas®, Zirabev®
15	Pegfilgrastim	Neulasta®	21/09/2018	8	Cegfila®/Pelmeg®, Fulphila®, Grasustek®, Nyvepria®, Pelgraz®, Udenyca®, Ziextenzo®
16	Insulin aspart	Novo Rapid®	25/06/2020	2	Insulin aspart Sanofi®, Kixelle®
17	Ranibizumab	Lucentis®	24/06/2021*	1	Byooviz®+

*Date of positive opinion, EC decision pending, + Received positive opinion (marketing authorization is expected), °Duplicate marketing authorisations separated by "/". Duplicate authorisations can exist for the same medicinal product and are often used to circumvent patent issues related to indications or for co-marketing reasons. INN: international non-proprietary name, IV: intravenous

2.4 BIOSIMILAR MARKET ENTRY

Once a biosimilar has received a centralised marketing authorization, decisions regarding pricing, reimbursement, and procurement as well as measures to steer its use are coordinated by the individual Member States in the context of their respective healthcare system.

The organization of healthcare systems varies greatly between European countries, and different approaches have been pursued in terms of developing and implementing policy measures related to the use of off-patent biologicals and biosimilars. This has translated in a variable use of biosimilars between and even within European countries (32),(35),(36),(37),(38). In addition, biosimilar use differs between active substances for which one or more biosimilars are available. Biosimilars are available for a heterogeneous group of active substances in a wide range of therapeutic areas, hence important differences exist in terms of the product's treatment setting (*acute versus chronic treatment*), dispensing context (*hospital versus ambulatory setting*), the product's administration (*intravenous versus subcutaneous*), the existence and availability of competing products (e.g. second-generation biologicals) and the deployed competition strategies which may explain for this variation in use. An empirical case in point of the important level of heterogeneity across EU markets is that no country has attained a high biosimilar market share across all available products, and similarly there is no particular biological for which biosimilar market shares are high across all European countries (39).

2.5 THE BIOSIMILAR VALUE PROPOSITION

Biosimilar medicines present an important opportunity to improve the affordability of biological treatment, by providing lower priced treatment options and stimulating wider price competition, while safeguarding safe and effective treatment.

Price decreases and subsequent savings from biosimilar competition can broadly be realized on two levels. Firstly, biosimilar market entry generally has a visible impact on list price. Biosimilars are often introduced in the market at a lower list price compared to that of the reference product. Additionally, biosimilar introduction may trigger mandatory price cuts, resulting in reduced list prices of the reference product (38). Secondly, savings are often realized through confidential discounts from competitive bidding in tenders (see section 3.2 for more information about tenders) (11),(39). On a list price level, biosimilar competition was reported to have reduced overall drug budgets by around 5% since 2014 (list prices have reportedly reduced on average by about one-third). The confidential savings, which may vary between 10-90% of the list price, were estimated to offer an additional 5-10% saving to the overall drug budget (11).

Cumulatively, savings as a result of biosimilar market introduction were projected to exceed EUR 50 billion in aggregate between 2016 and 2021, and reach as much as EUR 100 billion in the EU5 (France, Germany, Italy, Spain, UK) and the USA alone (8). These savings in turn may free up resources for the reimbursement of new innovative treatment options or translate in increased patient access to formerly expensive biological therapies, both in terms of earlier initiation of

biological treatment in the patient's disease pathway or access for a larger group of patients (8),(39),(40). Especially in countries with low access to biologicals due to limited healthcare resources, the latter may be a main benefit of biosimilars (39),(40). Examples of how biosimilar competition has shown to broaden patient access to biological medicines are presented in BOX 1. Finally, biosimilar competition arguably stimulates innovation. As their entry disrupts the market exclusivity based revenue model of the originator, developers of these originators are compelled to continue to invest in R&D to recover lost revenue streams (41).

BOX 1 | EXAMPLES OF BIOSIMILAR COMPETITION BROADENING PATIENT ACCESS TO BIOLOGICAL TREATMENT

Enabling access to biological treatment at an earlier disease stage: Biosimilar competition lowers the price of biologicals, altering as such the cost-effectiveness of biological treatment (8). A few concrete examples in which biosimilar introduction has resulted in updated treatment guidelines are given below:

- In response to infliximab, adalimumab, etanercept (anti-tumor necrosis factor (anti-TNF) biologicals) biosimilars becoming available, the National Institute for Health and Care Excellence (NICE) in England reviewed its treatment guidance, recommending to expand biological treatment access to patients with rheumatoid arthritis. Whereas biological treatment was previously only recommended for patients with severe rheumatoid arthritis, patients diagnosed with moderate rheumatoid arthritis who have not responded to conventional therapies will now also be eligible for treatment with biologicals (501).
- In Sweden, the launch of biosimilar filgrastim (a granulocyte colony-stimulating factor (G-CSF) used *inter alia* to reduce the duration of neutropenia and occurrence of febrile neutropenia) led to a relaxation of prescribing restrictions. While the agreement of three physicians was previously required to commence filgrastim treatment, the decision can now be made by the individual physician. As a result, the uptake of G-CSF was reported to have increased five-fold (8).
- Following the introduction of trastuzumab biosimilars, together with a commercial discount on the price of pertuzumab, NICE recommended pertuzumab in combination with biosimilar trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive early breast cancer patients (502),(485).

Giving wider access to biological treatment: In markets with low starting volumes of biological use, there is generally a significant increase in use upon biosimilar entry. In some cases, even countries which already had a high biologicals usage prior to biosimilar entry still show a consumption increase (39).

3. MAIN CHALLENGES AND RATIONALE FOR THIS PHD PROJECT

Although biosimilars bring instrumental benefits to healthcare systems and patients in terms of relieving healthcare budgets and increasing access to medicines, their adoption and implementation appears faced with several challenges. In fact, the slow and variable biosimilar uptake between countries, and even within countries and product classes suggests that countries and stakeholders are currently not geared up to capture the full potential from biosimilar competition (8).

Over the 2015 to 2020 period, a number of the best-selling originator biologics lost exclusivity, including the highest selling product in the world (Humira®, adalimumab) and a number of other high-value² mAbs. In the EU5 and US alone, the aggregate sales of eight such high-value biological medicines (adalimumab, etanercept, follitropine alfa, infliximab, insulin glargine, pegfilgrastim rituximab, trastuzumab) that lost exclusivity during this period amounted to EUR 42.3 billion in 2015 (8). The large market potential presented by this wave of loss of exclusivities (LOE) has incentivized a multitude of pharmaceutical companies to invest in biosimilar mAb development (42). While the advent of biosimilar medicines for these high-value originator medicines clearly presented a substantial opportunity for healthcare systems in terms of cost savings, their entry came accompanied with challenges on several levels.

3.1 CLINICAL AND REGULATORY BARRIERS FOR PRESCRIBERS AND PATIENT ADOPTION

Barriers appear to exist for prescribers and patients to implement biosimilars in clinical practice. First, healthcare professionals and patients appear to be unfamiliar with and lack understanding of biosimilars, making them hesitant to use these (24),(27),(43). The biosimilar development and evaluation paradigm is (relatively) new to many stakeholders and the underlying science and regulatory decision-making may not be well understood by them. This in turn may lead to rather low acceptance, especially so in therapeutic indications which are granted based on the principle of extrapolation of indications (24),(42). The tailored clinical development pathway for biosimilars may be received with scepticism as physicians are accustomed to traditional drug development, which generally includes large clinical trials. Furthermore, the “similar but non-identical” paradigm may invoke uncertainties regarding the efficacy and safety of biosimilars and assumptions that biosimilars may be of inferior quality (23),(24),(27). Misinterpretations of the biosimilar concept and an imprecise use of terminology may further contribute to negative perceptions and lowered acceptance among healthcare professionals and patients (44). Misinformation regarding biosimilars by, for example, discussing scientific facts regarding biosimilars in isolation (e.g. highlighting the non-identical nature of a biosimilar to its reference product without providing the broader context of the inherent variability of biological medicines in general) or by presenting factually incorrect information, is another factor that may exacerbate the knowledge gap about biosimilars (23),(45). As the commercial stakes are high in the multibillion-dollar biological medicines market, biosimilar arrival has been met with strong originator defensive strategies to fend off/delay competition and

² Defined as molecules that have annual sales of more than EUR 1 billion

protect their market share. This may also have contributed to disparagement and misinformation about biosimilars in the field, setting back their use (45),(46),(47). Overall, negative perceptions towards biosimilars may impact the willingness of physicians to prescribe them, and patients to use them.

Second, biosimilar adoption may be challenged by doubts regarding the appropriate use of biosimilars in clinical practice. One of the key issues surrounding biosimilar use in practice is the uncertainty around whether or not biosimilars can be safely exchanged with their reference biological product (24),(43),(48). Stakeholders have questions regarding the interchangeability of biosimilars, and the associated practices of switching and substitution. Interchangeability refers to the possibility of exchanging one medicine for another that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or *vice versa*) or replacing one biosimilar with another (6). If done by the physician such an exchange is called switching or transitioning (6),(49). In case the exchange takes place at pharmacy level without consulting the prescriber, this is known as (automatic) substitution (6). Especially the arrival of the more complex mAb biosimilars, which are often used in a chronic treatment setting, sparked the debate on the safety of switching and triggered questions and doubts on the appropriate clinical use of biosimilars. The concerns raised were largely centred around questions whether or not switching between non-identical biological versions would lead to increased immunogenicity, which in turn might negatively impact safety or efficacy outcomes (50). These concerns may subsequently largely limit biosimilar use to the treatment of naïve patients, curbing the size of the potential patient population addressable by biosimilars to a fraction of that of the reference product (51). A clear need exists to address the questions on the clinical impact of switching in order to appropriately inform clinical decision making, especially for products used in long-term treatments. In Europe, biosimilar evaluation by the EMA does not include a recommendation on whether a biosimilar is interchangeable with its reference medicine (6),(14). Decisions regarding the interchangeable use of the reference product and the biosimilar and whether the reference product can be switched or substituted with the biosimilar is the responsibility of the individual Member States (6),(14). This decentralized approach might lead to varying positions, and the vacuum at European level may suggest a lack of regulatory agreement. Furthermore, the differences in terminology and regulatory decision-making between the EU and the US with regards to interchangeability may be confusing for healthcare professionals and relevant stakeholders in the field (52).

Third, the willingness of healthcare professionals and patients to use biosimilars might be limited due to a lack of clear motivation or incentives as there is no direct benefit involved for them, nor on a clinical or financial level (42),(43). Biosimilar implementation requires an active change for physicians as they need to prescribe a lesser known biosimilar instead of the reference product that they are accustomed to. Moreover, in the context of a switch, additional effort is required to explain the change to the patient. Changes in prescribing may be unlikely without a tangible benefit for healthcare professionals and/or the patients involved (43).

The above-mentioned barriers for biosimilar clinical adoption relate to healthcare professionals and patients but are also pertinent for regulators, policy makers and payers. Clear and unambiguous evidence-based information regarding biosimilars and their appropriate use is essential to inform the development of fitting biosimilar implementation policies in national and local healthcare systems.

3.2 PROCUREMENT AND POLICY BARRIERS FOR SUSTAINABLE BIOSIMILAR COMPETITION

On the level of market entry mechanisms, procurement plays a central role in biosimilar introduction and uptake. In most European countries, biosimilars (particularly those dispensed in the hospital) are largely procured by means of tenders. Tendering can be defined as a formal and predefined procedure in which multiple suppliers enter a contract competition, with the aim to select a best value for money medicine or medicines (53),(54),(55),(56). While tendering aims at stimulating competition, and provides both the opportunity for a biosimilar to win market share based on the competitiveness of their bid as well as for the healthcare system to realize savings, barriers and knowledge gaps appear to exist on several levels (57). For instance, the offering of fringe benefits and the adjustment of specifications of the tender to (purposely) exclude or disadvantage biosimilars have been mentioned to negatively impact fair competition (57). Furthermore, it is unclear how tenders for off-patent biologicals and biosimilars are structured (e.g. in terms of scope and criteria to score candidates on), and it is unknown whether current practices are aligned with the goal of attaining long-term sustainable competition in the off-patent biologicals market segment (56).

On an aggregated level, the biosimilar policy landscape varies across European countries (32),(35),(36),(37),(38). Whereas some countries have already launched dedicated policy measures to support the use of biosimilars, this appears not to be consistently the case across all EU markets (9). The fact that some countries seem to lag behind highlights the need for more insight regarding best-practices in terms of biosimilar policy making. Moreover, some measures appear to focus on securing short-term savings rather than stimulating long-term biosimilar market competition, leading to questions regarding the sustainability of current biosimilar policy making.

In summary, it is clear that the challenges impacting biosimilar adoption are complex and multifactorial. They appear to involve and affect a variety of stakeholders and touch upon clinical, regulatory and policy areas, necessitating comprehensive and multifaceted/multidisciplinary research to study and advance possible solutions, and ultimately, unlock the full potential of sustainable biosimilar competition.

1. SCOPE AND OBJECTIVES

The aim of this PhD project is to address adoption challenges faced by biosimilars in Europe and identify proposals on how to leverage biosimilar competition in a more sustainable manner. This with the ultimate goal of formulating recommendations that can contribute to a long-term sustainable off-patent biological medicines market. To achieve this, the project draws insights from stakeholders and other sources from a regulatory, clinical, and policy perspective. The framework of this thesis is structured around four objectives looking to both understand the main barriers to biosimilar adoption as well as formulate potential solutions:

Objective 1: To investigate *stakeholders'* knowledge and perceptions of, and insights on biosimilars and their use, and explore solutions to overcome potential barriers in this context

Objective 2: To assess *regulatory and clinical* components that may impact biosimilar adoption

Objective 3: To study biosimilar *policies* and especially those related to procurement, and explore proposals for more sustainable practices

Objective 4: To integrate the findings from the individual studies and develop overarching *recommendations*.

2. RESEARCH DESIGN

This PhD thesis consists of five parts, twelve chapters, and includes nine studies. A schematic overview of the thesis is provided in Figure 2. Throughout the project, a combination of quantitative and qualitative research methods is used, i.e. (systematic) literature reviews, questionnaires, semi-structured interviews, and focus group discussions.

This dissertation and the studies included focus on the biosimilar landscape in the European context. In a selection of studies, a particular European country, group of countries, dispensing context or product category is purposively selected to derive specific learnings. Comprehensive insights are provided regarding biosimilar adoption in particular while consideration is given to the broader role that biosimilars have in ensuring a long-term sustainable and competitive off-patent biological medicines market.

Part 1 consists of two chapters. Chapter 1 includes a general introduction to the topic, together with the context and key challenges that formed the basis of the different studies in this PhD project. Chapter 2 outlines the project's objectives and the broader research design.

Part 2 addresses the first objective, focusing on *stakeholders'* knowledge of and attitudes towards biosimilars and their adoption in clinical practice. It consists of three chapters. In Chapter 3, we first review the scientific literature to study healthcare professionals' and patients' knowledge and perception of biosimilar medicines. Second, we collect multi-stakeholder insights on drivers and potential actions to improve stakeholder understanding on biosimilars. In Chapter 4, we explore

stakeholder views on challenges and needs regarding the use of biosimilars in clinical practice, with a focus on switching, patient communication, the nocebo effect, substitution and stakeholder motivation and incentives, and subsequently derive proposals on how to address these. Finally, in Chapter 5, we zoom in on Belgian healthcare professionals' knowledge of and perspective on biosimilar medicines and their use in ambulatory care.

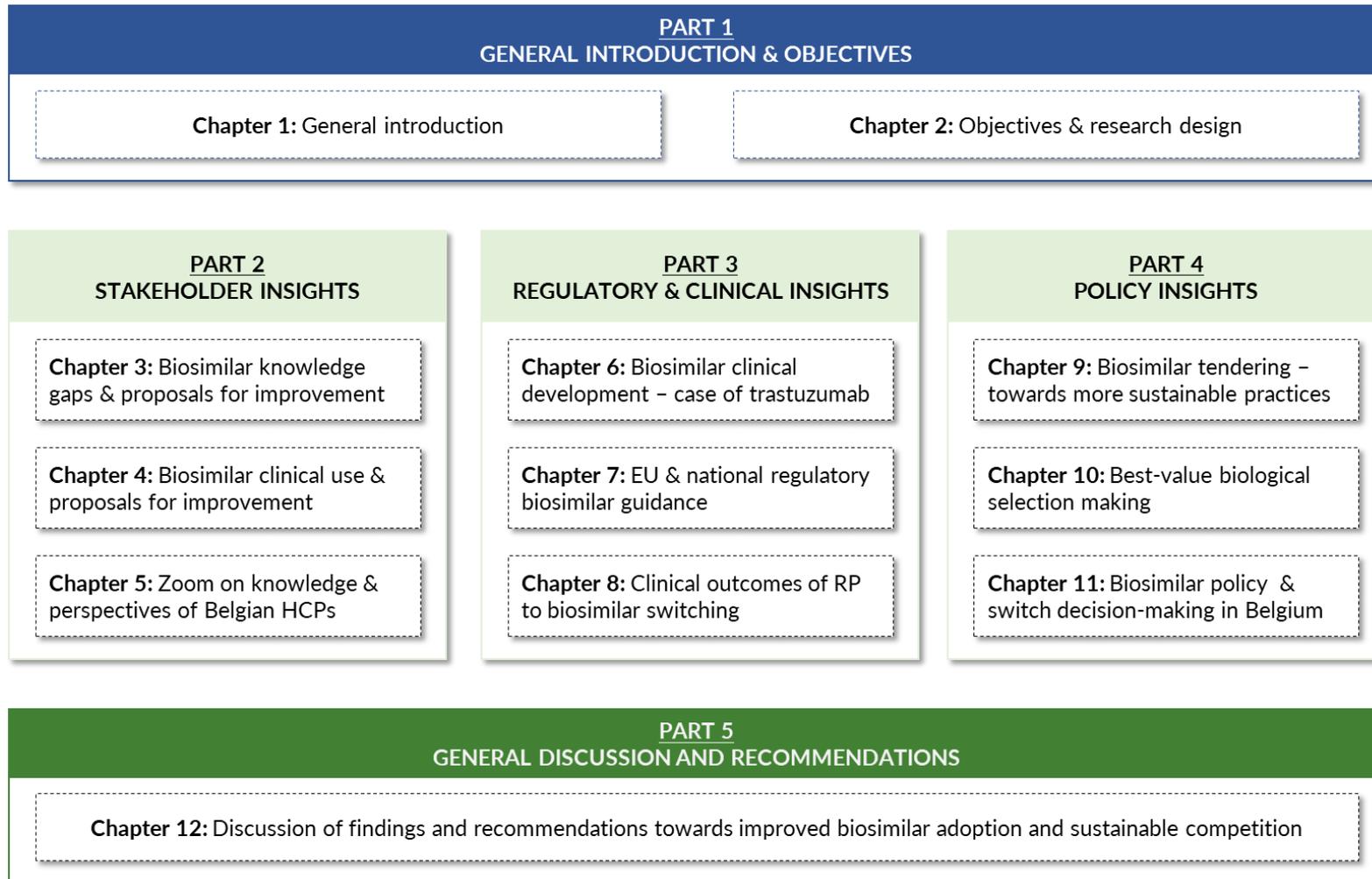
Part 3 focusses on the second objective, assessing *regulatory and clinical challenges* that may impact biosimilar adoption and consists of three chapters. In Chapter 6, we describe the biosimilar development pathway and in particular the clinical development program in order to clarify how biosimilar clinical development is tailored to meet biosimilar licensing requirements. In this context, the clinical development programs of the different biosimilars of a selected mAb (trastuzumab) are reviewed and discussed in relation to the EMA biosimilar (clinical development) guidelines. In Chapter 7, we study the role of European regulators, both on a central and Member State level, to improve knowledge of and confidence in biosimilar medicines and their use in clinical practice. As part of this, the availability and content of information and guidance provided by regulatory authorities (e.g. on interchangeability, switching and substitution) is assessed and stakeholder views are collected. In Chapter 8, the uncertainty regarding the medical act of switching is investigated. To this end, the switching studies between reference biologicals and biosimilars are systematically reviewed and the efficacy, safety and immunogenicity outcomes assessed.

Part 4 concentrates on the third objective of studying biosimilar *procurement and policy making*. It consists of three chapters. In Chapter 9, we study how tenders are organized for off-patent biologicals and biosimilars across Europe and draw learnings from industry and purchasing stakeholders with the aim of developing proposals for more sustainable practices. Chapter 10 puts forward a practical model to support best-value biological medicine selection making. Chapter 11 aims to develop consensus-based recommendations to inform coherent biosimilar policy making. To achieve this, a case study examining the needs of healthcare professionals on biosimilar market introduction in Belgium is conducted.

Part 5 (Chapter 12) addresses the fourth and final objective and provides a general discussion on and conclusion of the research. Here, based on the integrated insights from the different studies, *recommendations* to overcome biosimilar adoption challenges in Europe are provided.

This PhD project provides tangible guidance to stakeholders on biosimilar use and advances recommendations for sustainable biosimilar policy making. As such, the findings of this PhD project may inform both local practices and the development of policy measures.

FIGURE 2. SCHEMATIC OVERVIEW OF THE PHD PROJECT



HCPs: healthcare professionals, RP: reference product

PART 2

**STAKEHOLDER KNOWLEDGE,
ATTITUDES AND INSIGHTS ON
BIOSIMILARS AND THEIR USE**

1. ABSTRACT

Background: Despite the benefits offered by biosimilars in terms of cost savings and improved patient access to biological therapies, and an established regulatory pathway in Europe, biosimilar adoption is challenged by a lack of knowledge and understanding among stakeholders such as healthcare professionals and patients about biosimilars, impacting their trust and willingness to use them. In addition, stakeholders are faced with questions about clinical implementation aspects such as switching.

Objective: This study aims to provide recommendations on how to improve biosimilar understanding and adoption among stakeholders based on insights of healthcare professionals (physicians, hospital pharmacists, nurses), patient(s) (representatives), and regulators across Europe.

Method: The study consists of a structured literature review gathering original research data on stakeholder knowledge about biosimilars, followed by semi-structured interviews across five stakeholder groups including physicians, hospital pharmacists, nurses, patient(s) (representatives), and regulators across Europe.

Results: Although improvement in knowledge was observed over time, generally low to moderate levels of awareness, knowledge and trust towards biosimilars among healthcare professionals and patients are identified in literature (N articles = 106). Based on the provided insights from the interviews with European experts (N = 44), a number of challenges regarding biosimilar stakeholder understanding are identified, including a lack of practical information about biosimilars and their use, a lack of understanding about biosimilar concepts and a lack of knowledge about biologicals in general. Misinformation by originator industry is also believed to have impacted stakeholder trust. In terms of possible solutions and actions to improve stakeholder understanding, broad support exists to (i) organize initiatives focussed on explaining the rationale behind biosimilar concepts and the approval pathway, (ii) invest in education about biologicals in general, (iii) develop clear and one-voice regulatory guidance about biosimilar interchangeability and switching across Europe, (iv) disseminate real-world clinical biosimilar (switch) data, (v) share biosimilar experiences by key opinion leaders and among peers, (vi) provide practical biosimilar product information, (vii) provide guidance about biosimilar use, (viii) actively counterbalance misinformation and organize information initiatives by neutral entities, (ix) organize multi-stakeholder informational and educational efforts, aligning information between involved stakeholder groups, and (x) design initiatives in a way that ensures active information uptake. Furthermore, interviewees argue that governments should be proactive in these regards.

Conclusions: This study argues in favour of a structural, multi-stakeholder framework at both European and national level to improve stakeholder biosimilar understanding and acceptance. It proposes a number of actionable recommendations that can inform policy making and guide stakeholders, which can contribute to realizing healthcare system benefits offered by biosimilar competition.

2. INTRODUCTION

Following loss of exclusivity of original biological medicines, highly similar versions - biosimilars - can enter the market. Biosimilars are approved according to the same standards of quality, safety, and efficacy as any biological and need to demonstrate that any differences compared to their reference product are not clinically meaningful (14). Biosimilars can partly rely on data that have been gathered for the reference product, allowing tailoring of their clinical development, leading to lower development costs and subsequent prices (6). Biosimilars pose a timely opportunity to relieve budgetary pressured healthcare systems, as the price competition introduced by biosimilars has been recognized to significantly impact overall medicine expenditure. Further, biosimilar market access has shown to increase patient access to these formerly expensive biological therapies (39),(10).

Since the establishment of a regulatory approval pathway in 2004 and the first biosimilar approval in 2006 in Europe (6), more than 55 biosimilars for 15 distinct reference products have been approved, accumulating to more than 15 years of regulatory and clinical experience with biosimilars (58). Although the arrival of biosimilars has shown to provide benefits on a societal and patient level, so far biosimilar market shares vary across European countries and products, and are in some cases limited. Gaps in knowledge and understanding about biosimilars and their regulatory approval process among healthcare professionals (HCPs) and patients may limit biosimilar acceptance and curb their use (42),(43).

In addition to improving stakeholder understanding, other measures may be needed to fully capture the potential of biosimilars as uptake has also been challenged by discouraging procurement processes, lack of stakeholder motivation, and stakeholder uncertainties about interchangeability and switching (42),(43).

This study aims to provide recommendations on how to improve biosimilar understanding and acceptance based on a structured literature review and insights of expert-interviewees (physicians, hospital pharmacists, nurses, patient(s) (representatives) and regulators) across Europe.

3. METHODS

This study consists of a structured literature review and semi-structured interviews with expert-stakeholders.

3.1 STRUCTURED LITERATURE REVIEW

A structured literature review was carried out to identify HCPs' and patients' knowledge about biosimilars. PubMed was searched up to the 4th of January 2020 by combining search terms on biosimilars, HCPs, patients and knowledge ([Supplementary file 1](#)). Search results were screened based on predefined inclusion and exclusion criteria ([Supplementary file 2](#)). The inclusions were further supplemented by grey literature.

Original research studies describing the knowledge and understanding of HCPs or patients about biosimilars and biosimilar-related concepts were included. Articles describing expert-opinions or position statements were excluded. Study parameters and results were systematically extracted.

3.2 SEMI-STRUCTURED INTERVIEWS

Interviews with experts were conducted across five stakeholder groups (physicians, hospital pharmacists, nurses, patients and regulators) to obtain multi-stakeholder insights on how to improve knowledge and understanding about biosimilars among HCPs and patients. Experts were recruited across Europe and where possible from European organizations or institutions (e.g. representatives of European stakeholder associations) to capture pan-European perspectives. HCPs and patients were recruited across disease domains currently relevant for biosimilars. Participants were identified by screening websites of stakeholder associations and regulatory authorities, conference speakers, authors of biosimilar literature and the research group's network.

The interview questions were based on topics identified in the literature ([Supplementary file 3](#)). The interview questions were tested in three pilot interviews.

The interviews were carried out between October 2017 and June 2018. Interviews were conducted in English, with the exception of a few interviews in Dutch based on the interviewee's preference. The interviews were conducted by Skype®, phone or in person and digitally audio-recorded. Participation was voluntarily and interviewees did not receive any remuneration.

The recordings were transcribed *ad verbatim*. The transcripts were pseudonymised and analysed according to the thematic framework method using NVivo software® (59).

4. RESULTS

4.1 LITERATURE REVIEW –MAPPING KNOWLEDGE AND TRUST LEVELS OF HCPS AND PATIENTS

The screening and selection of 383 identified records led to the inclusion of 100 studies. In addition, six studies were identified in grey literature, resulting in a total of 106 studies reporting original research on HCPs' and/or patients' biosimilar perceptions. With the exception of a few studies involving focus group discussions, interviews or expert panels, studies consisted of a survey. The perspective of physicians and patients was surveyed the most (N: 37, 35% and N: 32, 30% respectively *versus* pharmacists: N: 10, 10%, nurses: N: 1, 1%, across stakeholder groups: N: 26, 25%). Approximately one third of the studies were either industry sponsored (N: 8, 8%) or conducted by industry (N: 28, 26%). The characteristics of the included studies are shown in Figure 3.

Although improvements were observed over time, gaps in knowledge and understanding about biosimilars and regulatory concepts were generally identified across regions, therapeutic areas and stakeholder groups. Overall, voiced concerns across studies included questions about biosimilar

immunogenicity, safety, efficacy, interchangeability, (automatic) substitution and extrapolation of indications (43),(60),(61),(62),(63),(64),(65),(66),(67),(68).

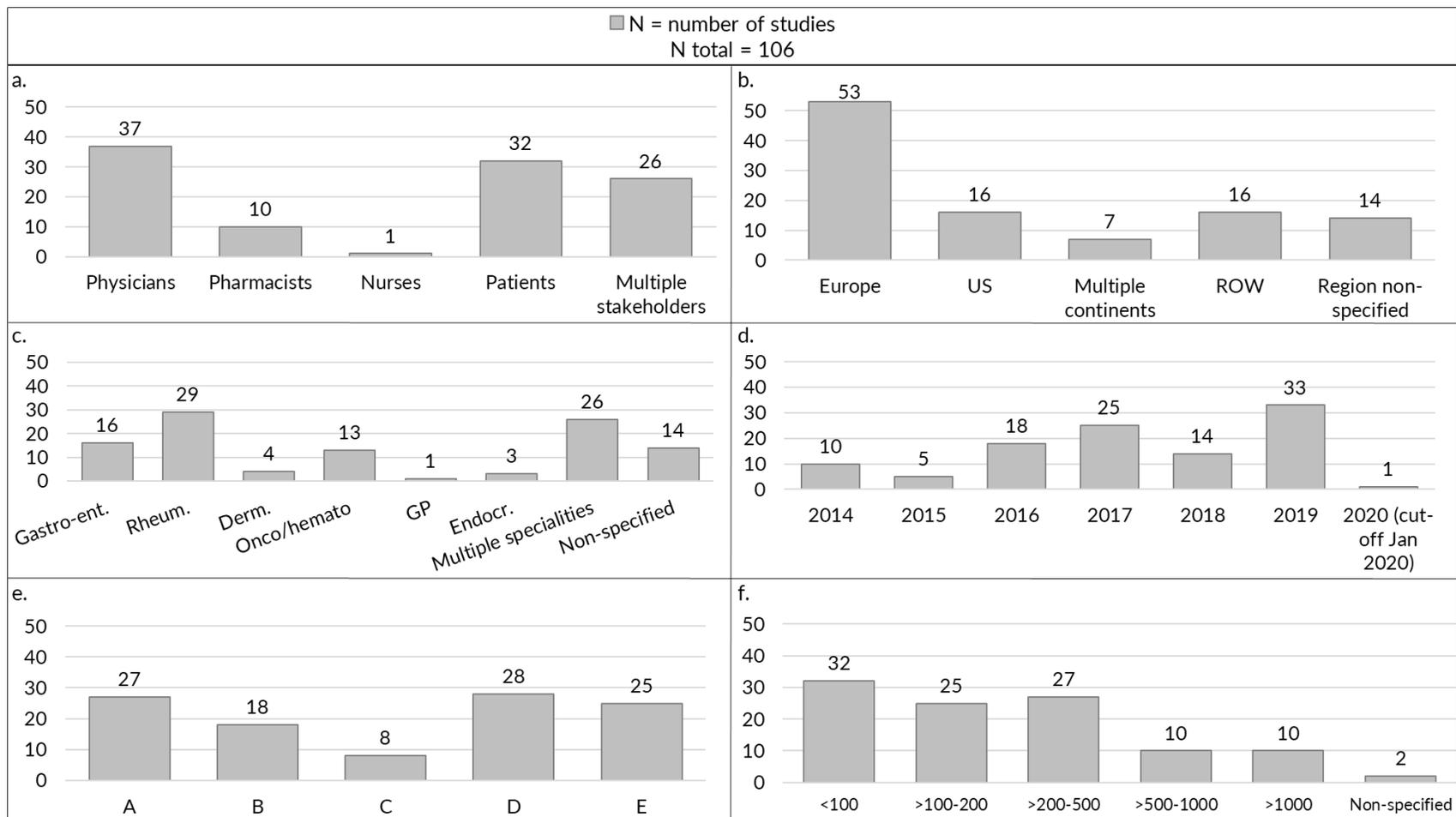
Various studies identified, if presented with a choice, patients would object to being switched or physicians would object to switch their patients to a biosimilar (69),(70). In contrast, patients who were switched generally reported a positive experience, suggesting that experience with biosimilars leads to increased trust (71),(72). Additionally, concerns existed among stakeholders about being forced to switch or being limited in prescription choice (73),(74),(75),(76).

In several studies, physicians showed willingness to use biosimilars if this would result in increased patient access to treatment or in reduced healthcare costs (77),(78). A survey among Hungarian oncologists and haematologists showed that prescribers would increase rituximab use if a biosimilar would be available, as 40% considered patient access to rituximab an issue (79).

Patients appear to heavily rely on the physician's decision to use a biosimilar, as identified across multiple studies (80),(81),(82),(83),(66),(84),(85),(86). Among suggested solutions to improve patients' biosimilar acceptance, communication and reassurance from HCPs, together with involvement in decision-making, were mentioned (87). A New Zealand survey identified the need among physicians for guidance on how to explain biosimilar treatment to patients (88).

Although earlier reports and overall literature identified relatively low to moderate levels of knowledge and acceptability of biosimilars among stakeholders, improvements over time were identified. A survey conducted in 2013 among European Crohn's and Colitis Organisation (ECCO) members reported that the majority of inflammatory bowel disease (IBD) specialists had little or no confidence about biosimilar use, expressing various concerns (60). In 2015, ECCO repeated the survey, reporting fewer concerns and more confidence about biosimilar use among participants. IBD specialists were generally well informed and educated about biosimilars compared to the 2013 data (89). Although improvements in stakeholder knowledge were mentioned in some studies, recent studies such as the European Federation of Crohn's and Ulcerative Colitis Association patient member survey published in 2019, signalled that awareness remains limited and stakeholders, in this case patients, remain concerned (90).

FIGURE 3. STRUCTURED LITERATURE REVIEW: CHARACTERISTICS OF STUDIES ON STAKEHOLDER KNOWLEDGE AND PERCEPTIONS OF BIOSIMILARS



a. Studies categorized per stakeholder group, b. Studies categorized per region, c. Studies categorized per therapeutic area, d. Studies categorized per publication year, e. Studies categorized per reported conflict of interest/funding type. A: no declared conflict of interest, B: declared author conflict of interest (or disclosure of interest) (e.g. HCPs/academics providing advice/paid consultancy to industry), C: industry sponsoring/educational grant from industry to support independent research declared, D: research conducted by industry/lobby organization/consultancy, E: potential funding/interest not specified, f. Studies categorized per number of participants. Abbreviations: Derm dermatology, Endocr endocrinology, Gastro-ent gastro-enterology, GP general practice, N number, Onco/hemato oncology, haematology, Rheum Rheumatology, ROW rest of the world, US United States

Recommendations on how to improve stakeholder acceptance mentioned in literature included: adapting clinical guidelines to reflect biosimilar use, implementing clear communication between physicians and patients, sharing real-world data with HCPs and educating prescribers about switch study data (91),(92),(93),(94). A few studies demonstrated that training stakeholders considerably improved their understanding and confidence in biosimilars (95),(96).

A structured overview of the original research studies about HCPs' and patients' biosimilar perspectives, including study parameters and main results, is given in [Supplementary file 4](#).

4.2 SEMI-STRUCTURED INTERVIEWS – IDENTIFYING CHALLENGES AND ACTIONS TO IMPROVE HCP AND PATIENT UNDERSTANDING AND TRUST IN BIOSIMILARS

In total, 44 interviews were carried out. Participant characteristics are shown in [Supplementary files 5 and 6](#).

Overarching identified stakeholder challenges and proposed actions to improve stakeholder understanding and acceptance of biosimilars are shown in Figure 4.

4.2.1 IMPROVING STAKEHOLDER UNDERSTANDING ABOUT REGULATORY BIOSIMILAR CONCEPTS

A lack of stakeholder knowledge and understanding of regulatory biosimilar concepts was identified as important hurdle by most interviewees. Communication about the biosimilar regulatory approval pathway, reducing misconceptions about the biosimilarity concept, was deemed essential. Regulators emphasized that they have undertaken actions to improve stakeholder understanding about biosimilars, including the development and dissemination of informational materials in lay language for HCPs and patients, and the publication of biosimilar concept papers. Several interviewees mentioned that the robustness of the regulatory approval procedure should be emphasized in biosimilar stakeholder information.

4.2.1.1 EXPLAINING THE RATIONALE BEHIND REGULATORY BIOSIMILAR EVALUATION TO ADDRESS THE PERCEIVED LACK OF CLINICAL DATA

Across physician, pharmacist and regulator interviewees, it was generally recognized that the physicians' understanding about the reduced role of clinical studies in biosimilar development and evaluation needs to be improved.

“The gold standard of clinical trials does not hold true for biosimilars, where the focus is on analytical techniques that allow to obtain a high level of understanding about how the molecule works”.

It was argued that this requires a mindset shift, as physicians are accustomed to the approval of new medicines, which undergo extensive clinical testing in phase I, II and III trials. Interviewees mentioned that many physicians are still arguing that there are too few clinical trials conducted for biosimilars, demonstrating that the concept of biosimilar development is not clear to all involved.

“Doctors are trained to say: ‘they don’t have the clinical trials, they didn’t do the effort”.

Awareness and understanding about the development steps prior to the clinical part was deemed lacking:

“Physicians need to learn that the clinical trial is the cherry on the cake, a confirmatory step of biosimilarity demonstrated in earlier development steps”.

Informing physicians about the framework through which biosimilars are evaluated was seen as key in increasing their and by extension also their patients' trust in biosimilars. Regulators argued that stakeholders must be informed that “phase III trials are a rather blunt tool to detect potential differences, and more attention is paid towards the more sensitive PK/PD trial” and that the clinical program is tailored towards the goal of the biosimilarity exercise, not a shortcut for developers, which may not be well understood by all. It should be explained that tailoring allows to avoid unnecessary delays, patient participation and development costs.

4.2.1.2 EXTRAPOLATION OF INDICATIONS – CONVEYING TRUST IN EMA'S EVALUATION

It was mentioned that the concept of extrapolation of indications, albeit an imperative part of biosimilar development, is often misunderstood by stakeholders. Overall, it was stressed that extrapolation should be trusted as a scientifically valid part of a rigorous registration procedure.

“Trust in the approval pathway also means applying the concept of extrapolation of indication.”

One pharmacist mentioned that the decision regarding extrapolation is the regulator's expertise field and should not be further questioned:

“As a pharmacist, I rely at what the EMA decides. I trust that what is decided is based on decent evidence.”

Although several nurses expressed some hesitations, the overall concept and application was accepted.

“Someone else has decided that it is OK, so I don't think any of us can say that more needs to be done”.

Among patients, opinions varied about the application of extrapolation, ranging from trusting EMA's evaluation and mentioning that doing more than what scientifically would be needed should be avoided, to considering it as shortcut for developers.

Regulators indicated that it should be explained to stakeholders that extrapolation is not granted automatically and that exceptions can be applied if the studied indication would not be clinically representative or if questions about the mechanism of action across indications exist. A few pharmacists argued that regulators could “speak louder” about what extrapolation of indications entails. Interviewees generally believed that education on the biosimilar regulatory approval pathway is needed to further instil trust in extrapolation among stakeholders.

FIGURE 4. HOW TO IMPROVE STAKEHOLDER UNDERSTANDING ABOUT BIOSIMILARS

Stakeholder hurdles	Stakeholder aligned recommendations	
<ul style="list-style-type: none"> Lack of understanding about biosimilar concepts and the biosimilar regulatory approval pathway (e.g. perceived lack of clinical trials) Lack of knowledge about biologicals in general (e.g. low awareness about existence of product variability, misconceptions about immunogenicity) Differences in approach and guidance (USA vs EU vs Member States) regarding interchangeability and switching Lack of clear and ready to use guidance about biosimilar use e.g. switch guidance Lack of practical and timely product information (e.g. on biosimilar pipeline, product features, practical implications for the patient) Misrepresentation of information and industry influence, leading to misconceptions and hindering effective communication Lack of effective dissemination and active uptake of the available information Possible evidence generation hurdles for biosimilar developers to respond to stakeholder requests for additional clinical data beyond the biosimilar licensing requirements, driven by stakeholder uncertainty and missing stakeholder guidance 	<p>Actions by national governments and policy makers</p> <ul style="list-style-type: none"> Implement education about biologicals (including biosimilars) in curricula and continued professional learning programs of HCPs, ensuring active training and information uptake Provide biosimilar product horizon scanning and structured product overviews, with information about characteristics of available products (reference product and available biosimilars) (similarities and differences in e.g. approved indications, device,...) Educate hospital-stakeholders on how to organize public procurement (e.g. application of selection criteria) 	<p>Actions by HCPs and stakeholder associations</p> <ul style="list-style-type: none"> Provide biosimilar position statements, endorsing regulatory concepts and associated messages, and update these over time Adapt clinical guidelines to reflect biosimilar use Translate regulatory information to the practical context relevant for HCPs and patients (e.g. to disease domain, hospital/ambulatory setting) Appoint biosimilar educators to guide biosimilar implementation in clinical practice Communicate experiences with biosimilars among peers Disseminate real-world-biosimilar (switch) data
	<p>Actions by regulators</p> <ul style="list-style-type: none"> Continue information provision about rationale behind the regulatory approval pathway with a focus on actively disseminating materials, e.g. leveraging EMA's biosimilar stakeholder guidance documents on a national/local level Stimulate collaboration between EU and national agencies to ensure one-voice regulatory information and guidance regarding interchangeability and switching Monitor and correct biosimilar misinformation Raise awareness about EPAR as product information tool and routinely update the EPAR over time 	<p>Multi-stakeholder actions</p> <ul style="list-style-type: none"> Stimulate active collaboration between regulatory authorities and professional stakeholder associations to <ul style="list-style-type: none"> draft and actively disseminate tailored and independent information in line with regulatory message to target audience (e.g. by writing and updating position papers) organize multi-stakeholder education initiatives orchestrate actions between involved parties to ensure effective information flows Communicate across different therapeutic areas and disciplines, leveraging and exchanging insights and experiences of previous 'biosimilar-exposed' specialties

EMA: European Medicines Agency, EPAR: European Public Assessment Report, HCPs: healthcare professionals, NCAs: national competent authorities

4.2.1.3 INTERCHANGEABILITY – A NEED FOR ONE-VOICE GUIDANCE FROM REGULATORS

Table 2 provides definitions and considerations on interchangeability, switching and substitution in Europe.

TABLE 2. INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION IN EUROPE: TERMINOLOGY AND CONSIDERATIONS

European context	<ul style="list-style-type: none"> ▪ The EMA does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar. In the EU, prescribing practices and advice to prescribers fall under the responsibility of Member States. Decisions and guidance regarding interchangeability, switching and substitution fall as such within the remit of the EU Member States (i.e. taken at national level) (6).
Inter-changeability	<ul style="list-style-type: none"> ▪ <i>“Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another.”</i> (6) ▪ Replacement can be done by switching or substitution (6). ▪ Although there is no official position on interchangeability on EU level, an opinion paper by European regulators, members of the Biosimilar Medicinal Products Working Party, opines that biosimilars licensed in the EU can be considered interchangeable (6).
Switching	<ul style="list-style-type: none"> ▪ <i>“When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.”</i> (6) ▪ Over previous years, concerns were voiced around the safety of switching, with the main concern being an increase in immunogenicity due to the subsequent exposure to highly similar but not identical versions of the same product. Based on the available data (178 studies involving a switch between reference product and biosimilar) there are no indications that switching is related to any major efficacy, safety or immunogenicity issues (51), and switching between reference products and biosimilars has become part of routine clinical practice. ▪ Several national competent authorities have taken national positions endorsing switching between reference biologicals and biosimilars (97),(98).
(Automatic) substitution	<ul style="list-style-type: none"> ▪ <i>“The practice of dispensing one medicine instead of another equivalent and interchangeable medicine <u>at pharmacy level</u> without consulting the prescriber.”</i> (6). ▪ The practice of (automatic) substitution for biological medicines is generally not allowed or advised against in most European countries. In some countries, such as France, it is allowed under special conditions (e.g. only for treatment naïve patients), but not implemented in practice. Changes are planned to legislation in Germany and Norway, which would allow (a selection of) biologicals to be substituted at pharmacy level (99).
Different approach in US	<ul style="list-style-type: none"> ▪ The FDA has created a dedicated regulatory pathway for the designation of interchangeability. Dedicated studies are requested to demonstrate interchangeability. The pharmacist would be allowed to substitute a prescribed reference product with the interchangeable biosimilar without intervention of the prescriber (if also allowed by state law). So far, there are no FDA designated interchangeable biosimilars. It appears that no official filings for the designation have been made so far (97),(51),(100),(101),(102).

EMA: European Medicines Agency, EU: European Union, FDA: US Food & Drug Administration, US: United States

Most pharmacists opined that a registered biosimilar could be considered interchangeable with its reference product.

“If you establish this level of analytical similarity, together with a clinical study in a reference indication, with the same mechanism of action, then for me, there is no discussion about interchangeability.”

Most physicians corroborated this opinion and believed that interchangeability between biosimilars and reference products is supported by the accumulated body of switch studies. Opinions of patients varied, ranging from a need for more data to agreeing with the physician’s decision. Regulators explained that additional clinical data, besides these requested in the registration procedure, are not needed from a scientific perspective, explaining why an interchangeability designation route imposing additional regulatory requirements as employed by the US Food and Drug Administration (FDA) (100) is not chosen in Europe. Although regulators explained that the mandate to regulate substitution lies outside EMA’s remit and therefore EMA does not provide guidance on interchangeability, approved biosimilars are considered interchangeable. It was mentioned that individual members of the Biosimilar Medicinal Products Working Party (BMWP) published a position paper about interchangeability (97), striving to provide guidance on the European level.

Some interviewees argued that the current divergent approach regarding interchangeability between FDA and EMA creates distrust among stakeholders. The FDA framework was believed to imply that some biosimilars are more similar to the reference product than others. Further, heterogeneity between positions of National Competent Authorities (NCAs) regarding interchangeability was believed to lead to confusion.

Several physicians and pharmacists mentioned that it would be preferable for EMA to address interchangeability by providing a clear position or by requesting switch studies as part of the registration procedure, similar to FDA’s approach. A few physicians advocated that this would encourage developers to conduct one methodologically robust study, which would be preferred over the scattered landscape of smaller, real-world switch studies. One interviewee argued that this would allow to settle the switch discussion before market entry.

Regulators deemed interchangeability studies to require unnecessary time (delay in access) and financial investments, imposing additional challenges for biosimilar developers. Further, some regulators questioned how FDA will address interchangeability over the product’s life cycle. Echoing the regulators’ viewpoint, some pharmacists deemed interchangeability studies a loss of time and resources, whereas others were in favour of extra data about sequential switching. Some interviewees believed that it is up to the physician to decide if they are comfortable with multiple exchanges. Some patients voiced concerns and argued that there is a lack of evidence to ensure the safety and efficacy of sequential switching.

Overall, interviewees deemed it important that robust records are retained that allow adequate traceability in case any issues would emerge and that random switches are avoided. Regulators emphasized that existing pharmacovigilance systems should be able to capture any adverse drug reactions. It was mentioned that more attention needs to be paid toward batch number recording.

4.2.1.4 IMMUNOGENICITY – NOT A BIOSIMILAR-SPECIFIC CONCERN

Many pharmacists and physicians emphasized that stakeholders should learn that immunogenicity is not a biosimilar specific topic, as it could occur with any biological.

“We need to explain what a biological is.”

The immunogenicity topic is believed to have been fueled by originator industry as an argument to instil fear and slow down biosimilar acceptance, as mentioned by several physician and pharmacist interviewees.

“No one talked about immunogenicity issues before biosimilars arrived to the market”.

Further, some regulators and physicians argued that immunogenicity’s relevance depends on the molecule and that a risk-based assessment should be applied based on the knowledge about the reference product.

“I think that for the majority of biologicals immunogenicity is not so much a problem and definitely we shouldn’t make it one.”

Although immunogenicity assessment was believed to be addressed by the combination of a rigorous registration procedure and pharmacovigilance measures that allow longer-term monitoring, several interviewees suggested that improved traceability is needed to be able to attribute any possible immunogenicity signals to the involved product and batch. A few regulators mentioned that awareness of the importance of batch number reporting should be raised. Regulators also explained that stakeholders would benefit from knowing that immunogenicity is considered during biosimilar evaluation. A few interviewees anticipated that there could be an increase in immunogenicity reporting for biosimilars, as stakeholders tend to report more for “new” products.

4.2.2 A NEED FOR EDUCATION ON BIOLOGICAL MEDICINES IN GENERAL

In addition to continue educating stakeholders about the scientific rationale behind the biosimilar regulatory approval process, several interviewees mentioned that educating stakeholders about biological medicines in general is necessary. Creating awareness among HCPs about the existence of manufacturing changes over the lifecycle of any biological and knowledge about their inherent variability was believed to provide perspective that the reference product is also not identical over time and to be pivotal to help stakeholders understand the concepts behind biosimilarity. It was mentioned that most clinicians are not aware about these aspects although this could generate understanding about variability between products and provide insight in the evaluation of these differences.

4.2.3 THE REQUEST FOR REGULATORY GUIDANCE ABOUT SWITCHING

Most HCP interviewees indicated that information about considerations for biosimilar use, such as guidance about switching, is needed. To address questions regarding switching, it was argued that governments need to take up a more active role in informing, educating and providing guidance about biosimilars to HCPs and patients. To this end, several physicians and pharmacists voiced that NCAs need to formulate clear statements about biosimilar use. The existing NCA guidance was generally considered too cautiously formulated and “*not fully in touch*” with practical realities by several HCPs. Some regulators also mentioned that most NCAs only address reference product to biosimilar switching, arguing that guidance needs to be deepened and broadened. Several interviewees argued that guidance about switching on an overarching European regulatory level would be preferred, as it is now left open to the individual NCAs, leading to differences in recommendations, impacting stakeholder trust and confidence. A regulator counterargued that trust in biosimilar use essentially has to be created by stakeholder education. A few interviewees cautioned that overarching guidance should not translate into forced switching and that the decision-making should remain with the physician.

4.2.4 REAL-WORLD CLINICAL DATA GATHERING TO INSTIL TRUST AMONG STAKEHOLDERS

Some physicians and nurses argued that real-world data could answer physicians’ demands for more clinical data, as it was argued to be reflective of clinical practice and often accompanied with expert-opinion insights. Physicians and regulators indicated that switch study results can reassure physicians about switching. The NOR-SWITCH trial (103) was raised as example of such a post-approval initiative that increased physician confidence in biosimilars.

Clinical data gathering via registries was also considered to be helpful to increase stakeholder confidence and reassure stakeholders that the product performs well in every indication, instilling trust in extrapolation of indications. Further, registries were mentioned to gather useful evidence about the long-term safety and efficacy of switching. In addition to clinical data, communication about real-life switch experiences was argued to be reassuring towards stakeholders.

Several regulators cautioned that these additional data gathering expectations from HCPs could pose a barrier for biosimilar development and timely market entry, as it requires the sponsor to conduct expensive clinical studies beyond the licensing requirements.

4.2.5 THE NEED FOR PRACTICAL AND STAKEHOLDER ORIENTED INFORMATION

Interviewees across stakeholder groups emphasized the need for practical information about biosimilar products and biosimilar use.

Nurses believed that the information gap about biosimilars among fellow nurses is high. Nurses mentioned the need for specific biosimilar training, to increase their knowledge to correctly address potential patient questions. Most nurses also wanted to receive training about switch management:

“What does it mean for the patient, why are we switching, what are the benefits?”

Several nurses also indicated the need for timely information about biosimilars entering the hospital. Organizing a product instruction moment when a new product enters the hospital was suggested. Several interviewees mentioned that lessons should be derived from previous experiences, where switches were implemented without providing HCPs with necessary information.

“One day we got the new medicine and we had to use it, change patients quickly without the right information, without a good answer why we needed to change”.

Several physicians also indicated that information should be tailored to the context in which the product is dispensed, i.e. to the hospital or ambulatory setting, and to the product category.

In addition to information about practical use, pharmacists asked for practical product-specific information, such as information about differences and similarities in approved indications, presentations, packaging and if applicable injection devices between the reference product and its biosimilar(s). Additionally, information about the expected biosimilar pipeline was considered needed to allow a timely procurement planning. Guidance about the construction of award criteria was also believed to be useful to support their work. A nurse mentioned that the number of different products that are available for the same medicine, with potential differences in names, devices, indications, can confuse patients and HCPs, also expressing the need for a clear overview of product characteristics.

Patients argued that information should be provided in a simple, understandable and accessible way, tailored to basic health literacy levels. Providing written information with graphic designs or video material were suggested to improve patient information. Several patients mentioned that information overshooting should be avoided, as not every patient is interested and it could instill concerns among patients).

“For many patients, it’s not an issue if it’s a biosimilar or a regular biological”

“Why is there so much attention about this?”

Several patients explained that patient information should be tailored to *“inform about what the patient actually needs and wants to know”*, i.e. informing about the implications for the patient. Further, it was emphasized that patients wish to be informed about any adverse event risk.

Several HCPs mentioned specific initiatives that helped to generate practical biosimilar guidance, such as the Dutch Association of Hospital Pharmacists (NVZA) toolbox (104) that provides practical switch guidance and the European Specialist Nurses Organisations (ESNO) biosimilar booklet (105) providing communication and information guidance for nurses.

4.2.6 THE NEED FOR IMPARTIAL AND HOMOGENOUS INFORMATION

Across interviews, the importance of impartial information regarding biosimilars, originating from independent bodies such as EMA and the NCAs, was stressed. Also regulators believed that they are best suited to provide information about biosimilars, acting from a neutral position with knowledge from actual biosimilar assessments. The EMA/European Commission biosimilar

stakeholder guidance documents (6),(106) were often mentioned during interviews as important and unbiased stakeholder information sources. One physician argued that awareness should be increased about the European Public Assessment Report (EPAR), as it provides insights in regulatory evaluation and decision-making.

Several interviewees across stakeholder groups considered that measures to actively counter misconceptions about biosimilars are necessary. Misconceptions were attributed by some to deceptive or commercially biased messaging from originator pharmaceutical industry protecting their market shares.

“The issue is not so much the lack of information, but how the information is framed and presented”

“Companies have been successfully casting doubts about biosimilars”, “I don’t only need to educate, I have to dispel the angled information that has been presented. I’m already fighting against the tide, before I start.”

Also patients and nurses indicated that misconceptions about biosimilars, including considerations about inferiority, should be tackled. Several regulators indicated that biosimilar regulatory concepts are misrepresented in an effort to set back stakeholder trust. Several interviewees advocated that existing sources should be interpreted with caution *“to distinguish facts from nonsense”*.

Convincing physicians who have been working with reference products for years, appears to be challenging due to established relations with pharmaceutical companies, as mentioned by some interviewees. In contrast to most interviewees, several nurses identified pharmaceutical companies and their umbrella organizations as potential biosimilar educators.

Additionally, most regulators believed that *“it’s not the lack of information, but the multitude and heterogeneity of information”* that contributes to stakeholder misunderstanding about biosimilars. This argument was also made by several physicians, who mentioned that informational initiatives are scattered, leading to confusion, emphasizing the need for homogenous information.

4.2.7 LEADING BY EXAMPLE - THE ROLE OF KEY OPINION LEADERS AND POSITION STATEMENTS FROM STAKEHOLDER ASSOCIATIONS

Across all HCP stakeholder groups, interviewees mentioned that colleague key opinion leaders could play an important role in translating regulatory information into clear, concise statements, focused on practical considerations for biosimilar use. Generally, information from within the own stakeholder group (peer-to-peer information) was considered best suited and impactful to improve trust.

Several physician, regulator and patient interviewees advocated that key opinion leaders are likely to be considered as a trustworthy information source.

“Prominent physicians who have experience are the best ones to deliver the experience to their colleagues”.

Biosimilar ambassadors could actively guide biosimilar implementation and inform colleagues. The conception of dedicated biologics/biosimilar expert offices on a local level was proposed as alternative route to help pave the way. Additionally, physicians considered that experience sharing by clinical disciplines that were already exposed to biosimilars could be leveraged to inform the next generation of stakeholders that will be confronted with biosimilars. Building from previous positive biosimilar experiences was argued to be an approach to increase trust by several interviewees.

“It is a domino effect, when a few big hospitals are doing the switch, the others will follow.”, “Once somebody else has done it, it takes some of the fear-factor away.”

Further, position statements by national and European scientific stakeholder associations were recognized as lever to increase understanding among peers. It was remarked that continuous updating of position statements to reflect increasing experience and knowledge about biosimilars is needed. The increasing endorsement of regulatory concepts, such as extrapolation of indications, by medical stakeholder associations was mentioned as a positive evolution in this context.

4.2.8 THE IMPORTANCE OF MULTI-STAKEHOLDER ALIGNED EFFORTS

Most interviewees across stakeholder groups advised that information and education should be a multi-stakeholder effort, ensuring that all stakeholders are able to communicate in the same way and can implement aligned decisions. Informing HCPs about biosimilars requires an orchestrated action, initiated at regulatory approval, followed by information and guidance from the NCA and national scientific stakeholder associations upon national market entry. Specifically regulators discussed that a more active collaboration between EU and national regulatory authorities should be established, ensuring homogenous biosimilar information and targeted education streams. Further, a fostered collaboration between stakeholder groups was deemed needed to translate regulatory information to stakeholder needs. Regulators and stakeholder organizations could write joint position papers or information made by EMA could, after tailoring to the therapeutic area and stakeholder needs, be used on a local level. Governmental support was deemed desirable and NCAs were believed to be best suited to organize neutral education events locally. Several physicians emphasized that NCAs, together with medical scientific societies, should take up a more active role.

It was argued that communication should also be an orchestrated multi-stakeholder effort on a hospital level. This multidisciplinary approach was deemed especially needed in the context of switch management. Several interviewees argued that hospital pharmacists would be best suited to guide these multi-stakeholder initiatives towards colleague HCPs (e.g. via Drug & Therapeutics Committees), acting as “biosimilar educator” and guiding biosimilar use in the hospital. Specialized nurses could in turn support patients when switching.

4.2.9 ENSURING ACTIVE UPTAKE OF INFORMATION

Several interviewees mentioned that approaches to ensure active uptake of the provided information should be explored, as the existing information is believed to only slowly penetrate the wider HCP and patient population. Incorporating education on biosimilars in the stakeholder

curricula was strongly supported across stakeholder groups. Suggestions were made to include biosimilar education as obligatory part in the HCP accreditation system.

Gaining own practical experience with biosimilars in clinical practice (including switching) was also believed to establish trust among HCPs and patients by several interviewees.

"It is not very scientific, but that is how it works for physicians".

Gaining experience with switching to a biosimilar was also argued to improve patient trust by some nurse interviewees:

"Patients who tried the switch now accept it. They don't think it is such a big thing anymore."

5. DISCUSSION AND RECOMMENDATIONS

First, this study presented a structured review of the existing research on HCP and patient perceptions about biosimilars, identifying a clear need for continued evidence-based information and education initiatives to improve biosimilar understanding among HCPs and patients as knowledge about and acceptance of biosimilars is still variable and mostly unsatisfactory. Second, multi-stakeholder learnings and proposed solutions on how to improve stakeholder understanding and acceptance of biosimilars in Europe were gathered in semi-structured interviews with experts across stakeholder groups to reflect the considerations of different stakeholders involved. In contrast to the studies identified in the literature review that mostly focussed on measuring stakeholders' biosimilar knowledge, the qualitative part of this study identified expert-insights on how to overcome stakeholder challenges to improve biosimilar understanding and adoption. This study also captured insights of nurses, whose perspective generally has been underreported so far.

As discussed during the interviews, increasing biosimilar understanding and acceptance among stakeholders requires a multifactorial and interdisciplinary approach. No silver bullet solution exists, rather a coordination of efforts of different stakeholder levels is needed. Based on the synthesized study findings, we propose actions to be centred on ten actionable multi-stakeholder recommendations, which are presented in Table 3. These recommendations may inform policy making and other stakeholder initiatives to increase biosimilar understanding.

TABLE 3. MULTI-STAKEHOLDER RECOMMENDATIONS: KEY POINTS FOR DECISION MAKERS AND HCPS IN EUROPE

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1. **Investing in education and information initiatives about biosimilars**, explaining the scientific rationale behind the regulatory approval pathway for biosimilars and conveying trust in the regulatory evaluation by independent, governmental and regulatory bodies, further continuing and complementing the efforts made by European regulators, and other scientific organizations, over previous years in providing unbiased information to the public.
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2. **Investing in education about biological medicines in general** and concepts such as comparability demonstration in the context of manufacturing changes, product characterization, immunogenicity, and batch-to-batch variability (and methods to cope with this). HCP training should also include courses on drug development, including clinical trial design.

-
3. **Developing clear and unified EU-overarching regulatory guidance about interchangeability and switching**
 - a. Continued regulatory guidance development about biosimilar use on both a national and European level
 - b. Collaboration between the EMA and the national competent authorities to provide one-voice guidance about interchangeability and switching

 4. **Disseminating real-world clinical data about biosimilar use and switching via academic detailing, key opinion leaders and peer-to-peer communication.** Government and competent authorities should collaborate with scientific/medical stakeholder associations to develop and support such initiatives.

 5. **Sharing stakeholder experiences with biosimilar use and switching via academic detailing, key opinion leaders and via peer-to-peer communication.** Government and competent authorities should collaborate with scientific/medical stakeholder associations to develop and support such initiatives.

 6. **Developing and providing product horizon scanning and practical biosimilar product-specific information** (structured product overviews with similarities and differences in product features of available options) on regional or national governmental level to support hospitals and HCPs with biosimilar implementation.

 7. **Developing guidance about biosimilar use in practice to support HCPs.** Existing initiatives and materials could be used as example and tailored to the national/regional/setting-specific context.
 - a. Developing HCP guidance about biosimilar use in clinical practice
 - b. Developing a structured switch protocol
 - c. Appointing coordinators to guide biosimilar implementation in clinical practice
 - d. Developing patient information about any practical implications

 8. **Designating an independent, governmental body to pro-actively monitor and correct biosimilar miscommunication/misconceptions,** and address stakeholder queries in this regard (serving as dedicated point of contact).

 9. **Fostering of multi-stakeholder initiatives and collaboration**
 - a. Fostering collaboration between regulatory authorities and scientific/medical stakeholder associations to translate regulatory guidance into practical information for HCPs and patients and to establish endorsement about biosimilar concepts by scientific stakeholder organizations. Position statements should be updated regularly to reflect the evolving knowledge and experience with biosimilars.
 - b. Organizing biosimilar informational and educational efforts from a multi-stakeholder perspective, aligning the information between the involved stakeholder groups
 - c. Governmental support and pro-active approach needed

 10. **Organizing efforts in such a way that ensures active uptake of information and education**
 1. Including courses in the curriculum of future HCPs
 2. Including courses in the mandatory continuous education (via accreditation programs) of practicing HCPs
 3. Pro-actively offering solution-oriented information and practical support programs on a local level, which can be tailored to the needs of the stakeholder (i.e. educational and support programs to the hospital at the time of new biosimilar introduction)
-

EMA: European Medicines Agency, HCPs: healthcare professionals

As recognized by the interviewees, extensive efforts have been made by European regulators to provide clear information regarding biosimilars and the science behind the regulatory evaluation to the public (6),(24),(106),(27),(107),(108),(109). Investments in providing unbiased biosimilar information and conveying trust in the regulatory evaluation must be continued (recommendation 1) to further improve stakeholder understanding. Especially efforts to make this information more widely known to the target audience and to stimulate its active uptake are necessary (recommendation 10). To this end, biosimilar education should be included in both the curricula of future HCPs and in mandatory continuous learning programs of practicing HCPs. Further, solution-oriented information programs could be offered to HCPs to support them with biosimilar implementation on a local level. In the Netherlands, the Ministry of Health has subsidized such a biosimilar implementation program that provides tailor-made support to hospitals (110),(111).

The basic training of HCPs should also focus on strengthening HCPs' knowledge regarding biologics in general (recommendation 2), as some misconceptions regarding biosimilars may stem from a limited understanding about biologics. Further, HCP training should be enhanced by courses on drug development.

In addition to including biosimilar education in continuous learning programs, sharing real-world clinical data about biosimilar use and switching may be effective to increase trust and acceptance among practicing HCPs (recommendation 4). Stakeholders indicated being reassured with regard to the safety of switching by the considerable number of switch studies that have been conducted over the last few years (51),(112). Also, stakeholder experiences with biosimilar use should be actively disseminated via university or non-commercial based educational outreach, key opinion leaders and peer-to-peer communication to build trust (recommendation 5).

EMA has no official position on interchangeability as prescribing practices and advice to prescribers fall under the responsibility of Member States (6). Several Member States have released clear statements regarding interchangeability and switching (98). An official, harmonized European regulatory position regarding interchangeability is however believed needed to provide clear and one-voice guidance to stakeholders across Member States. This will require a coordinated initiative and action between Member States and the EMA (recommendation 3).

On a practical level, stakeholders should be supported with product horizon scanning and structured product overviews to ensure timely and efficient biosimilar implementation (recommendation 6). Guidance materials, such as switch protocols, should be provided to support hospitals and HCPs on a local level (recommendation 7). Existing materials (104),(105),(110),(111),(113) could serve as example and be tailored to the specific context.

The knowledge gap and misunderstanding among HCPs and patients has likely been amplified by the (in some cases intentional) dissemination of misinformation on biosimilars. Biosimilar misinformation exists under many forms, ranging from presenting factually incorrect information to negatively framing factually correct statements (45). As shown in this study, industry involvement (from both originator and biosimilar manufacturers) in biosimilar stakeholder related research is

common (about one third of biosimilar stakeholder studies were either industry sponsored or conducted by industry). At times, originator industry involvement may have resulted in a more cautious or misleading representation of results to discourage biosimilar use. Originator industry's reach may further trickle down via relations with or by actively involving opinion leaders and prescribers to amplify misconceptions and concerns, and as such creating uncertainty among their peers. In addition to actively providing accurate and unbiased information to stakeholders, biosimilar misinformation should be countered. Independent, governmental bodies can act as designated entities to monitor and correct biosimilar misinformation, and address stakeholder queries in this regard (recommendation 8). Further, position statements from medical societies regarding biosimilar use should be regularly updated to reflect the evolving knowledge and experience with biosimilars. Continuing to foster the collaboration and dialogue between regulatory authorities and medical stakeholders can support this (recommendation 9) (114).

Chapter 4 provides recommendations on how to improve biosimilar use in clinical practice and focusses on elements such as switching (115).

Whereas this study specifically aims to inform the European context, recommendations may be applicable on a wider scale, taking necessary tailoring to regional, cultural and policy specificities into account. Results from studies conducted in different regions of the world (Figure 3) show that the main challenges with biosimilar stakeholder understanding are generally similar across jurisdictions. As most interviewed participants represent a Western European perspective, some findings may not be reflective of the needs of regions where for example accessibility is more challenging and therefore of greater concern. Shared expert insights mainly related to the experience with and considerations for anti-Tumour Necrosis Factor products. Further, as most biological medicines are administered in or dispensed via the hospital, interview discussions predominately focussed on the hospital context and as such no public pharmacists were interviewed. Future research aimed at identifying specific learnings applicable to biosimilar use in ambulatory care would be useful, as different from the hospital setting - where decisions are generally driven by tenders and involve a drug formulary committee - here the decision to use biosimilars is generally based on individual prescriber perceptions. Tailoring of strategies to the treatment-setting (hospital vs ambulatory care, chronic vs shorter term treatment), product-type (more simple biologicals vs complex mAbs) and patient's needs is desirable.

Realising the structural, multi-stakeholder recommendations outlined in this study to improve biosimilar acceptance will require a pro-active approach and a combination of governmental actions and policy measures on both a national and pan-European level.

6. CONCLUSION

The present study highlighted that measures are needed to improve understanding and willingness to use biosimilars among stakeholders, in order to capture their societal and patient benefits. The actionable recommendations proposed in this article can guide policy making and multi-stakeholder initiatives to improve stakeholder understanding about biosimilars. Providing stakeholders with objective information about the biosimilar approval pathway, ensuring active information uptake, dispelling biosimilar misinformation, providing product horizon scanning and communicating biosimilar implementation experiences are among the suggested actions.

1. ABSTRACT

Background: The adoption of biosimilars has been hampered by a reluctance among healthcare professionals and patients to use them, despite the advantages they offer in terms of cost savings and patient access. Besides having gaps in knowledge about biosimilars and trust in them, healthcare professionals and patients have questions regarding switching and the nocebo effect when using biosimilars in clinical practice. In addition, a lack of motivation among these stakeholders may curb biosimilar use.

Objective: This study aims to provide recommendations on how to improve biosimilar use on a clinical and practical level based on insights obtained from healthcare professionals (physicians, hospital pharmacists, nurses), patients (or representatives), and regulators across Europe.

Methods: Semi-structured interviews were carried out with experts from five stakeholder groups including physicians, hospital pharmacists, nurses, regulators and patients/representatives across Europe. Interviews were transcribed ad verbatim and transcripts were analysed according to the thematic framework method.

Results: In total, 44 semi-structured interviews were carried out. Based on the insights and considerations of the experts interviewed, a number of recommendations towards improved biosimilar use were identified. Regarding switch implementation, support was voiced to (i) disseminate evidence of and experiences with (multiple) switching, (ii) provide a clear, one-voice regulatory guidance about interchangeability between biosimilars and their reference product, (iii) apply a multi-stakeholder implementation and communication protocol to guide switching in clinical practice, (iv) apply a pragmatic approach when taking switch decisions, and (v) avoid mandated switching, allowing stakeholder communication and alignment. When discussing approaches to increase stakeholder willingness to use biosimilars, it could be concluded that actions should be centred on (i) communicating the benefits provided by biosimilars and the introduction of market competition, (ii) increasing awareness among stakeholders about medicine prices and their societal responsibility to use medicines in a cost-effective manner, (iii) transparent reporting about the allocation of savings, (iv) sharing biosimilar usage data among hospitals and prescribers to allow peer-to-peer benchmarking and (v) applying a balanced combination of tangible and non-tangible incentives, that can be tailored to offset the time and effort threshold experienced by stakeholders when switching to a biosimilar.

Conclusions: This study proposes a number of implementable recommendations on a practical and strategic level that can support healthcare professionals and inform decision-makers regarding improved clinical use of biosimilars and stakeholder willingness to use biosimilars. The proposed solutions to fully realise the potential of biosimilars for healthcare systems and patients include: developing practical switch guidance; transparently informing regarding the gains from biosimilar use (and how these are allocated); and developing a combination of non-tangible and tangible incentives for involved stakeholders.

2. INTRODUCTION

With the expiration of patent protection and other exclusivity rights of an increasing number of original biological medicines (also called reference products), the interest in biosimilar development and commercialization has soared (10). Biosimilars can reduce treatment costs by introducing market competition, relieving increasing budgetary pressure on healthcare systems. In addition to having an impact on pharmaceutical spending, biosimilar market entry has also shown to increase patient access to these formerly expensive biologicals (10),(39).

Since the first biosimilar approval in Europe in 2006, more than 55 biosimilars have received marketing authorization in Europe (116). So far, biosimilar use has varied across member states and product classes, and, in some cases, has been limited (10),(117). The differences in uptake across European countries and regions may be explained partly by varying approaches in terms of biosimilar (market entry) policies (10),(118). Furthermore, despite the potential of biosimilars to positively impact expenditure and patient access, biosimilar adoption may be hampered by healthcare professional (HCP) and patient reluctance to use biosimilars due to a lack of trust and understanding about biosimilars (43),(57). In Chapter 3, we provided recommendations on how to improve HCP and patient biosimilar understanding in Europe (119).

In clinical practice, HCPs are faced with questions regarding the use of biosimilars. As biological medicines are often used in chronic treatment settings, biosimilar use may involve switching a patient from a reference product to a biosimilar. Since their introduction in Europe, and especially with the introduction of monoclonal antibody biosimilars, the safety of switching a patient between highly similar but non-identical products has been questioned (120), and made HCPs uncertain about biosimilar use (43). The efficacy, safety, and immunogenicity of switching has been evaluated in several randomized controlled and real-world studies. Overall, the vast majority of studies did not indicate any major safety, efficacy, or immunogenicity issues due to switching from a reference product to a biosimilar (51),(112). However, a number of real-world studies have reported a relatively high therapy discontinuation rate among patients after switching, which was mostly attributed to the occurrence of the nocebo effect (51). The nocebo effect is defined as a negative impact on the patient's perceived treatment outcome resulting from the patient's negative expectation about the (change in) therapy (121),(122). In order to support HCPs and patients with biosimilar use, guidance on switch implementation and mitigation of the nocebo effect is required.

In addition to the need for guidance regarding switch implementation, biosimilar use may be hampered by a lack of motivation among HCPs and patients, as they are unlikely to change their behaviour without an incentive to do so (43),(57). Although several European countries are testing gainsharing models, where savings generated from biosimilar competition are shared among stakeholders (118), the experience with these arrangements is still fairly new (123). Insights into stakeholder willingness to use biosimilars and design of appropriate incentives may help decision-makers to improve biosimilar policy making.

This article is the second part in a study on European multi-stakeholder insights on biosimilars and their use. It aims to provide recommendations, based on insights obtained from physicians, hospital pharmacists, nurses, patients (or representatives), and regulators across Europe, on how to improve biosimilar use, both clinically (e.g. how to implement a switch) and practically (e.g. how to organize stakeholder incentives).

3. METHODS

This study consisted of 44 semi-structured interviews (described in Chapter 3 and included in [Supplementary file 1](#)) with biosimilar experts across five stakeholder groups (physicians, hospital pharmacists, nurses, patients and regulators) in order to gain insights about how to improve the clinical and practical use of biosimilars in Europe.

4. RESULTS

In total, 44 interviews were carried out. Participant characteristics are shown in [Supplementary file 1](#).

4.1. TOWARDS IMPROVED BIOSIMILAR USE IN CLINICAL PRACTICE

Stakeholder challenges and proposals to improve biosimilar switch implementation are shown in Figure 5.

4.1.1 WHAT TO CONSIDER WHEN DECIDING TO SWITCH

Most physicians, pharmacists and nurses found that patients may be switched safely, and felt reassured by the available data regarding switching. Although some patients felt reassured by the available data, several remained hesitant about switching. Some patients requested studies over a longer timeframe to better evaluate the long-term effects of switching. Furthermore, it was mentioned that the willingness to switch could depend on the product's complexity. Several interviewees argued that the uncertainty surrounding switching mostly resulted from misinformation from pharmaceutical industry.

Several HCPs advocated for a pragmatic approach when deciding whether to switch or not. Initiating only bio-naïve patients with a biosimilar in certain cases, such as shorter treatment periods, was preferred:

“It would be a lot of hassle and time investment to switch a patient in the last four months of his treatment”.

Also several patients favoured only starting new patients with a biosimilar, even regardless of the treatment setting (acute vs chronic).

Forcing a switch was believed to be counterproductive, possibly resulting in distrust towards biosimilars. Across stakeholders, most interviewees felt that the physician should remain in control of treatment decisions and be able to decide whether or not to switch based on individual patient

circumstances. Providing patients with the option to return to the reference product was believed to reassure patients.

Several interviewees argued for continued monitoring and allowing product traceability when switching.

FIGURE 5. HOW TO OVERCOME STAKEHOLDER HURDLES RELATED TO SWITCHING IN CLINICAL PRACTICE

Stakeholder challenges	Stakeholder aligned recommendations
<ul style="list-style-type: none"> • Uncertainty about the safety of switching, partly due to misinformation and industry influence leading to a lack of stakeholder confidence 	<ul style="list-style-type: none"> • Educate about and disseminate clinical switch data • Share positive switch experiences
<ul style="list-style-type: none"> • Fear of losing control of treatment and traceability with (multiple) switching 	<ul style="list-style-type: none"> • Involve physicians in the switch decision and avoid mandated/top-down organized switching • Avoid frequent switches • Provide the opportunity for motivated exceptions • In some cases, it may be more pragmatic to only start bio-naïve patients with the biosimilar (e.g. short treatment duration)
<ul style="list-style-type: none"> • Guidance lacking or unclear about <ul style="list-style-type: none"> • Switch implementation strategies • Nocebo effect management • Switching and interchangeability from EU and national regulatory authorities 	<ul style="list-style-type: none"> • Develop and provide guidance about switching (protocol) <ul style="list-style-type: none"> • How to organize a structured switch approach • How to effectively communicate to the patient, circumventing a possible nocebo effect • Develop one-voice regulatory interchangeability and switching guidance <ul style="list-style-type: none"> • Increase collaboration between authorities and HCPs • Translate regulatory guidance into practical stakeholder info
<ul style="list-style-type: none"> • HCP time and effort threshold to switch a patient • A lack of motivation (what's in it for me?) 	<ul style="list-style-type: none"> • Design and implement a stakeholder incentive to lower threshold <ul style="list-style-type: none"> • Involve a specialized nurse to support the switch process
<ul style="list-style-type: none"> • Possible additional investment and time-to-market hurdle for developers to conduct additional switch studies beyond licensing requirements as response to stakeholder uncertainty 	<ul style="list-style-type: none"> • Create stakeholder confidence about biosimilars to reduce the stakeholder need for additional data generation

4.1.2 HOW TO IMPLEMENT A SWITCH AND MINIMIZE THE NOCEBO EFFECT

Almost all interviewees indicated that switching should follow a structured process that is agreed upon and carried out by an aligned HCP team. Several pharmacists explained that the switch should follow a stepwise approach. First, a discussion about the switch should be organized among the relevant stakeholders, allowing for shared decision-making. Second, the patient should be informed that a switch will be organized at the next administration. Some interviewees referred to the Dutch Association of Hospital Pharmacists (NVZA) toolbox (104) as a supporting tool to implement a structured switch. Careful planning was considered necessary:

“Building trust takes a lot of time and only one incident to dissolve again”.

Several interviewees contended that the HCP team must be well informed and educated in order to coherently communicate and transfer confidence to the patient. Informing patients with an aligned, unified message was deemed essential. Verbal and non-verbal signals from HCPs could also impact the patient’s perception:

“If the nurse looks unsure, and cannot respond satisfactorily to questions, it doesn’t build patient’s trust”.

Several interviewees believed that the physician's confidence is key to minimizing a nocebo effect, as *"the patient is confident when the physician is confident"*. Moreover, a specialized nurse may help to guide the switch process more smoothly.

Several interviewees advocated that patient concerns and possible nocebo effects need to be taken seriously:

"To patients, those effects feel very real"

"Switching patients from an active drug that induced remission of a previously very impactful disease is very sensitive".

One patient remarked that distinguishing between a nocebo-related and true side effect may prove challenging. Several interviewees mentioned that communication should be fully transparent, to build trust towards the patient.

Almost all interviewees mentioned that starting a dialogue with the patient and informing them about the switch, is important. Dedicating time to explain the change to the patient was thought to be a necessity by several nurses, physicians and regulators. Although interviewees generally agreed that patients should be informed about the switch, disagreement existed about exactly how to involve them. Most interviewees believed that patients should not be involved in the decision-making. Others argued that patients should be involved to reduce reluctance, avoid nocebo effects and build trust in the HCPs.

No consensus existed over the level of detail that patients should receive about biosimilar concepts. One nurse argued:

"If the HCP tells the patient that the medicine is good, it is not very interesting for the patient if it is an original drug or a biosimilar".

Several nurses advocated that patient communication should not be overcomplicated:

"Now we said 'Well, we don't have the original product, so we treat everybody with the biosimilar', and I haven't heard any problems".

One nurse questioned the need for informing patients about biosimilars all together:

"It is an ethical problem. Must you inform patients when in fact there is no difference for them as far as you expect?"

Another interviewee mentioned that no questions were asked when they switched to filgrastim:

"Everybody called it another type of growth factor. As it was communicated that the product had all the same side effects and the same precautions were needed, there was no big deal about it".

Several interviewees considered that striking a balance between the amount and type of information to provide to patients is challenging:

“A patient might be triggered to think that there is something wrong if a lot of emphasis is put on the switch”.

Most interviewees mentioned that patients need to be informed as to why a switch is being made and about its positive impact. Some interviewees counter-argued that not all patients are interested in the cost benefit. Furthermore, it was argued that it should be made clear to the patient that less expensive does not equal inferior when discussing the financial benefit of the switch.

Generally, it was believed that information should be centred on explaining that the biosimilar is equally safe and effective as the reference product and that patients may expect the same outcomes. Reassurance regarding safety was considered important by nurses and patients. Some regulators claimed that the nocebo effect may be minimized if HCPs and patients were informed that biosimilars may only be authorized if their efficacy and safety profile is shown to be equal to the reference product.

Several interviewees across the groups advised that information should include the practical implications for the patient: *“what does the switch mean for the patient”*. It was mentioned that patients should be provided with a contact in case they would have questions or adverse effects. Other patient-communication aspects that were deemed important were: to inform patients timeously, provide different opportunities to discuss the switch, and follow up after the switch. Some patients mentioned that additional follow-ups could serve for monitoring of side effects.

It was stated that patient information should be understandable, readable, and concise. Layman's terms (such as those used in the patient biosimilar Question & Answer brochure from the European Commission (EC) (106) or the Dutch Medicines Evaluation Board (MEB) biosimilar booklet (124), as mentioned as example repeatedly) should be used and materials should be available in the patient's own language. Providing written information that patients can read and re-read was considered important. Several interviewees argued that there is no one-size-fits-all approach for good patient communication. Tailoring the communication strategy and level of detail to the needs and wishes of the patient is important.

Several interviewees mentioned that special consideration should be given to patients that self-administer their therapy, as they may need to receive training about the injection device.

One physician argued that patient communication should focus on the medicine's international non-proprietary name, as this requires a less active mind set-shift among patients when switching as physicians are able to maintain their treatment terminology.

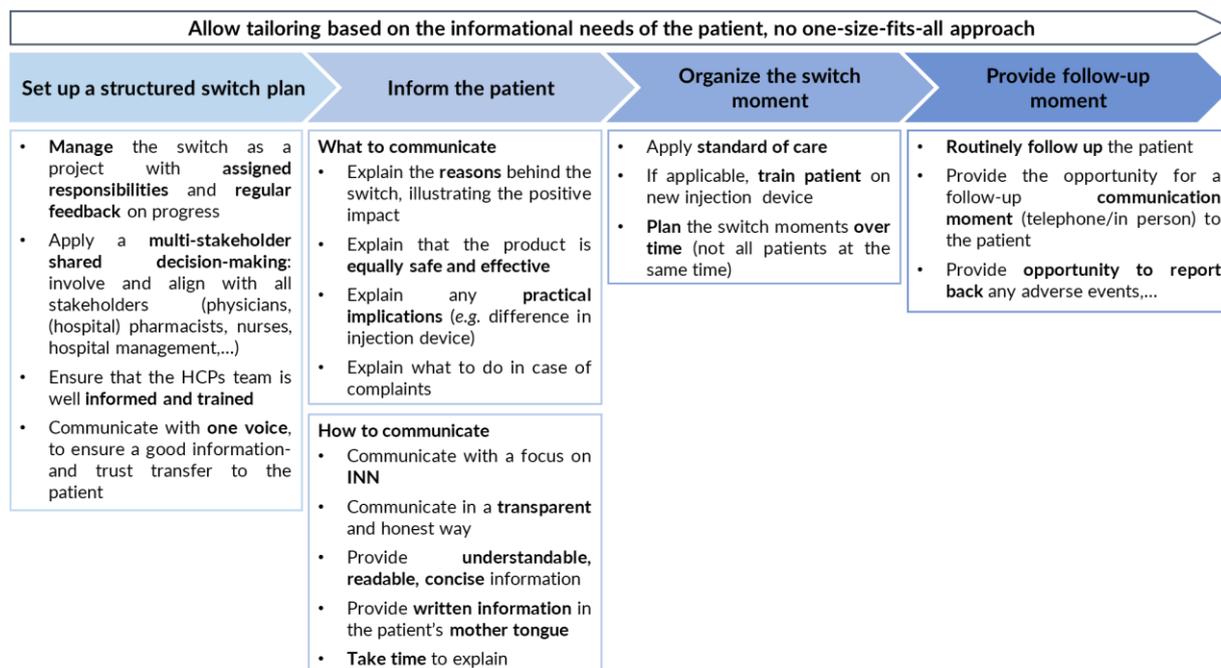
Several HCPs and one patient mentioned that the patient's treatment outcome expectation should be managed, as response to treatment may naturally wane over time for certain types of medicines. Patient trust in the HCP may be impacted if this were to coincide with the timing of the switch:

“It would only take one patient treated with infliximab that reached tolerance at the same time as the switch to undermine our complete program”.

Furthermore, it was mentioned that objectively assessing any changes pre- and post-switch by monitoring specific disease parameters for certain product types and patients, may help to reassure patients and HCPs throughout the switch process.

In summary, the general opinion was that a switch should be set up as a multi-stakeholder project, with clear decision lines, education to reach a unified approach, and a well-planned implementation and follow-up procedure. Figure 6 provides a structured overview of key steps regarding switch management.

FIGURE 6. KEY ELEMENTS ON HOW TO ORGANIZE A SWITCH & AVOID NOCEBO EFFECT



HCPs: healthcare professionals, INN: international non-proprietary name

4.1.3 MULTIPLE SWITCHING, SWITCHING BETWEEN BIOSIMILARS OF THE SAME REFERENCE PRODUCT, AND SWITCHING BETWEEN ADMINISTRATION ROUTES

Several HCPs and patients had reservations about multiple switching and indicated that constant changes should be avoided. It was argued that due to a lack of experience with this, more information and data was needed. Some interviewees mentioned that data on multiple switches is increasingly being generated. Several physicians contended that multiple switching discussions are misused to “bring noise to the discussion”, as it suggests that the physician could lose control over the process. Overall, most physicians and nurses maintained that frequent switches should be avoided, arguing that this could lead to traceability issues and confusion among the HCPs and patients involved. It was mentioned that agreements with the payer or hospital on multiple switching should be made:

“Now we decide that we can switch everyone, but that we cannot switch again within the first years. This is not based on evidence, it’s based on distrust, thinking that there are long-term effects. Over the next years, a discussion about multiple switching is needed”.

Questions rose about what would be considered an acceptable interval between switches. Furthermore, several interviewees argued that a pragmatic approach should be taken to avoid multiple switching of patients under chronic treatment: *“Patients cannot be switched all the time”*. Also, some reasoned that the cost savings of a second switch could be limited.

Switching between biosimilars of the same reference product was considered acceptable by most physicians and pharmacists:

“For me it is the same as switching between reference product and biosimilar. You have again a high level of similarity”.

It was not deemed necessary to provide confirmatory data in this regard. Sharing experiences and registries of biosimilar-to-biosimilar switches was considered informative for stakeholders. Some regulators doubted that developers would be interested in investing in biosimilar-to-biosimilar switch studies. Most nurses were hesitant towards biosimilar-to-biosimilar switching, due to a lack of practical experience with this.

It was argued that switching between different administration routes (i.e. from subcutaneous (SC) to intravenous (IV) products or vice versa) occurred often in clinical practice and was considered to be clinically unproblematic by physicians. It was mentioned that changes at an organizational and logistical level were required. In addition to practical considerations, it was suggested that the patient’s preference should be considered, as the change could have an impact on the patient’s life (e.g. home vs hospital administration, or the level of contact with HCPs). In contrast, one pharmacist argued that it would be fair to ask patients to switch back to IV if it would allow more patients to be treated. Maintaining SC patients on their current treatment, while starting naïve patients with the lower priced IV formulation was preferred by most interviewees. Furthermore, depending on the hospital’s organisation, it was argued that any discounts provided by biosimilar competition for IV products need to offset the possible increase in day-clinic costs.

4.1.4 STAKEHOLDER CONSIDERATIONS REGARDING SUBSTITUTION FOR BIOLOGICALS

Overall, most physicians and pharmacists were not against pharmacist substitution *per se*, provided that the physician is informed about the change. The importance for physicians to remain in control over the treatment was stressed. Several patients also emphasized that the patient should be informed about any change. Automatic substitution (i.e. change by the pharmacist without informing the physician) was strongly opposed by physicians, as this would lead to a loss of control and possibly to multiple subsequent transitions. Most nurses did not have objections to substitution as they deemed this to be the decision and responsibility of the physician and pharmacist:

“If we agree that biosimilars are as safe and effective as the originator, and we can treat more people and reduce the cost for the healthcare system, why shouldn’t we do automatic substitution?”

Overall, several interviewees considered that substitution practices for biologicals would likely evolve over time and perhaps be introduced in the future. Most interviewees emphasized that it

would be premature to introduce substitution for (monoclonal antibody (mAb)) biologicals, as the level of trust in biosimilars is still considered to be too fragile:

“Everyone is still learning about biosimilars”.

Enforcing or prematurely introducing substitution could negatively affect biosimilar acceptance. Most pharmacists compared the substitution discussions for biologicals to those at the time of generic market entry. Similarly, the debate was considered to stem from fears that the patient will not respond as well and that there would be problems tracking which product the patient receives. Another pharmacist argued that as the originator also changes over time due to manufacturing changes, the patient is already exposed to different versions over time.

In addition to psychological considerations, several regulators and pharmacists explained that organizational and policy barriers exist:

“Substitution could be done, but the conditions need to be appropriate”.

A good information system between pharmacists and physicians needs to be in place to allow pharmacist-physician communication. Furthermore, some pharmacists mentioned that clear mandate needs to be given by the national authorities is required. An adequate system for reporting adverse reactions was also deemed essential by several interviewees. Pharmacists should also be trained to educate patients about the (change in the) injection device. Alternatively, specialized pharmacies could be nominated to carry out substitution.

Furthermore, it was discussed that differentiation between therapeutic areas and product types could be applied (proportionality of risk) and physicians should be allowed to veto against a substitution if motivated. For example, where product effects are known to possibly wane over time, as tolerance development at the time of substitution may impact the patient-HCP relationship.

Stakeholder considerations regarding substitution for biologicals are shown in Figure 7.

FIGURE 7. STAKEHOLDER CONSIDERATIONS ABOUT (AUTOMATIC) SUBSTITUTION

Stakeholder considerations about current context	Outlook on possible future substitution
<ul style="list-style-type: none"> • Emotional barriers <ul style="list-style-type: none"> • More trust and experience with biosimilars may need to be gained by stakeholders before introduction of substitution • Physicians fear to lose control over treatment • Current landscape considered too fragile • Practical barriers <ul style="list-style-type: none"> • Pharmacists and systems (e.g. physician-pharmacist communication systems outside of the hospitals) may be insufficiently prepared • In most European countries, no mandate given to pharmacists to substitute biologicals 	<ul style="list-style-type: none"> • Could be considered in future years when practical and emotional barriers are addressed • Elements on how to organize: <ul style="list-style-type: none"> • Always inform the physician: no automatic substitution • Allow motivated exceptions for specific products or patients • Clear mandate from the National Competent Authority • Practical communication system between physician and pharmacist • Reliable system for reporting of adverse events • Patient counseling by pharmacist in case of change in injection device

4.2 TOWARDS IMPROVED STAKEHOLDER WILLINGNESS TO USE BIOSIMILARS – BIOSIMILAR VALUE PROPOSITION AND STAKEHOLDER INCENTIVES

Stakeholder specific considerations are presented in Figure 8 and Figure 9.

4.2.1 REASONS TO USE BIOSIMILARS AND POSSIBLE DIFFERENTIATORS BETWEEN PRODUCTS

Generally, the lower price of biosimilars was recognized as the most important benefit. Some viewed it as the only benefit. Several interviewees acknowledged that due to the introduction of market competition, savings could also be derived from reduced reference product prices. Some interviewees argued that biosimilars should not be favoured *per se* over the reference product, as the price of the reference product will generally also decrease.

Often, interviewees mentioned that lower treatment prices could translate to improved patient outcomes, by enabling a larger volume of patients to be treated with the same budget, or by treating patients earlier in the treatment pathway as it becomes more cost-effective at lower prices to do so.

Some interviewees reasoned that biosimilar savings could create budgetary headroom for the reimbursement of innovative medicines. Some mentioned increased physician's freedom to prescribe new therapies as benefit.

Some interviewees argued that the reasons to use biosimilars will vary regionally. In regions with good access to biological therapies, savings derived from biosimilar use are expected to be reinvested in the reimbursement of innovative medicines, whereas in regions with limited access, biosimilar entry could translate to increased patient access.

Several physicians and regulators indicated that biosimilars could also improve delivery of care, including improvements in the administration device or by providing administration routes that do not (yet) exist with the reference product. Furthermore, packaging differences were mentioned to potentially impact patient co-payment positively (e.g. introducing more units per package, while the out-of-pocket cost remains the same). It was mentioned that this differentiation could stimulate originator companies to also introduce extra services. One patient mentioned that the availability of different products could positively impact the patient's product choice.

Some pharmacists mentioned that the availability of biosimilars (i.e. presence of different suppliers of the product) could also be beneficial to secure supply in case of shortages.

Several interviewees remarked that more effort is required to ensure that the market becomes or remains sufficiently attractive, ensuring continued investment in development and market presence of already approved biosimilars. A few interviewees mentioned that decreased interest in the biosimilar segment and subsequent competition may lead to shortages:

"If prices are driven down too much, some players will go out of the market, certainly in smaller markets, putting such markets at risk of drug shortages".

Most interviewees identified price as the main, or sole, differentiator between the reference product and its biosimilar(s), as they perform equally in terms of efficacy and safety. Some interviewees considered factors beyond price when choosing between products. These included supply reliability, value-added services such as information support, and the delivery device and injection material for SC products. Some nurses argued that the patient friendliness of the product and its

ease of use should be assessed together with the patient. The presentation of different concentrations was mentioned by a few pharmacists as another possible differentiator.

It was argued that additional services should be considered as an extra bonus but do not trump price differences. Some interviewees questioned the value of some differentiators such as the citrate-free formulation for some adalimumab products:

“How much weight do we want to award to these, sometimes, low impact differences?”

Several pharmacists advocated for transparent award criteria to assess differentiators.

FIGURE 8. WHAT ARE THE ADVANTAGES OFFERED BY BIOSIMILARS?

Depending on the region/country, the value offered by biosimilars (balance between benefits) may be different			
Towards savings	Towards the patient/care		Towards innovation
Lowered treatment costs <ul style="list-style-type: none"> Lower priced biosimilar Price competition upon biosimilar market entry <ul style="list-style-type: none"> Lower priced reference product Lowered prices in broader therapeutic class* 	Increased patient access to biological treatment <ul style="list-style-type: none"> More patients treated within the same budget Earlier treatment of patients with a biological due to improved cost-effectiveness (advancing therapy to an earlier treatment-line) 	Improved delivery of care <ul style="list-style-type: none"> Support from specialized nurse Differentiation and improvements in injection device Value-added services (e.g. disease programs to enhance patient adherence)** 	Reinvestment of savings in reimbursement of innovative medicines Innovation in biologicals development (product differentiation) <ul style="list-style-type: none"> New administration routes New indications New formulations*** Next-generation biologics***
	Lowered patient co-payment	Plurality in suppliers, beneficial in case of shortages	

Asterisks indicate possible benefits from biosimilars mentioned in the literature that were not mentioned during the interviews. *QuintilesIMS, **Simoens and Cheung, ***Dutta et al. (55), (125),(126)

4.2.2 MOTIVATING STAKEHOLDERS TO USE BIOSIMILARS

4.2.2.1 CREATING AWARENESS ABOUT MEDICINE PRICES AND CALLING UPON STAKEHOLDERS SOCIETAL RESPONSIBILITY

Some interviewees expressed the need for increased awareness of medicine prices among HCPs and the public. Several regulators and physicians argued that it is the duty of the physician to prescribe and that of the society to utilize medicines in a cost-effective manner:

“As a society, we have the obligation to look at the economic aspects once the product is considered equal”.

Some physicians and regulators argued that decisions should be made from a common good perspective (“what is best for society”) and the stakeholders involved should not expect compensation. As a Danish nurse mentioned:

“It is money for the Danish people, it is not for our hospital to gain money. It is not the Danish way to gain something. Savings should go towards the society”.

Most pharmacists agreed as they considered biosimilar implementation to be part of the job. Some physicians mentioned that discounts should be sufficiently substantial to offset the effort invested

in biosimilar implementation. Some argued that the government should take a more active role in guiding which product(s) to use.

4.2.2.2 RAISING AWARENESS ABOUT BIOSIMILAR BENEFITS AND REPORTING USAGE DATA

Information about benefits derived from biosimilar use, often deemed lacking today, was considered an important motivational factor for biosimilar use by several physicians and pharmacists. One regulator mentioned that a powerful incentive for patients to use biosimilars would be increased patient access. Some nurses asserted that such arguments are not always convincing for patients:

“You should treat patients at patient level and not tell them, ‘You create access for many other patients worldwide’. It’s not convincing”.

Several patients and nurses explained that it is difficult to persuade patients who are satisfied with their current treatment. In contrast, one physician indicated that a few patients asked to be treated with the biosimilar. Earlier treatment access when using a biosimilar might be a more convincing incentive, as it could lead to a personal patient benefit. Overall, several interviewees across groups considered that the benefits derived from biosimilar use should be communicated more clearly.

“As sustainability of healthcare is for all of us, we should try to stimulate education about the impact of biosimilars as much as possible”.

Several patients mentioned that there is no tangible incentive for patients to use biosimilars when treatment is fully reimbursed. In settings where these medicines are only partly reimbursed, the willingness to change may be higher. Furthermore, with regard to motivating patients, one Dutch interviewee mentioned that lowering the patient’s “own risk” insurance payment when accepting to switch has been effective in the Netherlands.

Apart from improving awareness about biosimilar benefits, some physicians believed another stimulus for biosimilar use would be to report biosimilar usage data transparently among prescribers and hospitals, as this provides useful insights into colleague prescriber behaviour and, subsequently, gives confidence to less experienced stakeholders.

4.2.2.3 ALLOCATION OF SAVINGS – A BALANCE BETWEEN SOCIETAL AND STAKEHOLDER BENEFITS AND A NEED FOR TRANSPARENCY

Some HCPs and patients felt that the savings should (partially) remain at the departmental level or therapeutic area that helped to realize the savings. Others were indifferent to the allocation level, as long as savings were reinvested in healthcare. Some interviewees expressed concerns that savings would be reinvested towards structural or practical improvements (e.g. hospital infrastructure) and not towards patient care *per se*. Some argued that the government should decide on how to reallocate savings. Overall, interviewees asked for transparency regarding the savings allocation.

4.2.2.4 PROVIDING TANGIBLE INCENTIVES WHEN SWITCHING – APPLYING A GAINSHARING MODEL

Most physicians and nurses and some regulators considered that a tangible incentive would be appropriate to compensate stakeholders when biosimilar use requires significant HCP effort in terms of planning and time, *i.e.* when switching. Several regulators and HCPs considered that physicians lack motivation to invest energy and time in a switch if the impact is solely on an overarching, more abstract, financial level. Furthermore, it was argued that the incentive should be proportional to the effort (*e.g.* a larger incentive for switching a SC product, as this may require more time due to injection device training). Direct financial benefits on an individual level were deemed inappropriate by most. Most interviewees considered that allocating a part of the realized savings towards improving patient care, such as financial support for the hospital ward or hiring new staff (*i.e.* gainsharing) would be an adequate and acceptable stimulus. An additional nurse may help balance the extra workload and enable a more active follow-up of the switch. Reinvesting some savings to increase monitoring to reassure patients, was mentioned as another gainsharing example. Some physicians mentioned that publication opportunities may also be a motivator.

4.2.2.5 CONSIDERATIONS FOR INCENTIVE DESIGN IN HOSPITAL VS AMBULATORY CARE SETTING

Several physicians highlighted that defining incentives for biosimilar implementation in ambulatory care, particularly in countries where these are not part of the hospital budget, can be challenging. Some interviewees deemed that in the hospital context, a tender would be a satisfactory lever, making the need for accompanying incentives less pressing. As some pharmacists explained, introducing a negative incentive by lowering the product reimbursement level (*e.g.* 80% of list price) by payers (such as, in Belgium) motivated hospitals to organize competitive tenders, ensuring product acquisition costs below the lowered reimbursement limit.

FIGURE 9. HOW TO MOTIVATE STAKEHOLDERS: NON-TANGIBLE & TANGIBLE INCENTIVES

Non-tangible incentives	Tangible incentives/gainsharing
<ul style="list-style-type: none"> • Creating HCP awareness about treatment costs • Calling on/enforcing the societal responsibility to prescribe in a cost-effective manner <ul style="list-style-type: none"> • Stimulate the “what is best for society” perspective • Reinvest savings derived from biosimilar use (predominantly) in the healthcare system • Correct application and transparent organization of tender procedures • Reporting transparently about the gains from biosimilar introduction <ul style="list-style-type: none"> • Visualize and report about benefits • Communicate about allocation of savings • Reporting usage data to allow peer-to-peer benchmarking and monitoring of purchasing/prescribing <ul style="list-style-type: none"> • Among prescribers (prescribing behaviour) • Among hospitals (purchasing behaviour) • Can simultaneously instil HCP trust 	<ul style="list-style-type: none"> • Providing a tangible incentive to compensate for switch effort <ul style="list-style-type: none"> • Incentive towards improving care rather than a personal financial benefit <ul style="list-style-type: none"> • In terms of extra HCP staff • Financial benefit for hospital unit • Tailoring of incentive proportional to required effort <ul style="list-style-type: none"> • Effort to switch SC products may be larger due to possible differences in injection device (training of patients) • Threshold may be higher for products dispensed outside the hospital (less structural support and no tender driving the decision)

HPC: healthcare professional, SC: subcutaneous

5. DISCUSSION AND RECOMMENDATIONS

This article is the second part in a study on European multi-stakeholder learnings about biosimilars. The considerations of various stakeholders regarding how to implement biosimilar switching and design incentives to stimulate biosimilar use are provided in this article and translated into practical, overarching, and strategic recommendations (as shown in Table I). The results of this study may support HCPs and policy makers when planning to improve biosimilar use in healthcare systems. We propose that actions be centred on the 11 key recommendations outlined in Table 4. It is important to recognize that most expert-considerations shared are related to the experience with anti-Tumour Necrosis Factor products. Tailoring of strategies to the treatment setting (hospital vs ambulatory care, chronic vs shorter-term treatment), product type (more simple biologicals vs more complex mAbs), and patients' needs is desirable. The other strengths and limitations of this study are described in the Discussion section of Chapter 3.

In line with the considerable number of switch studies that have been conducted over the last few years (51),(112), switching from a reference product to a biosimilar was largely considered to be a part of clinical care among the expert-interviewees. Stakeholders, however, indicated a need for guidance regarding multiple switching, as regulatory guidance predominately focusses on a single switch from a reference product to a biosimilar, and a harmonized regulatory position about interchangeability across Europe is lacking (6),(51),(112). A clear European-wide one-voice regulatory position about interchangeability and switching is required to support stakeholders who are faced with switch decisions in Europe. Such a European position will require an active request by and collaboration between the national regulatory agencies, the EC and the EMA, and could be taken up by the Heads of the Medicines Agencies. Also, data regarding multiple switching between reference products and biosimilars, and between biosimilars of the same reference product, have been reported (127),(128),(129),(130),(131),(132),(133) and are likely to accumulate with increasing experience, which can further support stakeholders.

TABLE 4. MULTI-STAKEHOLDER RECOMMENDATIONS: KEY POINTS FOR DECISION MAKERS AND HCPS IN EUROPE

Practical recommendations addressing shorter term HCP needs regarding switching, supporting HCP biosimilar use
<ol style="list-style-type: none"> 1. Communication about results from RCTs, real-world studies and clinical experiences regarding (multiple) switching 2. Provision of a clear, one-voice EU overarching regulatory position regarding the interchangeability of biosimilars 3. Development of a multi-stakeholder implementation and communication protocol to guide switching in clinical practice <ol style="list-style-type: none"> a. Guidance development on how to structurally organize a switch with involved stakeholders b. Guidance development on communication strategies towards patients, limiting bias and mitigating a possible nocebo effect

- c. Possibility to allow tailoring of strategies to the context of the treatment setting, product type and individual patient needs

(more information provided in Figure 6)

4. Development and application of a balanced combination of non-tangible and tangible incentives for physicians and other stakeholders to use biosimilars

- a. Proportional tailoring of incentives to off-set the stakeholder effort invested in biosimilar implementation (i.e. effort may be higher when switching of subcutaneous products due to possible differences in injection device)
- b. Application of a gainsharing agreement, reinvesting a part of the savings towards improving care and lowering the time and effort threshold associated with a switch by for example hiring additional staff

Overarching recommendations regarding switch implementation

- 5. **Applying a pragmatic switch approach, considering the potential gains vs longevity of treatment.**
- 6. **Avoiding top-down organized switching, allowing and organizing stakeholder involvement, communication and alignment.**

Strategic recommendations towards long-term sustainable competition of biosimilars

- 7. **Raising awareness about medicine prices and stakeholders' societal responsibility to use and prescribe medicines in a cost-effective manner.**
- 8. **Public and active communication about savings/advantages** resulting from biosimilar use
- 9. **Sharing of biosimilar uptake and prescribing data** among hospitals and prescribers to allow **peer-to-peer benchmarking.**
- 10. **Transparent reporting about the allocation of savings resulting from biosimilar use**
- 11. **Development of policies with a long-term vision, beyond realizing short-term savings and with a focus towards creating a sustainable market with presence and competition of multiple suppliers**

HCPs: healthcare professionals, RCTs: randomized controlled trials

There was strong consensus for the adoption of a structured and collaborative approach to implementing a switch. Furthermore, several switch experiences in clinical practice showed the benefits of using a managed switch program in terms of cost savings while maintaining similar patient-reported outcomes (134),(135). Opinions on how to involve the patient varied and finding an appropriate balance for sharing information was deemed challenging. Overall, the possibility to tailor communication to the individual patient was considered important.

As also mentioned in previous publications (73),(74),(75),(76), this study found that stakeholders are concerned about mandated switching, as this may result in worsened patient perceived treatment outcomes due to a possible nocebo effect. Involving and aligning HCPs and patients when making switch decisions can positively impact acceptance and limit nocebo effects. Other strategies to mitigate a possible nocebo effect include delivering balanced information, focussing on treatment equality, explaining the reasons and the benefits of a switch, and transferring the physician's trust

in the biosimilar to the patient. As discussed in Chapter 3, disseminating switch experiences may translate into increased HCP and patient trust (119).

Several strategies to increase stakeholder willingness to use biosimilars emerged during the interviews. Although there were divergent opinions on how to design incentives (which were also culturally influenced), incentives to offset the work associated with a switch were generally deemed necessary. A combination of non-tangible incentives (such as, calling upon societal responsibility and transparent reporting about allocation) and tangible incentives (such as, extra staff) could be applied and tailored to the level of effort required in the local societal context. Gain-sharing agreements emerged as the preferred way to motivate stakeholders, as savings could partially serve to improve local clinical care. Visualizing and communicating clearly and transparently about biosimilar winnings and how these savings are allocated could improve stakeholder motivation.

As the learnings from this study primarily apply to the hospital context, future research could focus on switch and incentive approaches tailored to the ambulatory care setting.

6. CONCLUSION

This study proposes practical and strategic measures to improve biosimilar implementation practices and increase stakeholder willingness to use biosimilars, based upon the insights of different stakeholder groups (patients, physicians, pharmacists, nurses and regulators). Applying a structured switch and communication strategy, implementing a combination of non-tangible and tangible stakeholder incentives and actively providing information regarding the gains from biosimilar use are among the suggested solutions. The recommendations of this study can support HCPs with biosimilar use and decision-makers with designing biosimilar policies and stakeholder incentives.

1. ABSTRACT

Background: With the approval of biosimilars for subcutaneously administered products, such as adalimumab, etanercept and insulin, biosimilars become increasingly available in ambulatory care. Little is known about the knowledge and attitudes of healthcare providers who are in charge of dispensing and prescribing biosimilars in this context.

Objective: This study aims to assess the knowledge and perception about biosimilars amongst community pharmacists and physicians.

Methods: Belgian community pharmacists (n=177) and physicians (n=30) were surveyed on their knowledge, experience with dispensing/prescribing biologicals including biosimilars, perception regarding interchangeability, switching and substitution and informational and educational needs. Descriptive and statistical analyses were performed.

Results: Only 32% of community pharmacists and 52% of physicians had yet dispensed/prescribed a biosimilar. Approximately 35% of community pharmacists felt insufficiently trained to counsel patients with biosimilar therapy, which was significantly higher compared to their self-assessed competence to counsel patients with biological therapy in general ($p = 0,023$). Community pharmacists experienced questions about similarity between reference products and biosimilars (47%) and interchangeability (42%). Over 40% of physicians found patient uncertainty about efficacy and safety challenging when prescribing biosimilars. A similar proportion of physicians would only prescribe a biosimilar in indications for which the biosimilar has been tested clinically. The majority of pharmacists (58%) was in favour of substitution of biologicals, on the condition that the prescriber would be contacted. Also over 40% of physicians was open to this approach in case of substitution. Educational support, budget for additional staff and transparency about savings were considered suitable stimuli to incentivize biosimilar use. The need for information about biologicals including biosimilars was nearly unanimous among community pharmacists. Also 67% of physicians requested more information. Both community pharmacists and physicians preferred to be informed by their respective professional associations.

Conclusions: This study showed a substantial need for targeted educational measures to increase the knowledge and confidence about both biological medicines in general and biosimilars in particular among Belgian community pharmacists and physicians. The results may inform educational and policy measures to stimulate biosimilar use in ambulatory care.

2. INTRODUCTION

Biological medicines have substantially altered the treatment pathway of several chronic and life-threatening diseases, positively affecting the life of many patients. The use and success of biological medicines comes however at a considerable cost because of their generally high prices. The arrival of expensive innovative medicines increasingly challenges healthcare systems to find avenues to optimize spending while ensuring access to these therapies for their patients (136).

Following the expiry of exclusivity of a reference biological medicine, biosimilar alternatives can become available and introduce price competition in the market. As defined by the European Medicines Agency (EMA), a biosimilar is “*a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)*” (14). Competition created by biosimilar entry has shown to result in decreased treatment costs and in some cases to facilitate patient access to biological therapies (117). Moreover, savings derived from biosimilar competition may contribute to the financing of expensive innovative therapies (126).

In 2005, Europe took the lead in developing a tailored legal and regulatory pathway for the evaluation and approval of biosimilars (14). Fifteen years after the first biosimilar approval in Europe, over 60 biosimilars are approved for 16 distinct biological products across multiple therapeutic areas, including chronic inflammatory diseases and oncology (116).

Biosimilar development follows a different drug development paradigm compared to that of a new medicinal product. For a biosimilar, developers do not need to demonstrate *de novo* efficacy or safety, as these properties are well known and established for the reference product. Instead, biosimilars need to demonstrate high similarity in efficacy, safety and quality in relation to the reference product. Because of the inherent variability of biological medicines and the complexity of manufacturing, small differences may be present between a reference product and a biosimilar (which *nota bene* may also be the case between batches of the same biological). Biosimilars are thus highly similar but not identical versions of the reference product. In biosimilar development, it needs to be demonstrated that these small differences are not meaningful in terms of clinical outcomes. For this, regulators evaluate the totality of evidence gathered to demonstrate biosimilarity which finds its basis in an extensive physicochemical and biological characterization and comparison with the reference product. Biosimilar approval may rely in part on the knowledge of the reference product and is predominately based on comparative analytical and functional data, since this is a much more sensitive approach in detecting potential differences than a clinical study. As such, generally fewer clinical studies need to be carried out for a biosimilar than for the reference product (6),(19),(109).

After the evaluation and approval at European level, biosimilar market entry and implementation is organized by the individual European Member States. Biosimilar uptake varies among Member States, which may be partly explained by differing biosimilar market entry policies. In Belgium, 31 biosimilar products are reimbursed and available on the market (137), but biosimilar uptake is generally low compared to other European Union countries (10),(117),(118),(138),(139).

As biosimilars represent a different development and approval paradigm, their acceptance by healthcare providers, patients and policy makers may require a change in mind-set (109). Multiple studies have assessed the awareness and knowledge about biosimilars among healthcare providers and patients, identifying generally low to moderate levels of knowledge and trust in biosimilars and related concepts (119). Whereas the knowledge and perceptions of healthcare providers and patients have been assessed in different regions of the world and European countries (119),(140), research with Belgian healthcare providers and patients is rather limited. Early Belgian policy oriented research identified a lack of awareness, a lack of information and concerns about interchangeability among healthcare providers as factors limiting biosimilar adoption in Belgium (43),(141). In 2017, the results of a survey among 41 Belgian rheumatologists revealed that they have doubts about the safety and efficacy of biosimilars and have concerns about their interchangeability with its reference product (66). Interchangeable use refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean exchanging a reference product with a biosimilar (or *vice versa*) or replacing one biosimilar with another. When the prescriber decides to exchange, such practice is termed a “transition” or “switch”. If done at pharmacy level without consulting the prescriber, such an exchange is termed “(automatic) substitution” (6). While switching biological reference products with their biosimilar or *vice versa* has become common practice, substitution of biologicals is largely not allowed or covered by a legal framework in Europe (142). Also in Belgium, substitution of biologicals is not allowed (143).

Over previous years, several initiatives with the aim to increase biosimilar use have been implemented in Belgium. Policy actions include the establishment of a biosimilar usage target in hospitals, biosimilar use monitoring, and the stimulation of tender procedures. In 2018, a media campaign was launched to provide information on biosimilars to healthcare providers, patients and by extent the general public (138),(144),(145),(146). This joint initiative by the Belgian competent authority and the reimbursement agency included the launch of a website with biosimilar information, patient leaflets and radio spots (145),(147). Most of the above-mentioned measures focused on biosimilar use in hospitals, as the first available biosimilars are mainly used in the hospital in- or outpatient setting. Despite the multitude of policy initiatives taken, the use of biosimilars in Belgium continues to lag behind. Especially market shares of biosimilars dispensed in the community pharmacy are low (139),(11). With the approval of biosimilars for high-value subcutaneously administered products (such as adalimumab and etanercept), biosimilars become increasingly available outside of the hospital setting in Belgium.

The arrival of biosimilars in ambulatory care comes with a distinct set of additional challenges compared to biosimilar use in the hospital context. The relative newness of biosimilars in this setting, the limited difference in list price between reference products and biosimilars, the lack of incentives for involved healthcare providers and patients to use biosimilars, possible differences in injection device, and the lack of an organized mechanism that may drive biosimilar use via tenders and facilitate switch management, as present in hospitals, may further complicate biosimilar use. Table 5 shows an overview of available biosimilars in ambulatory care in Belgium.

Considering that biosimilars are increasingly available for a new group of Belgian healthcare providers, especially community pharmacists and general practitioners, and the criticality of their role in the use of biosimilars, this study aims to investigate their knowledge and perception regarding biological medicines including biosimilars.

TABLE 5. OVERVIEW OF AVAILABLE BIOSIMILARS IN AMBULATORY CARE IN BELGIUM

INN	Product type	Net 2019 expenditure	Reference product	Biosimilar	Reimbursement date biosimilar ⁺
Adalimumab*	TNF alfa inhibitor	95.207.248	Humira®	Amgevita®	1/10/2018
				Hulio®	1/01/2019
				Hyrimoz®	1/01/2019
				Idacio®	1/10/2019
				Imraldi®	1/10/2019
Enoxaparin*	LMWH	22.446.229	Clexane®	Ghemaxan®	1/01/2021
Etanercept*	TNF alfa inhibitor	45.197.777	Enbrel®	Benepali®	1/09/2016
				Erelzi®	1/07/2019
				Nepexto®	1/02/2021
Filgrastim	G-CSF	NPA	Neupogen®	Accofil®	1/06/2016
				Nivestim®	1/03/2014
				Tevagrastim	1/02/2010
Follitropin alfa	FSH	NPA	Gonal-F®	Bemfola®	NA
				Ovaleap®	NA
Insulin glargine*	LA insulin analogue	30.344.794	Lantus®	Abasaglar®	1/06/2016
Somatropin	GH	NPA	Genotropin®	Omnitrope®	1/04/2014

G-CSF: granulocyte colony-stimulating factor, GH: growth hormone, INN: International non-proprietary name, LA: long-acting, LMWH: low molecular weight heparin, NPA: not publicly available, NA: not applicable, non-reimbursed medicine, FSH: follicle-stimulating hormone, TNF: tumour necrosis factor. *Biologicals part of the top 25 medicine expenditures in the Belgian ambulatory sector. Insulin aspart is also part of this list (reference product: NovoRapid®, net 2019 expenditure: 22.229.748) and has an authorized biosimilar: Insulin aspart Sanofi®. Insulin aspart Sanofi® has however not (yet) been launched in Belgium (148). Also the EU-approved biosimilars of teriparatide (reference product: Forsteo®, EU-approved biosimilars: Movymia®, Terrosa®, Livogiva®, Qutavina®) and insulin lispro (reference product: Humalog®, EU-approved biosimilar: Insulin Lispro Sanofi®) are not (yet) available on the market in Belgium (32),(116),(148). ⁺Reimbursement date of the first available product package (149). (Status May 2021) (137),(148),(149)

3. METHODS

3.1 SURVEY DESIGN AND DATA COLLECTION

Two sets of surveys, one for community pharmacists and one for physicians, were developed. The surveys were designed based on a review of the literature and consisted of five main parts: (i) participant characteristics, including experience with dispensing/prescribing biologicals in general and biosimilars in particular, (ii) knowledge about biosimilars, (iii) attitudes regarding dispensing/prescribing biologicals in general and biosimilars in particular, (iv) attitudes regarding interchangeability, switching, substitution, and (v) informational and educational needs. In the physician survey, a sixth category was included: (vi) attitudes regarding drivers and incentives for prescribing biosimilars. Questions were tailored to the particular stakeholder group. Participants received definitions on biological medicines, biosimilars, interchangeability, switching and substitution where appropriate. The surveys consisted predominately of closed multiple-choice questions. For some questions, multiple answers could be selected. The survey also included Likert scale questions, in which participants were asked to indicate their level of agreement with a proposed statement. The survey was tested in and adapted based on three pilot surveys. Both surveys were made available in Dutch and French to cater to the two main language regions in Belgium. The web-surveys were created using the online survey platform, SurveyMonkey®. The survey launched in November 2018 and closed in March 2019. Ethics approval was granted by the Research Ethics Committee UZ/KU Leuven.

3.2 PARTICIPANTS

Two healthcare provider groups were targeted to participate: (i) community pharmacists and (ii) general practitioners and physician specialists who prescribe subcutaneous biologicals that are dispensed via the community pharmacy, for which EMA evaluated and European Commission (EC) approved biosimilar alternative is available on the Belgian market (i.e. endocrinologists, rheumatologists, gastro-enterologists and dermatologists).

Healthcare providers across Belgium were invited to participate. Medical and pharmacy professional organisations on a national and regional level were asked to disseminate the survey among their members. The invitation to participate and the link to the online survey was subsequently included in newsletters and professional websites or social media pages of participating professional associations. In addition to this, community pharmacists involved in the training program of KU Leuven Master students Pharmaceutical Care received an invitation to participate. Additionally, participants were identified via the network of the research group.

3.3 DATA ANALYSIS

Results were analysed descriptively for the overall participant group per stakeholder category. In the results section, relative numbers are presented as percentages and the considered sample size, which varied throughout the survey due to the logic applied in the survey questions and participant

dropout, is included. Additional inferential statistics to test for differences between certain groups of interest (i.e. experienced and less experienced pharmacists and questions of interest (i.e. self-assessed competence in dispensing biologicals in general vs biosimilars in particular) were performed using Statistica software (Version 14). The Fisher-Exact test was used to compare proportions of categorical data. This test was chosen since the retrieved samples were small for certain questions. All tests were performed on a significance level of 5% ($\alpha = 0,05$), meaning p-values of lower than 0,05 were considered significant.

4. RESULTS

To contextualize the results regarding the knowledge and perception of healthcare providers about prescribing or dispensing biosimilars, the surveys also enquired about their knowledge and perception regarding biological medicines in general.

4.2 COMMUNITY PHARMACISTS

4.2.1 PARTICIPANT CHARACTERISTICS

In total, 177 Belgian community pharmacists participated. All regions in Belgium were represented, although most participants worked in Flanders (86%, $n = 153/177$). Responses were gathered across different age groups and most participants were female (69%, $n = 123/177$) (Table 6). Of the 177 participating community pharmacists, 115 completed the survey in full.

4.1.2 EXPERIENCE WITH DISPENSING BIOLOGICALS INCLUDING BIOSIMILARS

Most pharmacists indicated to have experience with dispensing biological medicines (84%, $n = 148/177$). Not surprisingly, almost all had experience with dispensing Tumour Necrosis Factor (TNF)-alpha inhibitors (95%, $n = 119/125$) and hormones such as insulin, growth hormone, and follitropin-alpha (94%, $n = 118/125$), as both product classes are dispensed in the community pharmacy in Belgium (Table S1).

A smaller portion of pharmacists had experience with dispensing biosimilars (32%, $n = 45/139$). Noteworthy, an identical number did not know whether they had yet delivered a biosimilar or not. The majority who indicated to have dispensed a biosimilar, had experience with dispensing biosimilars of hormones (67%, $n = 24/36$) and TNF-alpha inhibitors (64%, $n = 23/36$) (Table S2).

4.1.3 KNOWLEDGE ABOUT BIOSIMILARS

To evaluate the knowledge of pharmacists, respondents were asked about the accuracy of a few statements on biosimilar medicines (Figure S1). The majority (67%, $n = 95/142$) correctly indicated a biosimilar to be highly similar in efficacy, safety, and quality to the reference product. Noteworthy, 18% ($n = 25/142$) had heard about biosimilars, but did not really know what the term means.

To test possible differences in knowledge about biosimilars between more recently graduated and more senior pharmacists, results of respondents with more versus less than 20 years of pharmacy

experience were compared statistically (Table S3). For none of the statements a statistically significant difference was found between less and more experienced pharmacists.

TABLE 6. COMMUNITY PHARMACISTS: PARTICIPANTS' CHARACTERISTICS

Characteristics	Community pharmacists (N=177)	
	n	%
Sex		
Female	123	69
Male	54	31
Age		
<30 year	44	25
> 30 year – 45 year	56	32
> 45 year – 60 year	72	41
> 60 year	5	3
Years of experience as community pharmacist		
< 2 year	18	10
2 – 5 year	28	16
6 – 10 year	23	13
11 – 20 year	30	17
21 – 30 year	59	33
> 30 year	19	11
Working region		
Brussels	10	6
Flanders	153	86
Wallonia	14	8
Working environment		
<i>Multiple answers possible</i>		
Community pharmacy	177	100
Professional pharmacist group	10	6
University	1	1
Other	3	2

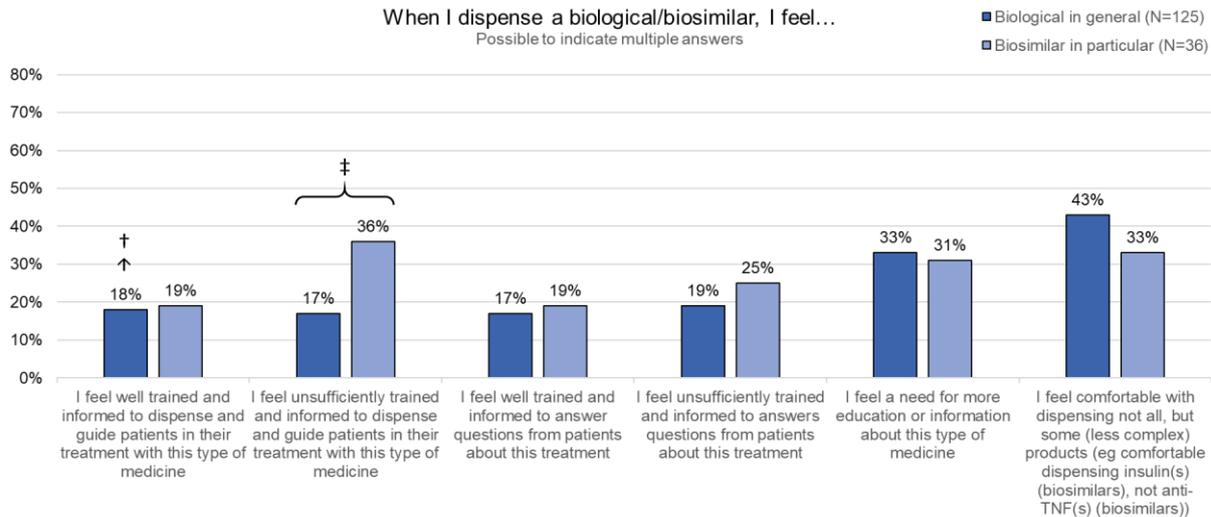
N: number, percentages are rounded to the nearest integer

4.1.4 ATTITUDES ABOUT DISPENSING BIOLOGICALS INCLUDING BIOSIMILARS

When examining the self-assessed competency of pharmacists to dispense biologicals in general and biosimilars in particular (Figure 10), over one third felt only comfortable with dispensing less complex biologicals (43%, n = 54/125) and biosimilars (33%, n = 12/36), such as insulin but not the more complex anti-TNF products. About one fourth of pharmacists (18%, n = 22/125) felt insufficiently trained to dispense and guide patients with their biological treatment. For biosimilars, this portion was larger (36%, n = 13/36). Pharmacists felt significantly less trained to dispense and guide patients with a biosimilar than a biological medicine in general ($p = 0,023$). For all other statements, no statistically significant difference in attitudes between dispensing biologicals in general and biosimilars in particular was found (Table S4). Also, no significant differences were found in the self-assessed competency to dispense biologicals in general and biosimilars between pharmacists with more *versus* less than 20 years of experience as community pharmacist. Only when

asked if they feel well trained and informed to dispense a biological, a statistically significant difference was found between groups ($p = 0,032$) (Table S5 and S6).

FIGURE 10. COMMUNITY PHARMACISTS' SELF-ASSESSED COMPETENCE TO DISPENSE BIOLOGICALS & BIOSIMILARS



Ant *i*-TNF: anti-tumor necrosis factor, N: number. Statistical testing: ‡: When testing for differences in self-assessed competence in dispensing biological medicines in general versus biosimilars in particular, a statistical difference was found for statement 2 (Table S4), †: When testing for differences in self-assessed competences in dispensing biological medicines between more recently graduated and more senior community pharmacists (more (N=47) versus less than 20 years (N=78) of pharmacy experience), a statistical significant difference was found for statement 1 (Table S5). When testing for differences in self-assessed competences in dispensing biosimilars between more recently graduated and more senior community pharmacists (more (N=17) versus less than 20 years (N=19) of pharmacy experience), no statistical significant difference were found for any of the statements (Table S6).

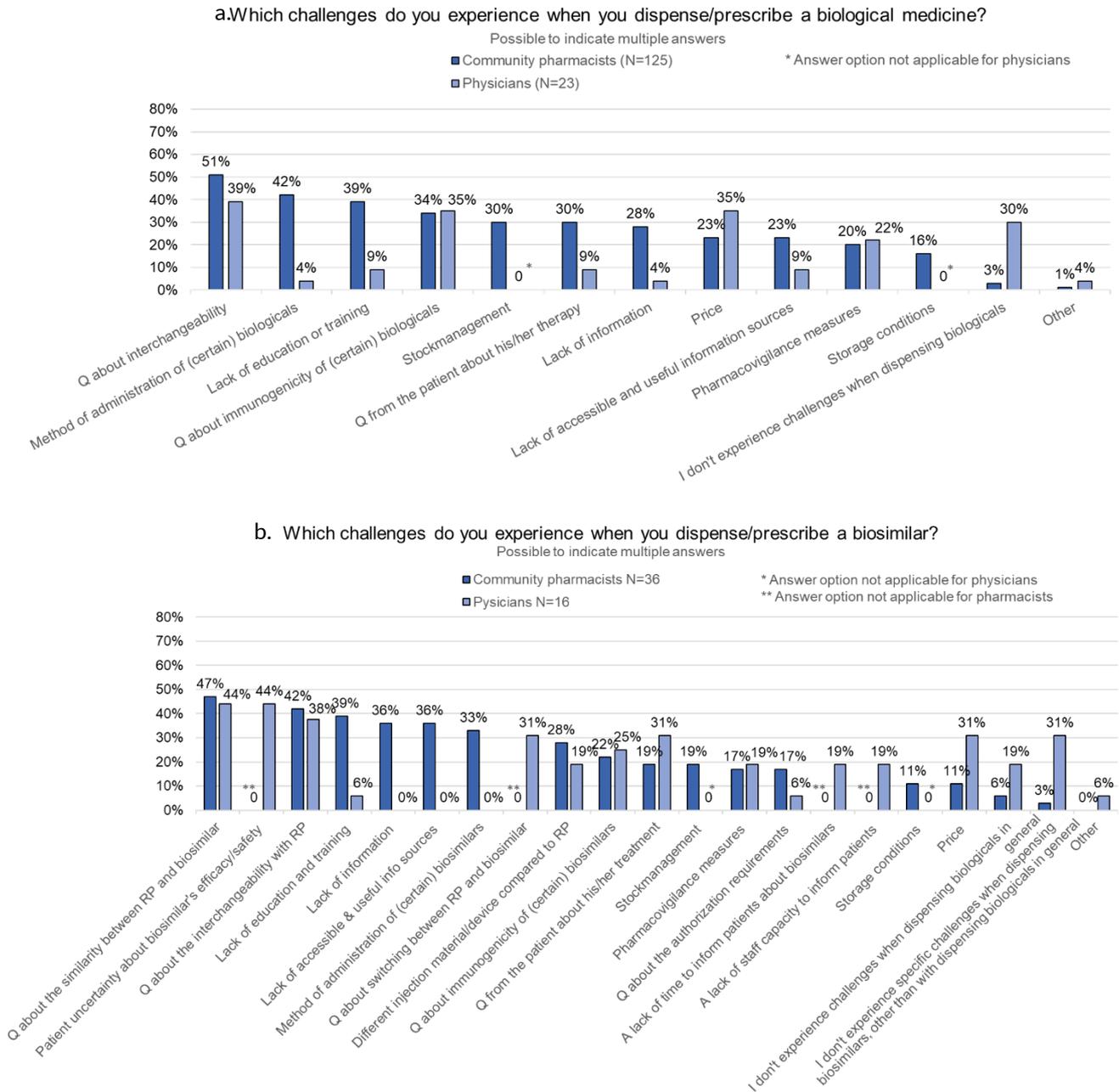
Only 22% ($n = 23/103$) agreed or fully agreed with the statement that they felt sufficiently trained to lead the dispensing discussion with the patient when dispensing biologicals (Figure S2). For biosimilars in particular, this proportion was even lower (13%, $n = 4/30$). While the majority felt neutral about this statement, both for biologicals in general (46%, $n = 47/103$) and biosimilars (57%, $n = 17$), about 30% of pharmacists disagreed with the statement for both.

When asked which challenges they experience when dispensing a biological, pharmacists selected questions about interchangeability (51%, $n = 64/125$), the method of administration (42%, $n = 53/125$), lack of education and training (39%, $n = 49/125$), and immunogenicity (34%, $n = 43/125$). Only four pharmacists (3%) indicated to experience no challenges when dispensing biologicals. (Figure 11a).

With biosimilars, almost half of the pharmacists indicated to experience questions about the similarity of the biosimilar with its reference product (47%, $n = 17/36$) as challenging when dispensing. Over one third also indicated to experience questions about interchangeability between the biosimilar and its reference product (42%, $n = 15/36$), a lack of education and training (39%, $n = 14/36$), a lack of accessible and useful information sources (36%, $n = 13/36$), and a general lack of information (36%, $n = 13/36$) here (Figure 11b).

The majority of pharmacists (73%, n = 88/120) considered a counselling treatment conversation needed when a patient starts a treatment with a self-injectable biological. Approximately 50% considered it needed when a patient switches from a self-injectable reference biological product to a biosimilar or vice versa (Figure S3).

FIGURE 11. PERCEIVED CHALLENGES WHEN DISPENSING/PRESCRIBING A BIOLOGICAL (IN GENERAL) OR A BIOSIMILAR AMONG COMMUNITY PHARMACISTS AND PHYSICIANS



N: number, Q: questions, RP: reference product

4.1.5 ATTITUDES ABOUT INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION

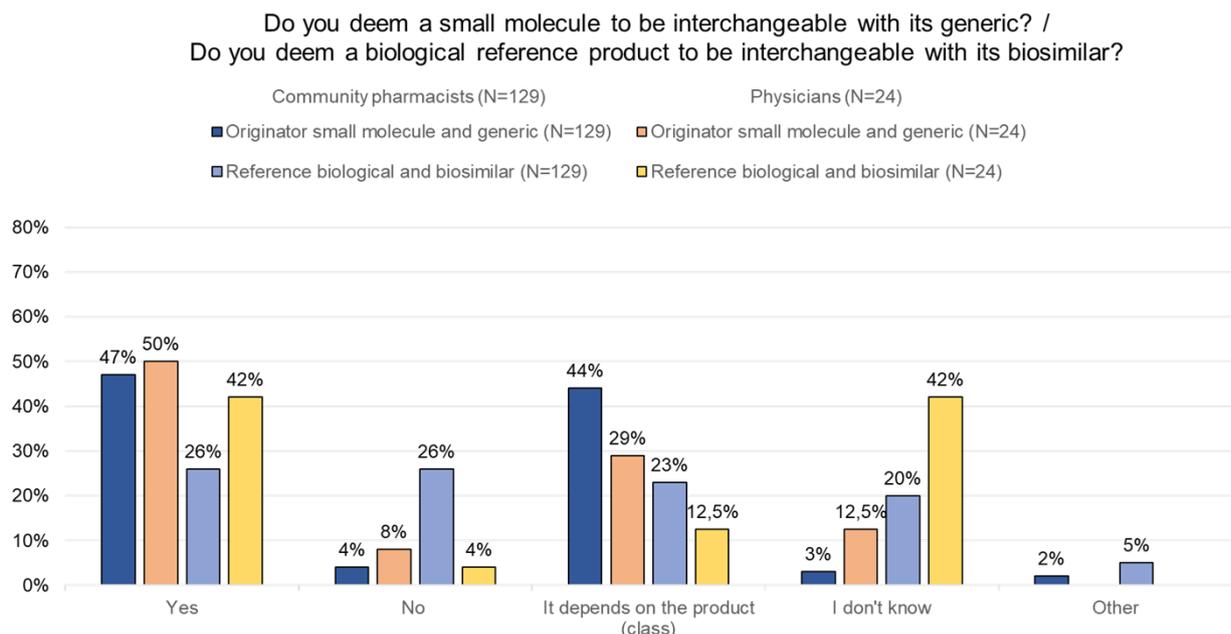
Approximately half of pharmacists (47%, n = 60/129) deemed a small molecule medicine to be interchangeable with its generic (Figure 12). For reference biological and biosimilar medicines this percentage dropped to about one quarter (26%, n = 33/129).

About one third of pharmacists (35%, n = 45/129) believed that an authorized biosimilar can be considered interchangeable with its reference product. The majority (60%, n = 77/129) believed that additional data are needed to demonstrate interchangeability besides these for marketing authorization (Figure S4 a). Opinions about the interchangeability of two biosimilars of the same reference product differed (Figure S4 b).

Over half of pharmacists (58%, n = 72/124) indicated to believe that they should be allowed to substitute the original biological with its biosimilar, after contacting the prescribing physician (Figure 13). Over a third (34%, n = 42/124) believed that automatic substitution could be applied in the future when more experience has been gained with biosimilars, while 26% (n = 32/124) thinks automatic substitution can be applied, depending on the complexity of the product. Only 10% (n = 13/124) believed that substitution between biological reference and biosimilar medicines should be allowed automatically.

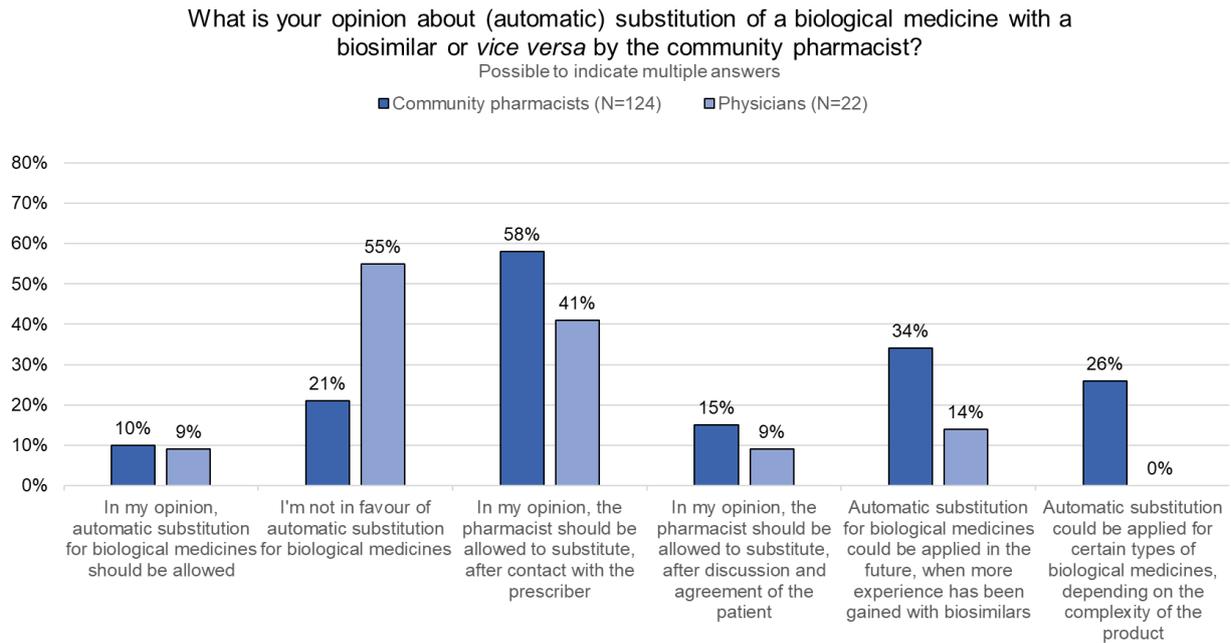
When asked to what extent they agreed with the statement that substitution of biological medicines could be done, after contact with the prescriber, the majority (73%, n = 91/124) either agreed or fully agreed (Figure S5a). Switching from a biological reference product to a biosimilar or vice versa should remain the responsibility of the prescribing physician, according to 66% (n = 82/124 agreed or fully agreed with the statement) of pharmacists.

FIGURE 12. COMMUNITY PHARMACIST AND PHYSICIAN VIEWS ON INTERCHANGEABILITY



Interchangeability: refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilars, vice versa, or replacing one biosimilar with another. N: number, RP: reference product

FIGURE 13. QUESTIONS ABOUT (AUTOMATIC) SUBSTITUTION



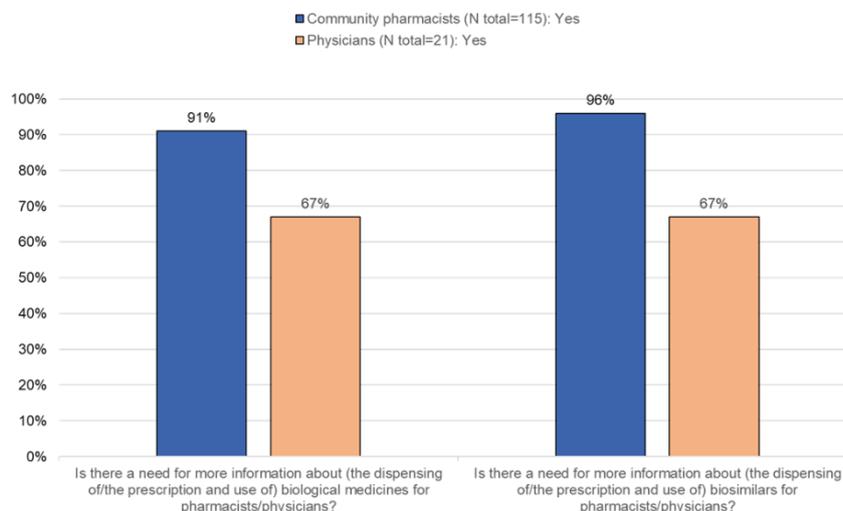
Automatic substitution: the pharmacist dispenses one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber. N: number, RP: reference product

4.1.6 INFORMAL AND EDUCATIONAL NEEDS

Less than half of pharmacists (42%, n = 47/113) had followed a training or educational symposium about biologicals in the past. A smaller portion had followed one specifically about biosimilars (22%, n = 25/113) ([Table S1](#) and [S2](#)).

A high need for information about biologicals in general (91%, n = 105/115), and biosimilars in particular (96%, n = 110/115) was expressed ([Figure 14](#)). Almost all (95%, n = 107/115) indicated they would like to follow a training about biological including biosimilar medicines ([Figure S6 a](#)). Pharmacists expressed interest in almost any type of the suggested topics ([Figure S6 b](#)). When asked by which organisation they prefer to be informed, national or regional professional organizations were ranked first by more than half (51%, n = 59/115) ([Figure S6 c](#)).

FIGURE 14. INFORMATION NEED ABOUT BIOLOGICALS (IN GENERAL) AND BIOSIMILARS (IN PARTICULAR)



4.2 PHYSICIANS

4.2.1 PARTICIPANT CHARACTERISTICS

In total, 30 physicians participated in this study. Most worked in Flanders (80%, $n = 24/30$), while a minority worked in Wallonia (20%, $n = 6/30$). Physicians were specialized in a variety of therapeutic domains, including rheumatology (33%, $n = 10/30$), dermatology (17%, $n = 5/30$) and general practice (13%, $n = 4/30$) (Table 7).

4.2.2 EXPERIENCE WITH PRESCRIBING BIOLOGICALS INCLUDING BIOSIMILARS

The majority of physicians (77%, $n = 23/30$) had experience with prescribing biological medicines. A few (10%, $n = 3/30$) did not know if they had prescribed a biological medicine (Table S7).

Over half of physicians (52%, $n = 14/27$) had prescribed a biosimilar. Seven percent indicated to have not prescribed a biosimilar, but to follow a patient under treatment with a biosimilar ($n = 2/27$). The majority (67%, $n = 16/24$) did not have experience with switching a patient under treatment with a reference product to a biosimilar (Table S8).

4.2.3 KNOWLEDGE ABOUT BIOSIMILARS

Most physicians recognized that biosimilars are similar in efficacy, safety, and quality with respect to their reference medicine (63%, $n = 17/27$). About ten percent had heard about biosimilars, but did not know what the term exactly means (11%, $n = 3/27$) (Figure S1).

TABLE 7. PHYSICIANS: PARTICIPANTS' CHARACTERISTICS

Characteristics	Physicians (N=30)	
	n	%
Sex		
Female	17	57
Male	13	43
Age		
<30 year	3	10
> 30 year – 45 year	14	47
> 45 year – 60 year	9	30
> 60 year	4	13
Years of experience as physician		
0-5 year	4	13
6 – 10 year	4	13
11 – 20 year	11	37
21 – 30 year	5	17
> 30 year	6	20
What is your function?		
<i>Multiple answers possible</i>		
Rheumatologist	10	30
Dermatologist	5	17
Gastro-enterologist	2	7
Endocrinologist	1	3
General practitioner	4	13
Representative medical association	1	3
Other	7	23
Working region		
Brussels	0	0
Flanders	24	80
Wallonia	6	20
Working environment		
<i>Multiple answers possible</i>		
Private practice	12	40
University hospital	5	17
General hospital	15	50
Professional medical association	1	3
University	1	3
Other	1	3

N: number, percentages are rounded to the nearest integer

4.2.4 ATTITUDES ABOUT PRESCRIBING BIOLOGICALS INCLUDING BIOSIMILARS

When asked about challenges that they experience when prescribing biologicals in general, most physicians indicated to have questions about the interchangeability of biological medicines (39%, n = 9/23). The price of biological medicines (35%, n = 8/23) and questions about their immunogenicity (35%, n = 8/23) were also recognized as challenging (Figure 11a).

When prescribing biosimilars, physicians indicated to experience questions about the similarity of biosimilars with their reference product (44%, n = 7/16), uncertainties of patients about the efficacy and safety of biosimilars (44%, n = 7/16), and questions about interchangeability between biosimilars and their reference product (38%, n = 6/16) (Figure 11b) as challenges.

4.2.5 ATTITUDES ABOUT INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION

Half of physicians believed generic medicines and their original product are interchangeable (50%, n = 12/24). This proportion was smaller for biosimilar and reference products (42%, n = 10/24) (Figure 12). The majority was of the opinion that additional data are needed to demonstrate that a biosimilar is interchangeable with its reference product upon authorization (63%, n = 15/24) (Figure S4 a).

Most physicians were not in favor of substitution in an automatic way (55%, n = 12/22). About 40% believed that the pharmacist should be allowed to substitute after contact with the prescriber (41%, n = 9/22) (Figure 13).

The majority of physicians (77%) disagreed or fully disagreed with the statement that substitution of a biological reference product with a biosimilar could be done by the general practitioner after contact with the initiating prescriber. Surprisingly, the percentage of physicians disagreeing was lower (45%, n = 10/22) when asked if they agreed this could be done by the pharmacist, after contact with the prescriber. Regarding switching, 36% of physicians disagreed or fully disagreed with the statement that insufficient data are available about switching between biological reference products and biosimilars (n = 8/22), while 32% was neutral and 32% agreed with the statement (n = 7/22) (Figure S5 b).

4.2.6 INFORMATIONAL AND EDUCATIONAL NEEDS

About 70% (n = 15/21) of physicians indicated to have followed a training or symposium about biologicals in general, and over half (52%, n = 11/21) specifically about biosimilars. (Table S7 and S8).

The majority indicated a need for more information both about (the prescription and use of) biologicals in general and biosimilars in particular (67%, n = 14/21) (Figure 14). When asked by which organisation they would like to be informed, the national or regional professional physician association was ranked first, followed by a European professional physician association (Figure S6 d). When asked which organisation would be suited to draft guidance about biosimilar use, also the national or regional professional physician association was ranked first. (Figure S6 e).

4.2.7 ATTITUDES ABOUT DRIVERS AND INCENTIVES FOR PRESCRIBING BIOSIMILARS

When asked for which reasons they would prescribe a biosimilar, the majority of physicians mentioned savings as reason (71%, n = 17/24). Confidence in the evaluation of biosimilars by the EMA (42%, n = 10/24), the fact that the biosimilar is similar compared to the reference product (42%, n=10/24) and a potential increase in patient access to biological therapies (25%, n = 6/24) were also selected. When asked for which patient they would prescribe a biosimilar, 42% (n = 10/24) would only prescribe the biosimilar if it was clinically tested for the specific indication of their patient or only for bio-naïve patients (21%, n = 5/24). When asked about reasons not to prescribe biosimilars, 42% (n = 10/24) selected the argument that the product is less clinically tested

compared to the reference product, uncertainty of their patient (33%, n = 8/24), and a lack of knowledge about the biosimilar concept and its evaluation (29%, n = 7/24). ([Figure S7](#)).

The majority of physicians recognized the need for some kind of incentive (55%, n = 12/22) to stimulate biosimilar prescription in the ambulatory setting ([Figure S8 a](#)). When asked what kind of incentive is expected, information about biosimilars by regulatory authorities, transparency about the realized savings derived from biosimilar market entry, and additional budget for staff to support biosimilar implementation were most frequently indicated ([Figure S8 b](#)). The majority (55%, n = 12/22) believed that a similar initiative like the Covenant “Restart biosimilar medicines in Belgium”, which aimed to stimulate the use of biosimilars in the hospital, would be useful to stimulate the prescription of biosimilars in the ambulatory setting ([Figure S8 c](#)).

5. DISCUSSION

Since biosimilar use has been predominately a hospital matter in previous years, earlier research in the domain of stakeholder knowledge about biosimilar medicines generally focussed on the knowledge and perception of hospital pharmacists and physician specialists (119). With the approval of biosimilars for subcutaneously administered biologicals (such as adalimumab, etanercept and insulin), biosimilars are finding their way to the community pharmacy in Belgium.

In view of the loss of exclusivities of different biologicals with high (therapeutic) value in the ambulatory care setting and the subsequent emergence of biosimilars, this study quantitatively assessed the knowledge and perceptions of Belgian community pharmacists and physicians about biological including biosimilar medicines in this particular setting.

5.1 A CLEAR NEED FOR ACTIVE EDUCATIONAL AND INFORMATIONAL MEASURES

The level of knowledge and understanding about biosimilars among Belgian community pharmacists was noted to be low. Also for physicians, a need for educational initiatives was clearly expressed. The results of this study show that there is a substantial demand for more information and education about different aspects about biological including biosimilar medicines for this group of Belgian healthcare providers.

These findings are consistent with previous research on healthcare provider perceptions about biosimilars, showing low to moderate knowledge and trust towards biosimilars across varying specialisms and countries (119),(140). While earlier research largely investigated the perspective of healthcare professionals active in the hospital context, a French web-based survey included also the perspective of community pharmacists in their study. Their 2017 survey results showed that about half of community pharmacist survey participants were “not at all” informed about biosimilars, compared to less than one fifth of participating hospital pharmacists (64). Even though experience with biosimilars may have grown in the ambulatory care setting over the past few years, the results of this current Belgian websurvey indicate that the self-assessed knowledge among community pharmacists about biosimilars is still limited in Belgium.

A survey conducted among Irish general practitioners in 2017 showed that 60% of participants were unable to define a biosimilar or had never heard of the term (150). A survey among Belgian rheumatologists in 2016, pointed at information gaps and doubts about biosimilar medicines. In particular, concerns about the interchangeability of biological reference products with biosimilars were found (66). A general lack of familiarity and trust in biosimilar medicines among Belgian physicians was already observed in 2013 (43),(141). The findings of this study show that physicians' uncertainty about biosimilars may have not been sufficiently addressed over the past few years.

Moreover, and more surprisingly, this study indicates that community pharmacists and physicians not only face challenges with dispensing or prescribing biosimilars but also with biological medicines in general. This statement is supported by the statistical analysis, where nearly no significant differences were found between the self-assessed competences between dispensing biological medicines in general and biosimilar medicines in particular among community pharmacists.

It is essential that physicians and community pharmacists are well trained to make treatment decisions and counsel patients regarding biological, including biosimilar, therapies. Although the biosimilar drug development and regulatory assessment paradigm originates from 2005 and the first biosimilar approval dates from 15 years ago, physicians still ask for clinical studies and pharmacists have questions about similarity and interchangeability concepts. As biosimilars are relatively recently available in ambulatory care in Belgium and their market shares remain low, general practitioners and community pharmacists may have been only confronted to a limited extent with biosimilars in clinical practice. Misunderstandings about biosimilar concepts may also stem from a lack of knowledge about biological medicines in general (119). Nonetheless, physicians and community pharmacists have the responsibility to prescribe/dispense these medicines in an informed and knowledgeable manner, and adequately counsel patients with their treatment. Healthcare providers are expected to keep up with developments in pharmaceutical therapies that enter clinical practice. University curricula should prepare physicians and pharmacists with up-to-date education and continuous education should provide support with lifelong learning during their professional career.

The results of this study ask for an examination of the existing education and outreach on biological medicines and biosimilars for Belgian healthcare providers. Whereas earlier research suggested that information lacks (43), informational material on biosimilars is now abundantly available. This suggest that the available informational material does not effectively reach the physician and pharmacist (119).

An important responsibility lies with the Belgian professional associations to disseminate objective information about biosimilars, and include biosimilar medicines in the continuing education of physicians and pharmacists. The emphasis should be on organizing (mandatory) educational sessions in the framework of life-long learning, rather than making information passively available. Professional associations and policy makers should collaborate to facilitate a coherent stream of information and develop targeted educational measures to reach healthcare providers maximally.

This may benefit from a pro-active and centrally coordinated approach from the Belgian competent authority and the Ministry of Social Affairs and Health.

In addition to the importance of permanent education courses to continuously update knowledge and insights of healthcare providers on emerging and evolving topics, the university curricula for future healthcare providers warrant a closer look. A follow-up study investigated the knowledge of Belgian medicine and pharmacy students about biologicals including biosimilars. Only low to moderate percentages of master students (ranging from 2% to 42%) appear to feel well prepared to work with biologicals in general and biosimilars in particular in the future (151),(152). Compared to master students Medicine and Pharmaceutical Care, Master students Drug Development seem to be more informed (151),(152). This survey also showed no statistical difference in terms of knowledge about biosimilars between more recently graduated and more senior community pharmacists. Based on an examination of the presence of biological including biosimilar topics in the learning objectives of the pharmacists' curriculum, it should be considered to expand training on this (151),(152). University education committees should appraise the courses within the Master's degrees regarding biological including biosimilar medicines and expand and update content where needed to prepare future healthcare providers with the necessary knowledge and competencies to prescribe/dispense these medicines (151).

5.2 SUBSTITUTION OF BIOLOGICAL MEDICINES

Whereas the marketing authorization of biosimilars is based on the recommendation of the EMA and the decision of the EC, decisions on interchangeability and substitution are made at the Member State level (6). Similarly to most European countries, pharmacy-level substitution is not allowed for biological medicines in Belgium (143). In this study, 58% of community pharmacists indicated to be in favor of introducing substitution for biological medicines, albeit after contacting the prescriber. Also 41% of physicians seemed to be in favor of substitution by the community pharmacist, if done with the prescriber's approval.

Substitution could be a potential strategy to stimulate biosimilar usage in ambulatory care. Since biosimilars have proven to be equally effective and safe as their reference product when they enter the market, substitution has become an organizational or political challenge rather than a scientific one (115). For example, in France and the US, pharmacist-led substitution for biologicals is legislatively possible (142),(140),(153). Some other European countries have new legislation planned to allow pharmacist-led substitution for (certain) biologicals (99),(142). Before this could be explored in the Belgian context, the demand for more information about biological including biosimilar medicines should be met to ensure that involved healthcare providers are well trained to counsel patients regarding biosimilar use and manage such an exchange. An earlier study among Finnish healthcare providers has pointed out several issues, and ways to solve them, regarding the implementation of substitution for biological medicines (153). Similar to the results of this study, specific educational requirements for all stakeholders involved in the substitution process were underlined as a condition (153). Community pharmacists and pharmacy staff should be educated

and trained to counsel patients including device training. Substitution may also facilitate stock management as it limits the number of expensive biological medicines that must be stocked in the community pharmacy (153).

5.3 THE ROLE AND DESIGN OF HEALTHCARE PROVIDER INCENTIVES

Besides the knowledge of healthcare providers, other factors may influence the adoption of biosimilars in clinical practice. Next to healthcare providers' uncertainty and questions regarding biosimilars, low biosimilar use may be explained by the fact that physicians identify no or insufficient benefits to prescribe biosimilars and change their patients in the ambulatory context. Whereas in the hospital setting the use of biosimilars is determined to a large extent by tender mechanisms, no such driver exists in the ambulatory care setting. As the difference in the list price between originator biologicals and biosimilars is generally limited in Belgium (137), physicians may not recognize direct benefits from prescribing a biosimilar. As a considerable proportion of patients treated with biosimilars in the Belgian ambulatory setting are initiated in the physician's private practice, incentive schemes outside of hospital-level incentives may be required.

The majority of physicians in this survey confirmed the need for prescriber incentives to support biosimilar usage in the ambulatory context. This finding is consistent with previous papers also pointing out the need for tangible incentives for healthcare providers (115),(154). Following the emergence of biosimilars in the ambulatory care setting, a pilot financial incentive was introduced in 2019 by the Belgian national health insurer linked to the prescription of etanercept and adalimumab biosimilars (155). The incentive has been discontinued because of its limited success (155). The current study reveals that prescriber incentives should not necessarily be monetary in nature, as participants ranked informational and educational support as first preferred incentive. When implementing an incentive, it should aim to improve patient care rather than to provide a financial benefit at the level of the individual physician (115),(154). Budget to remunerate additional staff to support the implementation of biosimilars could serve as a tangible method to incentivize prescribers.

In France such a gain sharing incentive was launched in 2018, as part of their national strategy aiming to achieve 80% biosimilar uptake by 2020 (156). For biologicals such as adalimumab and etanercept, the initiation of treatment in France is done at the hospital, after which the initiated product is continued in the ambulatory setting (156). The initiation in the hospital thus influences the subsequent use in the ambulatory setting. Therefore this incentive targeted the hospitals by rewarding them with 20% of the price difference between the originator biological and biosimilar for every insulin glargine, etanercept and adalimumab biosimilar prescribed in the hospital and dispensed in the community pharmacy or for every renewed prescription in the ambulatory setting resulting from the initiation in the hospital (156). Preliminary results showed a positive effect on biosimilar market shares (157),(158). Similarly in Ireland, the introduction of a prescribing incentive in the form of a gain-share of €500 per patient initiated or switched to a best-value adalimumab and etanercept was reported to have contributed significantly to an increase in biosimilar use (159).

In addition to a gain sharing incentive, the results presented here indicate that efforts should be made to report transparently about the generated savings from biosimilar competition and how they are used.

5.4 STUDY STRENGTHS AND LIMITATIONS

This study was the first to examine the level of knowledge and perception of Belgian community pharmacists about biologicals including biosimilars. The relatively large sample size (a sample size of 177 participants allows to report for the population of 9200 Belgian community pharmacists with a confidence level of 95% and error margin of 7.3%), representative distribution of the sex (70% female in both the general Belgian community pharmacist population and survey sample) and fair distribution of age groups among participating pharmacists ensure that these results are indicative for the larger population of Belgian community pharmacists (160),(161),(162).

Limitations to the survey include the fact that mainly pharmacists and physicians working in Flanders participated, and the limited sample of participating physicians. Because participants were mainly recruited via professional organizations, a response rate could not be calculated. In addition, one could argue that pharmacists and physicians that showed interest - and participated - in this survey may have a higher level of knowledge about biosimilars than the overall healthcare provider population in Belgium. Moreover, earlier research showed that the flow of information and the knowledge about biosimilars may be higher among Flemish physicians compared with Wallonian physicians (163). The results of this survey might therefore be even an overestimation of the actual level of awareness on biosimilars, which was already reported to be low in this study.

5.5 FUTURE PERSPECTIVES

Initiatives and incentives targeted at pharmacists and physicians should play a central role in future policy making to support biosimilar usage in ambulatory care. As drivers appear to be lacking for biosimilar use in ambulatory care in Belgium, the exploration of policies and incentives in the ambulatory care context is becoming more pertinent. A continuing low use of biosimilars may deter companies to launch future biosimilars on the Belgian market. In Belgium, no insulin lispro biosimilar has been launched so far. Also, Mylan's insulin glargine biosimilar (Semglee®) is not marketed in Belgium (137). Belgian policymakers should work closely together with healthcare providers to create incentives tailored to their needs, in order to create a balanced climate for off-patent biological and biosimilar medicines.

In addition to policy actions, the university curricula should be fit for purpose to prepare physicians and pharmacists for their prescribing and dispensing responsibility of best-value biologicals (both reference biologicals and biosimilars). Education should include elements on cost-effective medicine use.

Besides the perspective of Belgian healthcare providers, the views of Belgian patients should be assessed. The perspectives of ambulatory care patients were investigated in a subsequent study commissioned by the Belgian national health insurer (164). Based on a sample of 657 participants,

the survey results showed that Belgian ambulatory care patients have a rather limited understanding of biosimilars. Nonetheless, most patients who were treated with an original biological were open toward switching their current biological to its biosimilar. Patients expect that the decision is explained to them and count on support and information from their healthcare providers (165). The results of these two studies can inform the development of new educational initiatives to stimulate biosimilar adoption in clinical practice, tailored to the needs of both Belgian healthcare providers and patients.

6. CONCLUSIONS

This study shows that Belgian community pharmacists and physicians have considerable uncertainties with prescribing and dispensing biological medicines in general and biosimilars in particular. It appears that healthcare provider knowledge gaps about biosimilars have not been sufficiently addressed over previous years. Targeted educational measures that actively reach Belgian community pharmacists and physicians are required to reduce the information gap. Equally, policy interventions to stimulate the use of biosimilar medicines will be needed to ensure that Belgium captures their societal benefits over the longer term. The results of this study can inform the design of necessary educational and policy measures to support biosimilar use in ambulatory care in Belgium.

PART 3
THE REGULATORY & CLINICAL
LANDSCAPE

1. ABSTRACT

The monoclonal antibody trastuzumab (Herceptin®), which targets the human epidermal growth factor receptor 2 (HER2), is approved for the treatment of early breast and advanced breast and gastric cancer in which HER2 is overexpressed. Several biosimilar versions of trastuzumab are expected to enter the European market over the course of 2018 and 2019. The biosimilar development pathway consists of a comprehensive comparability exercise between the biosimilar candidate and the reference product, primarily focussing on data from analytical studies. Clinical studies for biosimilar candidates follow a different design to those for a new biological, as the aim is not to independently establish clinical benefit, but to confirm biosimilarity between the two agents. The different trastuzumab biosimilar candidates have followed diverse pathways in their clinical development, with differences in clinical trial design (equivalence or non-inferiority design), patient population (those with metastatic or early breast cancer) and endpoint (overall response rate or pathological complete response). These differences in approach in phase III testing must be viewed in the totality of evidence demonstrating biosimilarity. Adequate information on the biosimilar approval pathway, the nature of the biosimilarity exercise and how the clinical development of a biosimilar is tailored to meet the licensing requirements can help informed decision making in clinical practice.

2. INTRODUCTION

Biological medicines, and anticancer biological medicines in particular¹, represent a growing financial burden on healthcare budgets. The loss of exclusivity rights on original biological medicines has allowed biosimilar medicines to enter the market. Biosimilars offer cost-effective treatment options that can help contain the rising healthcare expenditure. The European Medicines Agency (EMA) defines a biosimilar as ‘a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product in the European Economic Area.’ (14). Due to the intrinsic variability that is inherent to all biological medicines and the complex manufacturing process of these products, a biosimilar cannot be considered an identical copy of the originally approved biological product (the reference product or originator) (5),(167). Minor differences can exist between the biosimilar and the reference product, but it needs to be demonstrated that these differences are not clinically meaningful (5),(14). ‘*Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.*’ (14). Table 8 provides an overview of the difference between biosimilars and copies of originally approved small molecule medicines, called generics.

TABLE 8. THE DIFFERENCE BETWEEN BIOSIMILARS AND GENERICS

-
- A generic is a copy of an existing small-molecule based therapeutic and its approval is based on the demonstration of bioequivalence with its reference product by appropriate pharmacokinetic studies (14),(168).
-
- A biosimilar is a biological medicinal product that is highly similar to an already licensed biological medicine, the reference product (14). Owing to the intrinsic variability that is inherent to all biological medicines and the complex manufacturing of these medicines, it is impossible to produce identical products. Minor differences can thus exist between the biosimilar and the reference product, however it needs to be demonstrated that these differences are not clinically meaningful (5).
 - The development of a biosimilar is based on the demonstration of biosimilarity via extensive head-to-head comparability studies with the reference product (14).
-
- Generics and biosimilars both follow an abbreviated development pathway for regulatory approval compared to that of an original medicine, however, the requirements are different. Since a biosimilar cannot be an exact copy of the reference product owing to the natural variability and complex manufacturing process of biological medicines in general, the ‘generic’ development and approval approach is not appropriate for a biosimilar (14),(168).
-

Regulatory authorities such as the EMA and the United States Food and Drug Administration (FDA) have developed a regulatory approval pathway for biosimilars (5),(14). Since the authorisation of the first biosimilar in 2006 in Europe, more than 40 biosimilars have received a positive opinion from the EMA and been subsequently authorised by the European Commission (EC) (169). Since 2015, the FDA has approved over 10 biosimilars (170). The number of approved biosimilars will grow substantially in future years, accompanied by an increasing loss of exclusivity of biological reference products, especially in oncology (171),(172). By providing more affordable treatment options and

introducing price competition to the market, biosimilar medicines can generate significant savings. The cumulative savings between 2016 and 2020 in the EU5 and the USA are estimated to range between 49 and 98 billion euros (171). Savings derived from biosimilar market entry can relieve burdened healthcare budgets and open up budgets for new treatment options. Furthermore, biosimilar entry can increase patient access to biological therapies (125),(171).

Biosimilars have been integrated in cancer care for over a decade, as the first biosimilars of epoetin and filgrastim were authorised by the EMA in 2007 and 2008, respectively (169). The number of biosimilars available in oncology is likely to increase rapidly, with the therapeutic focus shifting from supportive care for chemotherapy to targeted, potentially life-prolonging or curative monoclonal antibodies (mAbs). The first mAb biosimilar versions in oncology, of rituximab, were approved by the EMA in 2017 (Blitzima[®], Ritemvia[®], Rituzena[®], Truxima[®] by Celltrion Healthcare Hungary Kft and Rixathon[®], Riximyo[®] by Sandoz GmbH) (169).

The mAb trastuzumab (developed by Genentech, marketed by Roche as Herceptin[®]) targets the human epidermal growth factor receptor 2 (HER2) and is approved for the treatment of early breast and advanced breast and gastric cancer in which HER2 is overexpressed (HER2+) (173). HER2+ breast cancer accounts for approximately 15% and 20% of all breast cancers in the early and advanced stage, respectively (174). Trastuzumab in combination with pertuzumab and taxane chemotherapy is currently the standard first-line treatment for HER2+ metastatic breast cancer (175). Trastuzumab is also approved for the treatment of HER2+ early breast cancer in neoadjuvant or adjuvant settings (174). As the first therapeutic mAb targeted to HER2, trastuzumab has revolutionised the treatment of HER2+ breast cancer. However, its high cost (approximately 30,500 euros for 12 months' treatment in an adjuvant setting and approximately 41,500 euros for an average treatment period of 18.5 months in metastatic breast cancer, based on Belgian list prices for a patient that weighs 67 kg (176)) puts pressure on healthcare budgets and can restrict patient access in countries where limited or no health insurance coverage is available (177). Herceptin[®] had global sales of 6.6 billion euros (7.5 billion USD (178) at a 1.14 USD to 1 EUR conversion rate) in 2017 and, with the patent expiration of the intravenous reference product of Herceptin[®] in the European Union (EU) in 2014 and the expected patent expiration in the USA in 2019 (172), several companies have been pursuing the development of biosimilar versions of trastuzumab. Five trastuzumab biosimilars have been approved by the EC (179),(180),(181),(182),(183) and are expected to enter the European market over the course of 2018 and 2019. In the USA, three trastuzumab biosimilars have so far been authorised (184),(185) and are expected to enter the US market in 2019 (172).

However, not all markets are ready to capture the potential benefits offered by biosimilars, as the uptake of biosimilars across Europe is heterogeneous and limited in some countries (36),(171). The lack of knowledge and understanding among stakeholders about the biosimilar approval pathway and the different weight of clinical data in the development of biosimilars compared to that of an originator have been identified as hurdles for the uptake of biosimilars (186),(187). As more

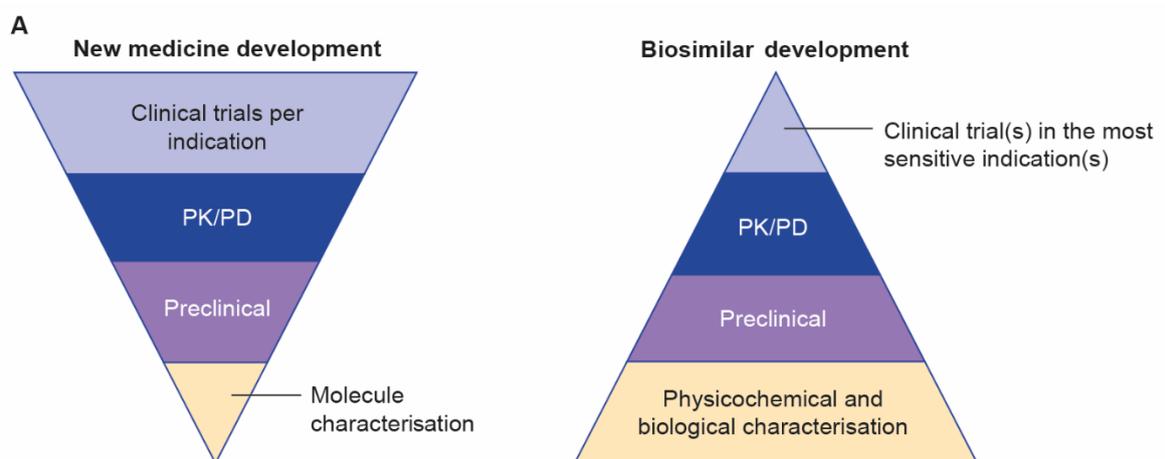
biosimilars are approved and prescribed, especially in the domain of cancer with the recent approvals of therapeutic oncology biosimilars, it becomes increasingly important that healthcare providers have a good understanding about the biosimilar approval pathway and the role of clinical data in this. To address this need, the aim of this manuscript is three-fold: first, to provide an overview of the biosimilar development pathway; second, to review the clinical trial parameters and published clinical data that have been collected to confirm similarity between the reference product – in this case, we will focus on trastuzumab – and its biosimilars in relation to the EMA guidelines on (mAb) biosimilar development; and, third, to provide information that can be useful in clinical decision making for prescribers and other healthcare providers who will be using trastuzumab biosimilars in clinical practice.

3. THE DEVELOPMENT OF BIOSIMILARS

The development of biosimilar versions of previously approved biological products is based on a rigorous comparability exercise between the biosimilar and the reference product. Different from the marketing authorisation application of the reference product, the goal of the biosimilarity exercise is not to independently establish the clinical benefits of the candidate, as this has already been demonstrated for the reference product (188), but to demonstrate a high degree of similarity to the reference product in terms of quality characteristics, biological activity, efficacy and safety, and to exclude any clinically relevant differences that might exist between the reference product and the biosimilar (14).

Biosimilar development starts with a comprehensive physicochemical and biological characterisation, including a comparison of quality attributes, followed by comparative nonclinical studies (5),(167). Further, clinical comparative testing is required to ensure similar pharmacokinetics (PK) and to confirm similar efficacy and safety to the reference product (5). Compared to the approval pathway for a new biological, the biosimilarity exercise places more emphasis on data from the extensive physicochemical and biological characterisation of the candidate and the comparative analytical testing with the reference product and less on those from clinical trials (5),(14),(168). The nature and extent of each step of the clinical development depends on the level of evidence obtained in the previous steps of the comparability exercise (5),(14). The clinical package generally consists of a phase I study followed by at least one phase III study for one of the approved indications of the reference product (5). In some cases, confirmatory PK and pharmacodynamic (PD) studies might be sufficient to demonstrate clinical biosimilarity (168). At the end of the process, the biosimilar is evaluated on the overall body of evidence for biosimilarity (5). Figure 15 provides a schematic overview of the differences in approach between the development of a new biological and a biosimilar.

FIGURE 15. BIOSIMILAR DEVELOPMENT: AN OVERVIEW OF THE DEVELOPMENT PATHWAY AND THE DIFFERENT TRASTUZUMAB BIOSIMILAR(S) (CANDIDATES) APPROVED OR IN CLINICAL DEVELOPMENT



B

Biosimilar (candidate)	Brand name	Company	Phase I	Phase III	MAA EMA	Status EMA	Status EC
ABP 980	Kanjinti®	Amgen/Allergan	█	█	█	Positive opinion	Approved
BCD-022		Biocad	█	█			
CT-P6	Herzuma®	Celltrion	█	█	█	Positive opinion	Approved
DMB-3111		Meiji Seika Pharma	█				
MYL-1401O	Ogivri®	Mylan/Biocon	█	█	█	Positive opinion	Approved
PF-05280014	Trazimera®	Pfizer	█	█	█	Positive opinion	Approved
SB3	Ontruzant®	Samsung Bioepis	█	█	█	Positive opinion	Approved

a. New medicine versus biosimilar medicine development. Adapted from McCamish (2011) *Mabs* (189). **b.** Key trastuzumab biosimilar candidates approved or in clinical development (status December 2018). EC: European Commission, EMA: European Medicines Agency, MAA: Marketing authorization application.

The EMA has issued several guidance documents to assist sponsors in the development of biosimilars (16),(17),(190), including a product-specific guideline for biosimilar mAbs (188). The EMA applies a case-by-case approach when guiding and evaluating the comparability exercise of a biosimilar (188). In this article, we discuss the clinical development of trastuzumab biosimilars in relation to EMA guidelines; some minor differences exist with FDA guidelines, but they are based on the same principle of establishing biosimilarity to the reference product (5). As the goal of the biosimilarity exercise is different to that of the development of a new product, the design of the clinical studies for the evaluation of biosimilars is also different to that for a new product (5). The studies should primarily be sensitive enough in the choice of design, population and primary endpoint such that any relevant (clinically meaningful) differences between the reference product and the biosimilar could be detected (14),(188).

4. EMA BIOSIMILAR MAB GUIDELINES ON PHASE I PK/PD TESTING

The primary goal of PK studies in biosimilar development is to show comparability in PK between the biosimilar candidate and the reference product. Unless the product carries specific safety concerns, the EMA guideline on mAb biosimilar development and the EMA guideline on investigation of bioequivalence recommend performing PK testing in healthy volunteers (188),(191), as they are less likely to show variability in PK compared to patients, and thus are a more sensitive and homogenous group in which to detect potential clinically meaningful differences in PK

characteristics between the two products (188). It is also advisable to collect supportive PK data in the clinical patient studies. A single-dose study with a parallel group design is advised, due to the long half-life of mAbs and the potential impact of immunogenicity. In addition to conventional PK parameters, including the area under the curve (AUC) and C_{max} , it is advisable to measure safety and immunogenicity parameters in parallel, such as the presence of antidrug antibodies (188).

PK studies can, when available, be combined with PD endpoints, which can add valuable information for the comparability exercise, especially if the PD endpoints are sensitive enough to detect small differences between the biosimilar and the reference product, and if they can be measured with sufficient precision (188). PD testing can potentially also be considered as pivotal evidence to establish clinical biosimilarity, provided that a clear dose-response relationship can be shown and a PD marker that is accepted as surrogate marker of a patient outcome is available (188). If this is not the case, similar clinical efficacy needs to be demonstrated in a phase III comparative trial (188).

5. EMA BIOSIMILAR MAB GUIDELINES ON PHASE III STUDIES

The primary objective of a phase III biosimilarity trial is to demonstrate similar clinical efficacy and safety between the candidate and its reference product. To this end, the EMA advises conducting an adequately powered, randomised, parallel group comparative clinical trial, preferably double-blind, with an equivalence study design, for at least one representative indication (188).

To allow detection of potential differences between the candidate biosimilar and the reference product, the EMA advises conducting the phase III trial in the most sensitive and homogenous patient population (188). Reducing patient-related factors and disease-related factors (e.g. differences in disease severity or different previous lines of treatment) to a minimum will allow potential differences to be attributed to the product, rather than to the patient or the disease (188).

Progression free survival (PFS) and overall survival (OS) are conventional endpoints that are used to demonstrate efficacy in cancer indications. However, it might not be feasible to use these as primary endpoints for phase III biosimilarity trials, as they require a long follow-up period. Furthermore, they might not be sensitive enough to demonstrate comparability, as they can be influenced by non-product-related factors, such as tumour burden, performance status and previous and or later lines of treatment. Therefore, the use of a sensitive endpoint that measures shorter-term activity is recommended, although, when feasible, it is advisable to record PFS and OS in addition (188).

As well as comparable efficacy, comparable safety needs to be demonstrated during phase III evaluation. Adverse events, particularly those described for the reference product, and immunogenicity, by measuring antidrug antibodies, should be assessed (188).

6. TRASTUZUMAB BIOSIMILARS IN CLINICAL DEVELOPMENT

Several trastuzumab biosimilar candidates have been developed, with at least seven of them entering clinical development (Figure 15). Five developers, Samsung Bioepis (SB3), Celltrion (CT-

P6), Mylan/Biocon (MYL-1401O), Amgen/Allergan (ABP 980) and Pfizer (PF-05280014) have submitted their candidate for marketing authorisation to the EMA. In September 2017, the committee for medicinal products for human use (CHMP) recommended the granting of a marketing authorisation for Samsung Bioepis' candidate, SB3 (Ontruzant[®]) (192). Four other recommendations for approval followed for Celltrion's product (CT-P6, Herzuma[®]), ABP 980 from Amgen/Allergan (Kanjinti[®]), Pfizer's candidate (PF-05280014, Trazimera[®]) and Mylan's product (MYL-1401O, Ogivri[®]) (193),(194),(195),(196). These products received a marketing authorisation from the EC (179),(180),(181),(182),(183) and are gradually entering the European market.

Mylan/Biocon, Celltrion, Amgen/Allergan, Samsung Bioepis and Pfizer also submitted a Biologics License Application (BLA) for their candidate to the FDA (178),(197). In December 2017, the FDA announced the approval of Ogivri[®] (MYL-1401O) as first trastuzumab biosimilar in the USA (184). Herzuma[®] (CT-P6) and Ontruzant[®] (SB3) have been approved in December 2018 and January 2019, respectively (185). Pfizer's and Amgen's candidates were rejected by the FDA (198),(199). Pfizer reported that the FDA requested additional technical information, unrelated to submitted safety or clinical data (199). No explanation was given for the rejection of Amgen's candidate (198).

Some of these recently EC/FDA-approved trastuzumab biosimilars or candidates are already on the market in other regions of the world. For example, the candidate co-developed by Mylan and Biocon was launched in India in 2013 (under the brand names Hertraz[®] and CANMab[®], respectively). Celltrion has marketed its candidate as Herzuma[®] in South Korea since 2014 and Biocad's product has been marketed in Russia under the brand name HERTiCAD[®] since 2016 (178). As the regulatory approval process is less stringent in countries such as Russia and India, these products should not be considered as biosimilars before being assessed by regulatory authorities such as the EMA and FDA (178).

6.1 CLINICAL DATA FROM PHASE I TRASTUZUMAB BIOSIMILAR TRIALS

All seven trastuzumab biosimilar candidates showed an equivalent PK profile to the reference product, as primary PK outcomes fell within the pre-specified bioequivalence margin of 80–125%, with a 90% CI. Although EMA guidelines recommend PK testing for mAbs in healthy volunteers, Celltrion and Biocad performed PK testing in HER2+ patients with metastatic breast cancer (200),(201). Other developers, however, followed the EMA guidelines and conducted PK testing for their candidate in healthy volunteers (202),(203),(204),(205),(206),(207). Table 9 provides an overview of the trial parameters and phase I PK outcomes for the different biosimilar candidates. The patient population size varied from 46 (BCD-022) to 174 (CT-P6) healthy volunteers or patients.

TABLE 9. PHASE I PK EQUIVALENCE RESULTS FOR THE TRASTUZUMAB BIOSIMILAR(S) (CANDIDATES)

Biosimilar (candidate)	Study population	Comparator	Dosing	Primary endpoints	Bio-equivalence margins	Primary outcome results	Equivalence to RP established?	Ref
ABP 980 (Amgen/Allergan)	HV (N=157)	EU-RP + US-RP	1 x 6 mg/kg	AUC _{inf}	90% CI, 80–125%	1.00 (0.95, 1.06)	Equivalent to EU-RP and US-RP	(202) (203)
				C _{max}		1.06 (0.99, 1.12) 0.99 (0.95, 1.03) 1.04 (0.99, 1.08)		
BCD-022+ (Biocad)	HER2+ MBC (N=46)	RP	1 x 8 mg/kg	AUC ₀₋₅₀₄	90% CI, 80–125%	80.42-120.87%	Equivalent to RP	(200)
CT-P6 (Celltrion)	HER2+ MBC (N=174)	RP	1 x 8 mg/kg, 8 x 6 mg/kg	AUC _{SS} at cycle 8	90% CI, 80–125%	104.57 (93.64, 116.78)	Equivalent to RP	(201)
DMB-3111 (Meiji Seika)	HV (N=70)	RP	1 x 6 mg/kg	C _{max} AUC _{inf} t _{1/2}	90% CI, 80–125%	log(0.9384)-log(1.0554) log(0.9429)-log(1.0627) log(0.9450)-log(1.0777)	Equivalent to RP	(204)
MYL1401O (Mylan/Biocon)	HV (N=120)	EU-RP + US-RP	1 x 8 mg/kg	AUC _{0-inf}	90% CI, 80–125%	0.97 (91.17, 102.97)	Equivalent to EU-RP and US-RP	(205)
				AUC _{0-last}		0.96 (89.96, 101.94) 0.97 (91.31, 103.05) 0.96 (90.34, 102.29)		
				C _{max}		1.04 (99.00, 109.82) 1.02 (96.42, 107.26)		
PF-05280014 (Pfizer)	HV (N=105)	EU-RP + US-RP	1 x 6 mg/kg	AUC _{0-last}	90% CI, 80–125%	92.66 (86.44, 99.34)	Equivalent to EU-RP and US-RP	(206)
				AUC _{0-inf}		99.94 (93.08, 107.31) 92.15 (86.03, 98.69) 99.83 (93.06, 107.09)		
				C _{max}		91.49 (85.32, 98.09) 97.41 (90.71, 104.62)		
SB3 (Samsung Bioepis)	HV (N=109)	EU-RP + US-RP	1 x 6 mg/kg	AUC _{0-inf}	90% CI, 80–125%	0.969 (0.908, 1.034)	Equivalent to EU-RP and US-RP	(207)
				AUC _{0-last}		0.930 (0.872, 0.991) 0.971 (0.911, 1.034) 0.934 (0.878, 0.994)		
				C _{max}		1.001 (0.935, 1.072) 0.988 (0.924, 1.057)		

AUC: area under the curve, CI: confidence interval, EBC: early breast cancer, HV: healthy volunteer, MBC: metastatic breast cancer, N: number, RP: reference product. +BCD-022 is authorised in Russia, but has not been submitted to FDA or EMA and most likely would not be considered as a biosimilar following stringent FDA or EMA requirements. Data are derived from published scientific literature (full text or abstract).

TABLE 10. PHASE I SAFETY RESULTS FOR THE TRASTUZUMAB BIOSIMILAR(S) (CANDIDATES)

Biosimilar (candidate)	Adverse events	Cardiotoxicity	Antidrug antibody formation	Source/Ref
ABP 980 (Amgen/Allergan)	TEAEs occurred in 84%, in 75% and in 78% of subjects receiving ABP 980, US-RP and EU-RP respectively. One grade 3 SAE in EU-RP group.	NR	No ADA were detected	Abstract (202),(203)
(FTMB)*	No differences in AE between groups (double-blinded, dose-escalation part). In the open-label part, flu-like symptoms and fatigue more frequently reported for the biosimilar.	No signs of cardiotoxicity	No ADA were detected	Full text (208)
BCD-022+ (Biocad)	No significant differences between groups.	NR	NR	Abstract (200)
CT-P6 (Celltrion)	SAEs in 15.8% and 20.9% in CT-P6 and RP group, respectively. TEAEs in 40,8% for CT-P6 and 46.3%, for RP group	2.6% cardiotoxicity in CT-P6 group, 7.5% in RP group	NR	Abstract (201)
DMB-3111 (Meiji Seika)	No significant differences between groups	NR	No subjects developed ADA	Full text (204)
MYL-1401O (Mylan/Biocon)	31, 28, 24 subjects experienced in total 227 (91, 80, 56) TEAEs, (mild to moderate in severity) in the biosimilar, EU-RP and US-RP group respectively. No serious AEs detected. No significant differences between groups.	NR	No subjects developed ADA	Abstract (205)
PF-05280014 (Pfizer)	Numerically higher incidence of pyrexia in biosimilar arm, but severity generally mild. (in 10, 3, 2 patients in biosimilar, EU-RP, US-RP, respectively)	No unusual LVEF values reported	One case of ADA after EU-RP	Full text (206)
SB3 (Samsung Bioepis)	AEs: 69.4%, 63.9%, 69.4%** TEAEs: 36.1%, 44.4%, and 61.1%** Infusion related reactions: 9, 8, 16**	NR	No subjects tested positive for ADA	Full text (207)

*FTMB: biosimilar candidate developed by Synthon Biopharmaceuticals. Synthon entered into a global license agreement with Amgen/Watson in 2012. Amgen/Watson continued further development (incl. phase III clinical trial), global manufacturing and commercialization (2019). **In SB3, EU-RP and US-RP group respectively. +BCD-022 is authorised in Russia, but has not been submitted to FDA or EMA and most likely would not be considered as a biosimilar following stringent FDA or EMA requirements. Data are derived from published scientific literature (full text or abstract). ADA: anti-drug antibody, AEs: adverse events, LVEF: left ventricular ejection fraction, NR: not reported, RP: reference product, SAE: serious adverse event, TEAE: treatment emergent serious adverse event

The reported safety results were overall comparable between the respective biosimilar and the trastuzumab reference product. An overview of phase I safety outcomes is shown in Table 10. Amgen/Allergan reported a treatment emergent adverse event (TEAE) incidence of 84%, 75% and 78% in subjects receiving their candidate (ABP 980), US-sourced trastuzumab and EU-sourced trastuzumab, respectively (202),(203). PF-05280014, Pfizer's candidate, showed a numerically higher incidence of pyrexia in the biosimilar treatment arm, but the severity of this adverse event was reported to be generally mild (206). Phase I comparative testing of SB3 showed a numerical higher TEAE incidence for the EU-sourced trastuzumab and the US-sourced trastuzumab compared to SB3 (44.4%, 61.1%, and 36.1%, respectively) (207). Events related to cardiac function – patients treated with trastuzumab have a small–moderately increased risk of cardiotoxicity – were reported for some of the candidates. In addition, a phase I study for the candidate of Amgen/Allergan (at that time referred to as FTMB, developed by Synthon (209)) by Wisman *et al.* investigated the cardiotoxicity of ABP 980 in healthy volunteers and added a dose-escalation part while monitoring the cardiac function. During the dose-escalation period, no safety concerns that would impede progression of the study towards its bioequivalence phase were detected using either the biosimilar or the reference product (208).

A lack of clinically validated PD markers for trastuzumab means it is necessary to confirm clinical comparability via a phase III trial (188),(210).

6.2 PHASE III EFFICACY AND SAFETY TESTING FOR TRASTUZUMAB BIOSIMILAR CANDIDATES

Six trastuzumab biosimilar candidates have been tested in phase III trials. Reported phase III data are in support of biosimilarity between the candidates and the trastuzumab reference product. For five candidates equivalence in efficacy to trastuzumab was considered to be established (for ABP 980, CT-P6, MYL-1401O, PF-05280014 and SB3) (211),(212),(213),(214),(215),(216),(217),(218). For BCD-022, non-inferiority in efficacy to trastuzumab was demonstrated in metastatic breast cancer patients (219). Differences in the selected patient population, primary endpoints and trial design exist between the different candidates. Table 11 shows a summary of comparative efficacy results for the phase III trials. Candidate-specific phase III results are further discussed in the [supplementary information](#) of this article. The reported safety data of phase III testing can be viewed in Table 12.

TABLE 11. PHASE III TRIAL PARAMETERS AND RESULTS FOR THE TRASTUZUMAB BIOSIMILAR(S) (CANDIDATES)

Biosimilar (candidate)	Company	N patients	Patient setting	Primary endpoint	Equivalence (E)/ Non-inferiority (NI) margin	Primary endpoint results	Ref	EU MAA/MA Status (178)
ABP 980	Amgen/ Allergan	725	Neoadjuvant + adjuvant EBC	tpCR	E margin: -13%, +13% with 90% CI for RD*; 0.759, 1.318 with 90% CI for RR**	RD: 7.3% (1.2, 13.4) ^o 5.8% (-0.5, 12.0) ^{oo} RR: 1.19 (1.033, 1.366) ^o 1.14 (0.993, 1.312) ^{oo}	(217) (218)	Approved as Kanjinti [®] on 16/05/2018(182)
BCD-022⁺	Biocad	126	MBC	ORR	NI margin: -20% with 95% CI for RD in ORR	RD: -0.13% (-19.83%, 18.35%)	(219)	No application
CT-P6^x	Celltrion	475	MBC	ORR	E margin: -0.15, 0.15 with 95% CI for RD*	RD: 5% (-0.14, 0.04)	(220)	Approved as Herzuma [®] on 08/02/2018(181)
		549	Neoadjuvant + adjuvant EBC	tpCR	E margin: -0.15, 0.15 with 95% CI for RD* 0.74, 1.35 with 95% CI for RR**	RD: -0.04 (-0.12, 0.05) RR: 0.93 (0.78, 1.11)	(221)	
MYL-1401O	Mylan/ Biocon	500	MBC	ORR	E margin: -15%, +15% with 95% CI for RD* 0.81, 1.24 with 90% CI for RR**	RD: 5.53 (-3.08, 14.04) RR: 1.09 (0.974, 1.211)	(222) (223)	Approved as Ogivri [®] on 12/12/2018(183)
PF-05280014~	Pfizer	707	MBC	ORR	E margin: 0.8, 1.25 with 95% CI for RR**	RR: 0.940 (0.842, 1.049)	(224)	Approved as Trazimera [®] on 26/07/2018(180)
		226	Neoadjuvant EBC	% pts with cycle 5 C _{trough} >20µg/mL	NI margin: -12.5% with 95% CI for stratified difference in C _{trough}	92.1% for PF-05280014 vs 93.3% for RP-EU (- 8.02%, 6.49%)	(225)	
SB3	Samsung- Bioepis	800	Neoadjuvant + adjuvant EBC	bpCR	E margin: -13%, +13% with 95% CI for RD*; 0.785, 1.546 with 95% CI for RR**	RD: 10,70% (4.13, 17.26) RR: 1.259 (1.085, 1.460)	(216) (226)	Approved as Ontruzant [®] on 15/11/2017(179)

^oBased on local review, ^{oo}Based on central independent review, *EMA advised, **FDA advised, +BCD-022 is authorised in Russia, but has not been submitted to FDA or EMA and most likely would not be considered as a biosimilar following stringent FDA or EMA requirements. ^xThe phase III data in MBC for CT-P6 were not submitted to EMA as part of the marketing authorization application and were thus not evaluated when assessing the totality of evidence for biosimilarity (212). [~]The pivotal phase III trial for PF-05280014 was conducted in the MBC setting. Supportive efficacy data have been gathered in a phase III clinical trial in patients with early breast cancer in the neoadjuvant setting (PK endpoint as primary endpoint) (214).

bpCR: breast pathological complete response, CI: confidence interval, E: equivalence, EBC: early breast cancer, MA: marketing authorisation, MAA: marketing authorisation application, MBC: metastatic breast cancer, N: number, NI: non-inferiority NR: not reported, ORR: overall response rate, RD: risk difference, RP: reference product RR: risk ratio, tpCR: total pathological complete response (breast + lymph nodes). Data are derived from published scientific literature (full text or abstract).

TABLE 12. PHASE III SAFETY RESULTS FOR THE TRASTUZUMAB BIOSIMILAR(S) (CANDIDATES)

Biosimilar (candidate)	Adverse events	Cardiotoxicity	Antidrug antibody detection	Ref
ABP 980 (Amgen/Allergan)	≥1 AE: 80.2% vs 79.5%, Grade ≥3 AE: 14.8% vs 14.1% for ABP 980 and RP respectively ^o	6 patients in the ABP 980 group and 1 in the RP group had cardiac failure adverse events. All events were grade 1 or 2, and patients completed planned doses with no worsening of the cardiac failure event	2 patients in each group developed binding antibodies. Neither tested positive for neutralising antibodies ^o	(217) (218)
	AE: 52.0% vs 57.3% for RP-RP group and switch group, Grade ≥3 AE: 10 in each group ^{oo}	1 patient (0.6%) with cardiac failure in each group ^{oo}	1 patient with binding, non-neutralizing ADAs (switch group) ^{oo}	(227)
BCD-02⁺ (Biocad)	No statistically significant difference in AEs, including SAEs, between groups	Tachycardia (34.92 vs 19.67%), arterial hypertension (20.63 vs 18.03%) atrial fibrillation (0 vs 3.28%), extrasystoles (0 vs 1.64%), aggravated myocardiodystrophy (1.59 vs 0%)	Neutralizing ADA in 1 patient in each group	(219)
CT-P6^x (Celltrion)	AEs comparable between groups [*]	Cardiotoxicity in 8 (3.3%), 10 (4.3%) in biosimilar and RP group respectively [*]	NR [*]	(220)
	STEA: 7% vs 8% for CT-P6 and RP group Grade ≥3 TEAE: 6% vs 8% for CT-P6 and RP group ^{**}	TEAEs due to heart failure in 2% vs 1% for CT-P6 and RP group respectively. Of these, 1 patient (RP group) withdrawn from study (confirmed decrease in LVEF). One grade 1 heart failure (CT-P6 group), but no substantial decrease in LVEF ^{**}	All post infusion ADA tests were negative ^{**}	(221)
MYL-1401O (Mylan/Biocon)	TEAEs and SAEs similar between groups	No difference in median LVEF between groups	ADAs similar between groups	(222) (223)
PF-05280014 (Pfizer)~	SAEs similar in both arms [*]	NR [*]	1 patient developed ADA (EU-RP) [*]	(224)
	Grade 3-4 TEAEs: 38.1% vs 45.5% for PF-05280014 and RP ^{**}	No TEAEs of congestive heart failure or clinically significant LVEF abnormalities were reported in either arm. No notable differences between the treatment groups in mean LVEF results ^{**}	No patients with ADA for PF-05280014 vs 1 patient for RP ^{**}	(225)
SB3 (Samsung-Bioepis)	SAEs: 10.5% vs 10.7% for SB3 and RP ^{**}	2 patients in SB3 group presented with CHF ^{**}	ADA 0.7% vs 0.0% for SB3 and RP ^{**}	(216)
	TEAEs (97.5% vs 96.1% for SB3 and RP) similar between groups ^{***}	14 LVSD events in 11 (2.5%) patients in biosimilar group, 9 LVSD events in 8 (1.8%) patients in RP group. 4 patients (3 in SB3, 1 in RP) reported CHF ^{***}	0.7% in both groups ^{***}	(226)

^oResults from neoadjuvant setting, ^{oo}Results from the single switch treatment arm vs continuing arm in adjuvant phase of the study, ^{*}Reported results are the safety results of the phase III trial in metastatic breast cancer population, ^{**}Reported results are safety results of the phase III trial in early breast cancer patients (neoadjuvant period), ^{***}Reported results are safety results of the phase III trial in early breast cancer patients (neoadjuvant + adjuvant period), ^{****}No phase III safety results yet reported for PF-05280014 in metastatic breast cancer population, ^{*}BCD-022 is authorised in Russia, but has not been submitted to FDA or EMA and most likely would not be considered as a biosimilar following stringent FDA or EMA requirements. ^xThe phase III data in MBC for CT-P6 were not submitted to EMA as part of the marketing authorization application and were thus not evaluated when assessing the totality of evidence for biosimilarity (212). [~]The pivotal phase III trial for PF-05280014 was conducted in the MBC setting. Supportive efficacy data have been gathered in a phase III clinical trial in patients with early breast cancer in the neoadjuvant setting (PK endpoint as primary endpoint) (214). ADA: antidrug antibody AE: adverse event, CHF: congestive heart failure, LVEF: left ventricular ejection fraction, LVSD: asymptomatic left ventricular systolic dysfunction, NR: not reported, RP: reference product, SAE: serious adverse events. Data are derived from published scientific literature (full text or abstract).

A first point of variation in the phase III clinical development of the different trastuzumab biosimilar candidates is the selected patient population. As trastuzumab is approved in the treatment of patients with metastatic breast cancer, early breast cancer and metastatic gastric cancer, the sponsor can decide between different patient settings in which to test its candidate. Without specifying its preference for metastatic breast cancer or early breast cancer, the EMA advises conducting phase III testing in the most sensitive and homogenous population (188). It could be argued that patients with metastatic breast cancer potentially represent a less homogeneous, and thus less sensitive, group due to a number of confounding factors, such as location of metastases, comorbidities, disease severity and the number and type of prior therapies (210),(228),(229),(230). Unless adequately controlled for in the statistical design of the study, this heterogeneity is likely to have an impact on the validity of the trial's conclusions (210). In this regard, early breast cancer might represent a more sensitive and homogeneous population, as patients with early breast cancer generally have fewer confounding characteristics (little or no prior therapy and generally a better performance status) (210),(228),(229),(230). Mylan/Biocon and Biocad chose to conduct their phase III trial in patients with metastatic breast cancer (219),(222),(223), whereas Samsung Bioepis and Amgen/Allergan performed their phase III trial in early breast cancer patients (216),(217),(218), (226). Pfizer and Celltrion conducted two phase III trials, one for each patient setting (225),(224),(220),(221). The phase III Pfizer trial in early breast cancer was based on a PK primary endpoint (225). Celltrion's phase III trial in metastatic breast cancer was not submitted to EMA as part of the marketing authorization application. Table 4 provides an overview of phase III trial parameters for the different candidates. The patient population size varied from 126 (BCD-022) to 800 (SB3) patients.

A second point of variation in clinical testing is the choice of clinical trial endpoint. According to the product-specific EMA guideline of biosimilar mAbs, the clinical endpoint that is most sensitive at detecting product-related differences should be selected (188). A surrogate clinical endpoint that measures shorter-term activity as the primary endpoint may be considered (188). Response rates such as overall response rate (ORR; the proportion of patients in whom a complete response (CR) or partial response (PR) was observed) and pathological complete response (pCR) might be suitable for detecting meaningful differences in activity between the candidate and its reference product, if any (188). In the case of trastuzumab biosimilars, pCR could be deemed as the more favourable endpoint, as it has been shown to correlate with long-term survival in patients with early breast cancer (229),(231). A pooled analysis of 12 randomised controlled trials of neoadjuvant therapy in early breast cancer with approximately 12,000 patients showed that pCR was associated with a long-term survival outcome (232). In this regard, pCR in early breast cancer (Amgen/Allergan, Celltrion, Samsung Bioepis) might be a more desirable approach in establishing clinical biosimilarity than ORR in metastatic breast cancer (Biocon, Mylan, Pfizer).

The definition of the primary endpoint also differs across studies. Of the three sponsors who chose to conduct their (main) phase III trial in early breast cancer, two – Amgen/Allergan and Celltrion – selected pCR in both breast tissue and axillary lymph nodes (total pCR (tpCR)) (217),(218),(221). The

third, Samsung Bioepis, chose pCR in breast tissue alone (breast pCR (bpCR)) as the primary endpoint (216). The tpCR could potentially be deemed as a more convincing primary endpoint by the prescriber, as the eradication of tumour from both breast and lymph nodes has been shown to have a stronger association with improved long-term survival outcomes, than eradication from the breast alone (232),(233).

The selected endpoints for the evaluation of biosimilarity might be less acceptable for oncologists, as they are different from the conventional efficacy endpoints that show patient benefit. However, the goal of the comparability exercise is to demonstrate biosimilarity rather than patient benefit, which has already been demonstrated for the reference product. Therefore, it is important to inform clinicians and other healthcare providers about the rationale behind the biosimilar development pathway and its stepwise approach.

The choice between an equivalence or a non-inferiority trial design is a third point of variation. As the biosimilar concept is based upon demonstrating similarity of the biosimilar to its reference product, the EMA advises an equivalence study design for phase III testing of mAb biosimilars (188). An equivalence trial is intended to demonstrate that neither the candidate nor the comparator (the reference product) is inferior or superior to the other, by showing that any difference in response between the two is likely to lie within a pre-specified range of clinically acceptable differences (234). Most of the companies have adhered to EMA guidance by deciding on a two-sided equivalence test to demonstrate similar clinical efficacy and safety to trastuzumab.

In contrast, Biocad's candidate (BCD-022) was tested in a non-inferiority trial (219). A non-inferiority trial tends to require a smaller sample size than equivalence testing, but only rules out inferiority, not potential superiority, to the reference product (234). The clinical trial of BCD-022 was performed in a relatively small patient cohort of 126 patients with metastatic breast cancer with the non-inferiority margin set at -20% with a 95% CI for risk difference in ORR. The results showed that the lower limit of the 95% CI for risk difference in ORR between the groups (-19.83%) did not exceed the non-inferiority margin, demonstrating non-inferiority to trastuzumab (219). BCD-022 was approved by the Ministry of Health of the Russian Federation at the beginning of 2016, but has not been submitted for approval in Europe or in the USA (178). Based on the results of this study it is unlikely that BCD-022 would be granted marketing authorisation as a biosimilar by rigorous EMA standards. Pfizer also performed a non-inferiority phase III trial (in a neoadjuvant setting, C_{trough} at steady state as the primary endpoint with secondary efficacy endpoints) (225). However, Pfizer's pivotal phase III trial adhered to an equivalence design (in patients with metastatic breast cancer, with ORR as the primary endpoint) (224).

For SB3, the upper boundary of the 95% CI for risk difference in bpCR (95% CI: 4.13, 17.26) exceeded the predefined equivalence margin (-13%, +13%) (216), ruling out non-inferiority but not potential superiority. The boundaries of the 95% CI for the ratio of bpCR (95% CI: 1.085, 1.460) fell within the predefined equivalence margin (0.785, 1.546), demonstrating equivalence (216). For ABP 980, based on predefined local review, the lower boundaries of the 90% CI for both risk difference

and risk ratio of pCR fell within the pre-specified equivalence margins and the upper boundaries of the CI for both exceeded the equivalence margins, thereby excluding non-inferiority but not potential superiority (217),(218). In sensitivity analyses based on central independent review of tumour samples by blinded pathologists, the risk difference and risk ratio of pCR fell within the equivalence margins (217),(218). These observations for SB3 and ABP 980 were deemed at least partially confounded by a small downward shift in ADCC activity in the EU trastuzumab batches (as described in the literature (235)) that were used in their phase III comparative trial, as stated in the European public assessment report of both Ontruzant® (SB3) and Kajinti® (ABP 980) (211),(215). Both SB3 and ABP 980 have been approved as a biosimilar of trastuzumab, as the overall body of evidence sufficiently demonstrated biosimilarity compared to the reference product (211),(215).

7. EXTRAPOLATION OF INDICATIONS

A biosimilar candidate can be considered for approval for one or more indications for which the reference product is approved, without itself being subjected to clinical testing for all of these indications. This regulatory concept is called extrapolation of indications (27),(188). The main rationale for extrapolation of data to other indications is to avoid unnecessary clinical studies (27),(236),(237). Extrapolation is decided on a case-by-case basis, taking into account the overall evidence gathered in the comparability exercise of the candidate, including safety, efficacy and immunogenicity data, in a key indication that is suitable to detect clinically meaningful differences, and the scientific justification for extrapolating (188). The scientific justification requires detailed knowledge of the mechanism of action and the targets involved, the PK profile, immunogenicity and adverse events that might be expected in the different indications (17), (27),(188). If the mechanism of action is complex and involves multiple receptors or binding sites that contribute differently to the different therapeutic indications, additional data might be required to allow for extrapolation (237).

Extrapolation is an established regulatory principle that is not only applied in the context of biosimilars, but also for example when a new formulation of a licensed product is developed (27),(236). For instance, Roche has developed a subcutaneous formulation of trastuzumab, which was clinically tested in the neoadjuvant setting and was approved in Europe in 2013 for all indications after extrapolation to the metastatic setting (27),(238). Although the concept of extrapolation is essential in the biosimilar development pathway, the use of extrapolation of indication has raised concerns amongst healthcare providers (27),(186). In particular, if the reference product is used across different therapeutic areas (e.g. autoimmune disease and oncology), different pathologies (e.g. breast cancer and gastric cancer) or different disease settings (e.g. first line and second line) extrapolation can be perceived as challenging. The first biosimilar of rituximab, Truxima®, was approved for all indications of rituximab including B-cell lymphoma, after it was tested in a pivotal phase III trial in rheumatoid arthritis patients and supportive data were gathered in patients with advanced follicular lymphoma (similarity in PK and non-inferiority in efficacy) (239). For trastuzumab biosimilars, extrapolation has already been granted by the EMA both from early

breast cancer to metastatic breast cancer and metastatic gastric cancer (SB3, ABP980 and CT-P6) as well as from metastatic breast cancer to early breast cancer and metastatic gastric cancer (MYL-1401O), based on the totality of evidence for biosimilarity (211),(212),(213),(215).

8. CLINICAL IMPLEMENTATION AND STRATEGIC CONSIDERATIONS FOR TRASTUZUMAB BIOSIMILARS

8.1 SWITCHING BETWEEN THE REFERENCE PRODUCT AND BIOSIMILAR VERSIONS OF TRASTUZUMAB

Initiating treatment with an approved trastuzumab biosimilar is as safe and effective as initiating treatment with the reference product. However, questions have been raised about switching between a reference product and its biosimilar or between biosimilars of the same reference product (240). Although no issues have been identified thus far with switching from a reference product to its biosimilar (112), a concern is that switching could potentially lead to increased immunogenicity, due to the subsequent exposure to potentially different sets of epitopes due to minor differences that might exist between the reference product and the biosimilar. An increasing amount of data from both phase III extension trials and real-world studies evaluating the impact of switching is available for biosimilars of various products, including infliximab, etanercept and adalimumab (112),(241).

In 2016, the European Society for Medical Oncology published a position paper about biosimilars, indicating that the decision to switch from the reference product to a biosimilar should be taken by the physician (242). Furthermore, when switching, the patient should be adequately informed and subsequently monitored, allowing any adverse events to be traced to the relevant product (242).

Thus far, eight switching studies with anticancer mAb biosimilars have been published (241). Seven of these studies were conducted for rituximab biosimilars and one study has been conducted for a trastuzumab biosimilar, ABP 980 (241). Reported results indicated that switching from the trastuzumab reference product to ABP 980 following surgery was safe in patients with early breast cancer (single switch, parallel arm, N=171 in each arm). The frequency and severity of adverse events did not increase, no unexpected safety signals were noted and no increased incidence of antidrug antibodies was reported (227).

Trastuzumab is a relatively safe molecule with a low immunogenic potential for a mAb, limiting the risk of immunogenicity-related adverse events. Although switching will normally occur less frequently than for diseases requiring lifelong chronic biological treatment, it still remains a possibility in practice, as trastuzumab is administered for up to one year in early breast cancer or until disease progression in metastatic breast cancer and metastatic gastric cancer (173). Although no safety issues are to be expected when switching, a cost-benefit assessment could be of interest to investigate the trade-off between the savings from switching to a less expensive version and the costs from implementing the switch, given the relatively short treatment period.

8.2 STRATEGIC CONSIDERATIONS

The different companies developing trastuzumab biosimilars have followed a variety of clinical development pathways, demonstrating the leeway given to biosimilar sponsors in determining the clinical development strategy. There might be various reasons for these different approaches, although we believe there are also important strategic considerations behind the decisions. These considerations could apply to obtaining marketing authorisation as quickly as possible or supporting the biosimilar in such a way that it will receive higher product acceptance by stakeholders and more support in the market. Running a trastuzumab biosimilarity trial for metastatic breast cancer might benefit from faster patient accrual and possibly more quickly attainable clinically relevant endpoints compared to early breast cancer, for example. Once licensed, early breast cancer will be an extrapolated indication for these biosimilars (if decided so by the EMA), but with potentially more reluctance among prescribers to accept this. On the other hand, running a trial for early breast cancer might be more difficult in terms of attracting patients, but clear proof in this indication might be more convincing and avoid discussions by healthcare providers relating to extrapolated indications once the product is on the market.

8.3 POTENTIAL IMPLICATIONS OF THE MARKET ENTRY OF TRASTUZUMAB BIOSIMILARS

Roche has developed a subcutaneous formulation of trastuzumab, which is reported to be more time efficient (shorter patient chair time and active healthcare professional time) than intravenous infusion (243). When the total treatment costs of intravenous trastuzumab and the subcutaneous version were compared in the Netherlands in 2017, the subcutaneous preparation and administration cost (including staff, material, premedication and societal costs) was found to be 45% lower than the intravenous administration. However, this cost accounts for a limited share (less than 10%) of the total treatment cost (preparation and administration cost plus the medicine price) (244). The administration cost is thus unlikely to outweigh the potential difference in medicine prices (lower priced intravenous reference product due to competition or lower priced intravenous biosimilar, versus patent protected, more expensive subcutaneous version).

The arrival of biosimilars can potentially encourage manufacturers to invest in the development of new, innovative products (171),(245). Besides the subcutaneous formulation, Roche has developed additional anti-HER2+ biopharmaceuticals, Perjeta[®] and Kadcyra[®] (245),(246). Perjeta[®] blocks receptor dimerisation by targeting domain II of the extracellular component of HER2, whereas Kadcyra[®] combines the actions of trastuzumab with an anti-microtubule cytotoxic agent to facilitate intracellular delivery of the drug (246)(247). Both therapies are implemented in clinical practice and are even more expensive than Herceptin[®], with treatment costs of approximately 75,000 euros (18.5 months of treatment with Perjeta[®]) and 57,000 euros (10 months of treatment with Kadcyra[®]), based on Belgian list prices (176). Despite these innovations, trastuzumab is likely to remain a cornerstone in the treatment of HER2+ cancer (246),(248) and trastuzumab biosimilars can play a significant role in cost containment. Biosimilars have a good value proposition, as their adoption allows to reduce the healthcare budgetary burden and or potentially relocate funds to new therapies

(10). Biosimilar discounts can be as high as 60–90% of the originator list price (depending on the product class and country) (39). Furthermore, the increased competition can drive down prices not only for the reference product, but also for the total therapy area segment, as previously identified by IMS Health for other biosimilar classes (125),(249).

Beyond financial benefit, the use of biosimilars ultimately provides patient benefit, too. Biosimilar market entry has previously been shown to improve patient access to biological medicines (an increase in the number of treated patients and/or more timely access to therapy) (171). For example, in Sweden, the launch of the biosimilar filgrastim led to the reassessment of physician guidance on granulocyte colony-stimulating factor (G-CSF) prescribing, and promoted filgrastim to first-line supportive care in cancer. Subsequently, the uptake of filgrastim increased five-fold (171). As trastuzumab is not currently widely accessible around the world due to its high cost (177), the entry of more affordable versions of trastuzumab could open up treatment access. Accordingly, this requires a sufficiently reduced price of the trastuzumab biosimilars and/or the reference product itself (250). In a physician survey in the USA and emerging markets by Lammers and colleagues in 2014, nearly half of the oncologists questioned reported that they would increase the use of HER2 targeted therapy across treatment settings if a trastuzumab biosimilar was available at a lower cost (177). The extent of the savings that can be realised and the improvement in patient access to trastuzumab will ultimately depend on the understanding and subsequent confidence of oncologists to prescribe trastuzumab biosimilars. Physicians may expect products that are equally safe, qualitative and effective as the reference product, and that have been rigorously evaluated by regulatory authorities such as the EMA, based on sound scientific principles.

The different routes taken in the clinical development of trastuzumab biosimilars demonstrate that sponsors have some flexibility in setting up the clinical development of their product. This should, however, not influence the confidence in a trastuzumab biosimilar once approved. Although a hierarchy could be made based on the clinical assessment of biosimilars (230), this would not automatically allow the ranking of one trastuzumab biosimilar above another, as biosimilarity is first established through analytical studies and further evaluated on the total body of evidence, not solely on the design and results of the clinical studies. Furthermore, this would not correspond with the concept of biosimilarity. One biosimilar might have a more extensive or sensitive clinical data package than another, but this does not mean that this biosimilar should be considered more similar to the reference product than the other, as all candidates need to prove their overall similarity to the reference product. However, a more elaborate and sensitive clinical package might gain acceptance more convincingly by healthcare providers.

9. CONCLUSION

Several trastuzumab biosimilars are gradually entering the European market. These biosimilars represent an important opportunity for society in terms of cost savings and for patients by opening up treatment access. Although some differences do exist between the clinical development packages (in terms of trial setting, clinical endpoint and patient population) of the trastuzumab biosimilars, these differences need to be viewed in the context of the totality of evidence approach for biosimilarity, in which the clinical program is a confirmatory step. In order to make informed decisions and to capture the potential of biosimilars, it is essential to provide oncologists with adequate information on the nature of the biosimilarity exercise and how the clinical development of a biosimilar is tailored to meet the licensing requirements.

1. ABSTRACT

Background: Access to reliable information on biosimilars and the scientific principles underlying their development, regulatory approval and appropriate use in clinical practice is indispensable for healthcare professionals and patients. Beyond evaluation and approval, which generally takes place at EU-level for biosimilars, European and national regulators have a key role in providing stakeholders with information and clear guidance on biosimilars and their use. The latter includes guidance on interchangeability, and its related practices switching and substitution, which fall under the responsibility of the individual Member States.

Objectives: This study aims to (i) review information and position statements on biosimilars from the EMA and national medicines agencies and (ii) explore the perspective of healthcare and pharmaceutical industry professionals on the role of regulators in enabling acceptance and use of biosimilar medicines.

Methods: This study consists of (i) a comparative review of information and position statements about biosimilars by the European and national regulatory medicines agencies (n =32) and (ii) qualitative semi-structured interviews with healthcare providers and pharmaceutical industry representatives in Europe (n=14).

Results: The comparative analysis of regulatory information showed that information and guidance on biosimilars offered by national medicines agencies varies across European countries, and is limited or absent in multiple instances. Approximately 40% (13/31) of the national medicines agencies' websites did not offer any information regarding biosimilars, and for about half (15/31) no educational materials about biosimilars were provided. Approximately half of websites that did offer educational material made use of EMA's biosimilar stakeholder material. Only less than half of national medicines agencies provided guidance on biosimilar interchangeability and switching (8/31 and 12/31 respectively). Among the national medicines agencies that did offer guidance, the extent (e.g. elaborate position document versus brief statement) and the content (e.g. full endorsement versus more cautious statement) of the guidance differed substantially. Study results indicated that strong involvement in EU-level biosimilar regulatory activities seemingly correlates with the availability of more elaborate information and guidance on the national level. Ten national medicines agencies offered information regarding automatic substitution of biologicals, a practice which is at present not allowed in most European countries. Interviewees underwrote the need for (national) regulators to intensify biosimilar stakeholder guidance, especially in terms of providing clear statements regarding biosimilar interchangeability and switching, which in turn can be disseminated by the relevant professional societies to the local stakeholders.

Conclusion: This study revealed that, despite strong EU-level regulatory biosimilar guidance, information and guidance about biosimilars and their use differs considerably across European national regulatory medicines agencies in terms of availability, extent and content. This heterogeneity, together with the absence of a clear EU-wide position on interchangeability, may

instil uncertainty among stakeholders about the safety of an exchange between a reference product and biosimilar. Regulators should strive for a clear and common EU scientific position on the interchangeability of biosimilars to bridge this gap. Without aiming to interfere with local policy making or prescriber practices, such unified position is required to unambiguously inform healthcare professionals and patients. Furthermore, there is an important opportunity to expand information on biosimilars and the science underpinning their evaluation and safe use at the national level, and leverage existing, EU developed healthcare professional and patient information materials more actively in this regard.

2. INTRODUCTION

With the expiration of patents and other exclusivity rights on many best-selling and high-cost biologics, biosimilar alternatives have gradually been entering the European market over the past years. As defined by the European Medicines Agency (EMA), a biosimilar is a biological medicine that is highly similar in quality, safety and efficacy compared to an already approved biological product (also called the reference product) (6),(14). Biosimilar market entry and the resulting price competition has shown to positively impact healthcare systems across Europe, in terms of lowering treatment cost of biological therapies and in some instances by broadening patient access to biological medicines (22),(39). Europe has pioneered the regulation of biosimilars by establishing a robust regulatory framework for marketing authorization in 2004, and the very first biosimilar approval (Omnitrope®, a biosimilar of somatropin) in 2006 (6),(19).

Over the past fifteen years, considerable experience with biosimilar evaluation has been accumulated, and the EMA has issued and updated scientific guidelines outlining biosimilar development data requirements (251). Biosimilar approval is based on the demonstration of biosimilarity, i.e. a high level of similarity to the reference product in terms of quality, safety and efficacy to the reference product. To this end, comprehensive comparability studies with the reference product are carried out (6),(14). With the exception of some low-molecular weight heparins, all biosimilars approved for use in the EU have been approved via the centralised procedure, i.e. through the EMA, as they use biotechnology for their production (6). Since the first biosimilar approval in 2006, over 65 biosimilars have been granted marketing authorization in Europe, and are available in different disease areas such as haematology, rheumatology, gastroenterology and oncology (116). The European biosimilar landscape is likely to continue to expand in future years. Presently, ten biosimilar marketing authorization applications are under review by EMA's Committee for Medicinal Products for Human Use (CHMP) and approximately 120 originator biologicals products are expected to lose exclusivity in the next ten years, opening up more opportunities for biosimilar development and competition (11).

Despite the strong EU track-record in terms of biosimilar evaluation and approval, which resulted in the availability of a multitude of biosimilar products with an EU-wide marketing authorization, biosimilar adoption has been of varying success across healthcare systems and products (39).

Reasons for low biosimilar use are multifaceted and some may be specific to local context and healthcare organization. However, overall, one of the main commonalities appears to be a limited understanding of biosimilars among healthcare providers and patients which in turn may hamper willingness to use them (119). Several studies have shown rather limited knowledge and confidence levels in biosimilars among European healthcare providers and patients, indicating uncertainty and resulting in hesitation to use them (89),(252),(68),(64),(90),(87),(253),(78),(254). Limited understanding and trust in biosimilars may in part be explained by the fact that the science underpinning biosimilar development poses a new paradigm, different from that of the development of novel drugs, for stakeholders to become acquainted to, understand and trust, and a general lack of understanding of biological medicines and biotechnology (109),(255). Furthermore, disparagement and misinformation about biosimilars, whether intentional or otherwise, may have contributed to misconceptions about biosimilars among healthcare providers and patients (45),(47).

Over the past years, the science behind biosimilars has been progressively adopted by healthcare professional societies, endorsing biosimilar use in their position statements (242),(256),(257). The EMA, together with the European Commission (EC), took an active stance and made considerable efforts in developing biosimilar educational resources for healthcare professionals and patients. The EC committed itself to the organization of a yearly multi-stakeholder conference on biosimilar medicines, providing a platform to relevant stakeholders to share experiences on the use of biosimilars and discuss relevant policy choices and practices (258). Also national medicines agencies, and various healthcare professional and patient organizations on both pan-EU and national level did so (6),(105),(106),(259),(260),(145),(258). Yet, uncertainties and a general lack of familiarity with biosimilars appear to persist among the broader population of healthcare professionals and patients, underlining the need for continued information and guidance and possibly more integrated approaches in terms of reaching the relevant stakeholders (119),(140).

Guidance may be especially needed regarding the interchangeable use of biosimilars with their reference product, since most best-selling biologicals are used in a chronic setting (97). Interchangeability is defined as *“the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another”* (6). Questions on the appropriateness of exchanging a reference product with a biosimilar (or *vice versa*) or exchanging one biosimilar with another of the same reference product (if done by the prescribing physician, termed ‘switching’, or if done by the pharmacist, termed ‘substitution’) (6) should be addressed in a clear and unambiguous manner. Contrary to the evaluation and approval of biosimilars, which is generally centrally organized, decisions related to prescribing practices of approved medicines, including on interchangeability, fall under the responsibility of the individual EU Member States (6). As such, EMA has no official position or does not make recommendations on the interchangeability of biosimilars with their reference product (6),(261). The vacuum of guidance on EU level in this regard may be understood by some as a lack of crystallization of regulatory knowledge and endorsement of the safety of switching a reference product to its biosimilar or *vice versa*.

It is essential for healthcare professionals and patients to have access to trustworthy information about biosimilars, and their use. Regulators, as trusted and unbiased stakeholder, have a crucial role in providing this type of information. The availability of guidance and clear position statements on interchangeable use, including switching and substitution practices, from medicines agencies about biosimilars may be especially important to build confidence in biosimilars and enable their appropriate use.

The aim of this study is twofold. First, we aim to analyse how regulators on pan-European and national level provide information and guidance on biosimilars and their use, with a focus on guidance related to interchangeability, switching and substitution. Second, we explore the perspective of two demand side stakeholder groups; healthcare and pharmaceutical industry professionals, on the role that regulators have in enabling acceptance and use of biosimilar medicines.

3. METHODS

A mixed methods design was employed, consisting of (i) a review and comparative analysis of available regulatory information on biosimilars in Europe and (ii) semi-structured stakeholder interviews to gain qualitative insights.

3.1 REVIEW AND COMPARATIVE ANALYSIS OF INFORMATION AND POSITION STATEMENTS FROM EMA AND NATIONAL MEDICINES AGENCIES ABOUT BIOSIMILARS AND THEIR USE

To analyse the availability, type and extent of information and guidance provided by the European and national medicine agencies on biosimilars, the EMA and the national competent authority (NCA) websites in Europe were reviewed for content on biosimilars. Websites of the EMA and NCAs of the 27 EU Member States, the European Economic Area (EEA) (Norway, Liechtenstein and Iceland) and the UK, were screened (31 European countries in total). NCA websites were identified via the list provided on EMA's website and screened up to March 2019 (262). The overview of consulted NCA websites can be found in [Supplementary Table S1](#). For countries for which two agencies were listed, information was integrated and counted as one in the results section. In total, 36 websites were screened for biosimilar information, both in English and with translated terms in the local language. Non-English retrieved information was translated to English with the help of an online text translator. Identified information was extracted based on a predefined set of parameters and subsequently tabulated in Microsoft Excel.

Next, a sub analysis was conducted to explore a potential positive correlation between the information and guidance provided on biosimilars on a national level and the country's involvement in EU-level biosimilar regulatory activities. In order to assess the latter, countries' representation in the EMA's Biosimilar Medicinal Products Working Party (BMWP) and their involvement in the central evaluation of biosimilars was reviewed. To this end, the publicly available information on the composition of the BWMP was consulted (overview provided in [Table S2](#)) and the European Public Assessment Report (EPAR) of every centrally approved biosimilar with a valid marketing

authorization was screened for information on rapporteur and co-rapporteurships (overview provided in [Figure S1](#)). The analysis covered biosimilars that received marketing authorization or a positive opinion pending EC decision between 2006 and 2020. Products that were withdrawn post-authorization and duplicate marketing authorizations were excluded.

3.2 QUALITATIVE STAKEHOLDER INTERVIEWS

To elicit qualitative insights, needs and proposals regarding regulatory guidance and information dissemination for biosimilars, exploratory semi-structured interviews (n=14) were conducted with two European demand-side stakeholder groups, i.e. healthcare professionals and pharmaceutical industry representatives. A purposive sample of interview participants was gathered via professional organizations and via the network of the research group. A topic guide was designed, evaluated and piloted with one participant per stakeholder group. [Table S3](#) in Supplementary information provides an overview of the topics discussed during the interviews. Interviews were conducted face-to-face or via teleconference between February 2019 and April 2019. Interviews were audio-recorded and transcribed *ad verbatim* with the written informed consent of the participant. Interviews were conducted until data saturation (263). The *ad verbatim* transcripts were pseudonymized, coded and thematically analysed according to the thematic framework approach, using NVivo qualitative data analysis software (59).

4. RESULTS

4.1 COMPARATIVE ANALYSIS OF INFORMATION AND POSITION STATEMENTS FROM EMA AND NATIONAL MEDICINES AGENCIES ABOUT BIOSIMILARS AND THEIR USE

4.1.1 BIOSIMILAR INFORMATION AND EDUCATION RESOURCES FOR HCP AND PATIENTS FROM REGULATORS ACROSS EUROPE

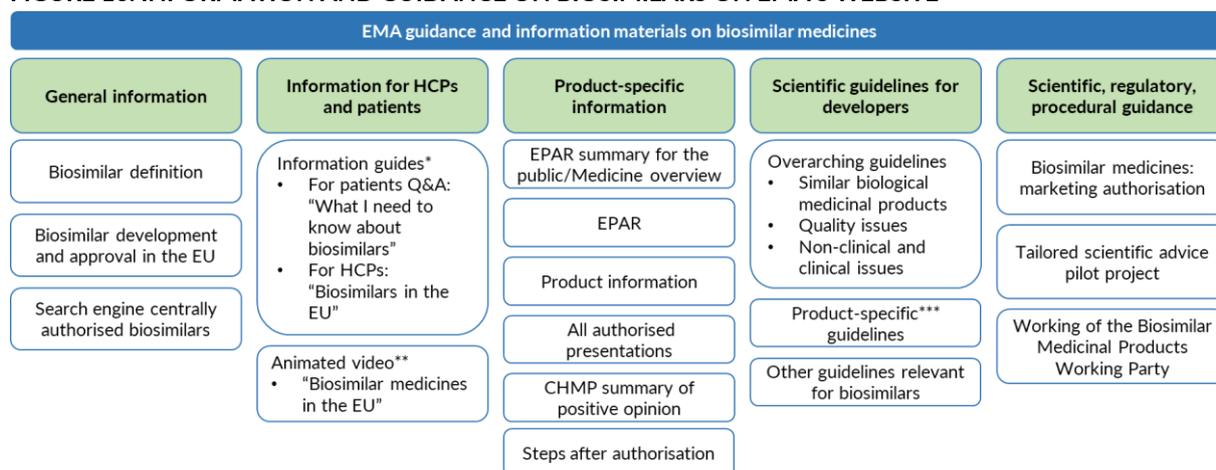
Besides providing scientific, regulatory and procedural guidance as part of one of the Agency's principal responsibilities as regulatory authority, the EMA developed together with the EC educational materials on biosimilars for healthcare professionals and patients (6), (106),(264). Both the information guide for healthcare professionals and the information leaflet for patients were made available in all 23 official EU languages. In addition, an animated educational video "*Biosimilar medicines in the EU*" was developed and translated into multiple EU languages. The EMA's website has a dedicated landing page for biosimilar related information, which includes hyperlinks to these educational materials and other relevant information resources, on biosimilars in general and on a product-specific level (264). [Figure 16](#) provides an overview of the information and guidance that is provided by EMA on biosimilar medicines.

On the level of the individual Member States, the provision of information and educational materials on biosimilars varied between countries. Surprisingly, of the 31 medicines agencies, only 19 offered information about biosimilar medicines ([Figure 17](#)). Of the national medicines agencies that offered information about biosimilars, all except for Austria, Malta and Norway, also provided

educational resources on biosimilars. The type of educational material displayed differed across agencies. Either these were designed by the NCA itself or originated from the EMA/EC prepared stakeholder information material. Eight agencies relied fully or in part on one or multiple of the EMA's/EC's educational resources on biosimilars.

Table 13 presents an overview of the availability of information and educational materials on biosimilars by national medicines agencies. Educational materials provided by regulators included videos, radio spots, booklets, workshops, conferences, position papers, campaigns and presentations. An overview of educational materials and initiatives per NCA is presented in Supplementary Table S4.

FIGURE 16. INFORMATION AND GUIDANCE ON BIOSIMILARS ON EMA'S WEBSITE



*Available in 23 official EU languages, **Available in English and other EU languages (Dutch, English, French, German, Italian, Polish, Portuguese, Spanish), ***for recombinant granulocyte-colony stimulating factor, low-molecular-weight heparins, recombinant human insulin and insulin analogues, interferon beta, monoclonal antibodies, recombinant erythropoietins, recombinant follicle-stimulating hormone, somatropin. N: number, NCAs: national competent authorities

FIGURE 17. AVAILABILITY OF INFORMATION AND POSITIONS ON BIOSIMILARS AND THEIR USE BY NATIONAL MEDICINES AGENCIES

N total = 31

■ Available □ Not available

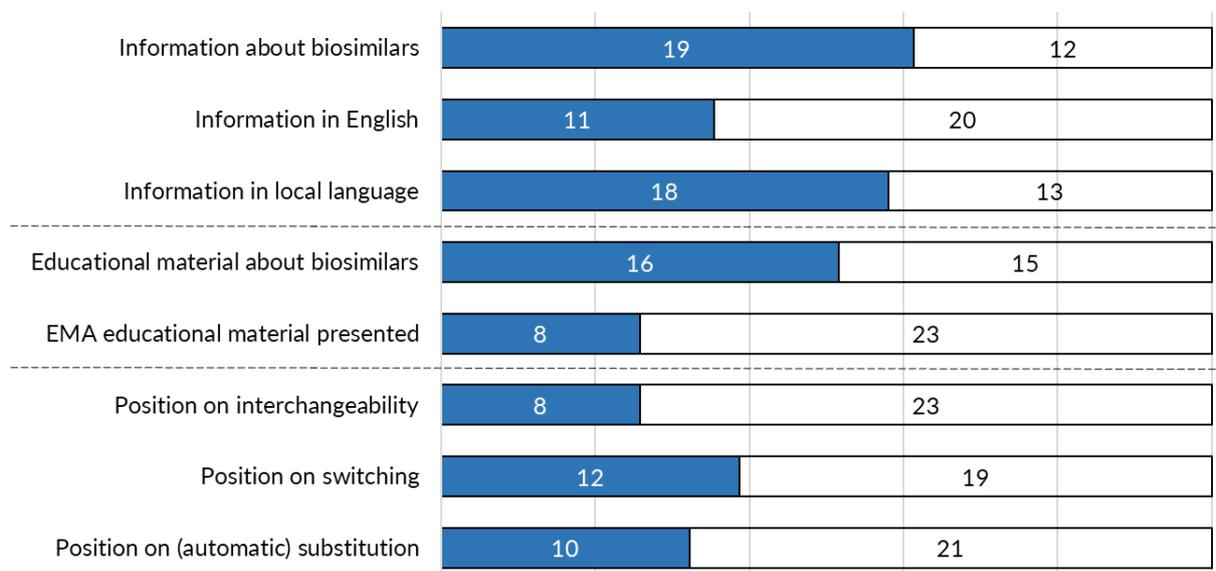


TABLE 13. AVAILABILITY OF INFORMATION AND GUIDANCE ON BIOSIMILARS BY NATIONAL MEDICINES AGENCIES

Country	Information on biosimilars	Educational material		Inter-changeability position	Switching position	Substitution position
		Available	EMA/EC material*			
Austria	Y	N	N	N	N	N
Belgium	Y	Y	N	N	Y	Y
Bulgaria	N	N	N	N	N	N
Croatia	Y	Y	Y	Y	Y	Y
Cyprus	N	N	N	N	N	N
Czech Republic	N	N	N	N	N	N
Denmark	Y	Y	N	N	Y	N
Estonia	N	N	N	N	N	N
Finland	Y	Y	N	Y	Y	Y
France	Y	Y	N	Y	N	N
Germany	Y	Y	N	N	Y	Y
Greece	N	N	N	N	N	N
Hungary	Y	Y	Y	N	N	N
Iceland	Y	Y	Y	N	N	N
Ireland	Y	Y	N	Y	Y	Y
Italy	Y	Y	Y	Y	Y	N
Latvia	N	N	N	N	N	N
Liechtenstein	N	N	N	N	N	N
Lithuania	N	N	N	N	N	N
Luxembourg	N	N	N	N	N	N
Malta	N	N	N	N	N	N
Netherlands	Y	Y	Y	Y	Y	Y
Norway	Y	N	N	N	Y	Y
Poland	N	N	N	N	N	N
Portugal	Y	Y	Y	N	Y	Y
Romania	N	N	N	N	N	N
Slovakia	Y	Y	Y	N	N	N
Slovenia	N	N	N	N	N	N
Spain	Y	Y	Y	N	N	N
Sweden	Y	Y	N	Y	Y	Y
UK	Y	Y	N	Y	Y	Y

*EMA/EC's HCP and/or patient guide and/or animated video presented on website

4.1.2 REGULATORY POSITION STATEMENTS ON INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION

As prescribing practices and advice to prescribers falls within the remit of the individual Member States, there is no official position or recommendation on the interchangeability of biosimilars at the EU level (6). However, a group of regulators, members of the Biosimilar Medicinal Products Working Party (BMWP), EMA/CHMP's European expert group on biosimilars, published under personal name an article stating that biosimilar products authorized in the EU are interchangeable (97). More in particular, they conclude that the demonstration of biosimilarity, together with post-marketing surveillance, adequately ensures interchangeability of EU-approved biosimilars under supervision of the prescriber. Further, they mention that, if needed, the patient should receive proper training on the administration of the new product (97).

In the EMA/EC biosimilar information guide for healthcare professionals, clear definitions have been provided on interchangeability, switching and substitution. The guide goes further with stating that *"there is no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines"*. Furthermore, it includes that *"any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines"* (6). In the EC's patient Q&A leaflet on biosimilars, mention is made that switching is a growing practice in some Member States" (106).

In 2019, the International Coalition of Medicines Regulatory Authorities (IMCRA), bringing together heads of 29 medicines regulatory authorities from different regions of the world – of which the EMA and EU national medicines agencies are member - released a position statement for healthcare professionals aiming to provide them with assurance and confidence in biosimilar use. On switching, they comment that it is *"an accepted clinical practice in many countries"* (22). Table 14 provides an overview on available statements and guidance by regulators and regulatory agencies at the European level.

On the level of the individual Member States, positions on interchangeability, switching, and substitution for biological medicines were not provided by all and varied in extent and content. Despite this being the responsibility of the Member States, guidance about interchangeability, switching, and substitution was absent from more than half to two third (60% to 74%) of national medicines agencies (

Table 13). Figure 18 provides a schematic overview of the type of positions provided by national medicines agencies on interchangeability, switching, and substitution.

With regards to interchangeability, only eight out of 31 medicines agencies offered an explicit statement. When available, positions varied between agencies in terms of message. While some regulatory agencies endorsed interchangeability of biosimilars, such as the Finnish Medicines Agency (FIMEA) or the Dutch Medicines Evaluation Board (MEB) providing already an explicit position in 2015, others provided a more reserved statement (Overview of positions on interchangeability in Supplementary [Table S5](#)). The Swedish agency was more cautious, stating that

“the risk of immunological reactions during frequent changes is incompletely elucidated”. Contrary to most agencies which generally provided a brief statement of a few sentences, FIMEA published a dedicated four page report to define their position on the interchangeability of biosimilars, providing information on context and explaining the scientific rationale behind their position (265).

TABLE 14. EUROPEAN BIOSIMILAR INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION POSITIONS

EMA/EC HCP and patient biosimilar information guides (2017)

- The HCP guide explain that EMA does not regulate interchangeability, switching or substitution as these practices are under the responsibility of Member States. As such, no position is provided about interchangeability or substitution.
- However, some supportive messages dispelling concerns about switching were included:
 - HCP guide: “There is no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines”, “if a patient is switched from one biological medicine to another with the same active substance, it is important to record the tradename and batch number for each of the medicines”, “any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines.”
 - Patient Q&A: “It is possible to switch from a biological reference medicine to a biosimilar medicine and this is a growing practice in some Member States. Any decision on switching should be taken by your doctor in consultation with you, and taking into account any policies that your country might have regarding the use of biological medicines.”

Scientific publication by group of individual European regulators Kurki *et al.* (2017) (97) - ‘Interchangeability of Biosimilars: A European Perspective’

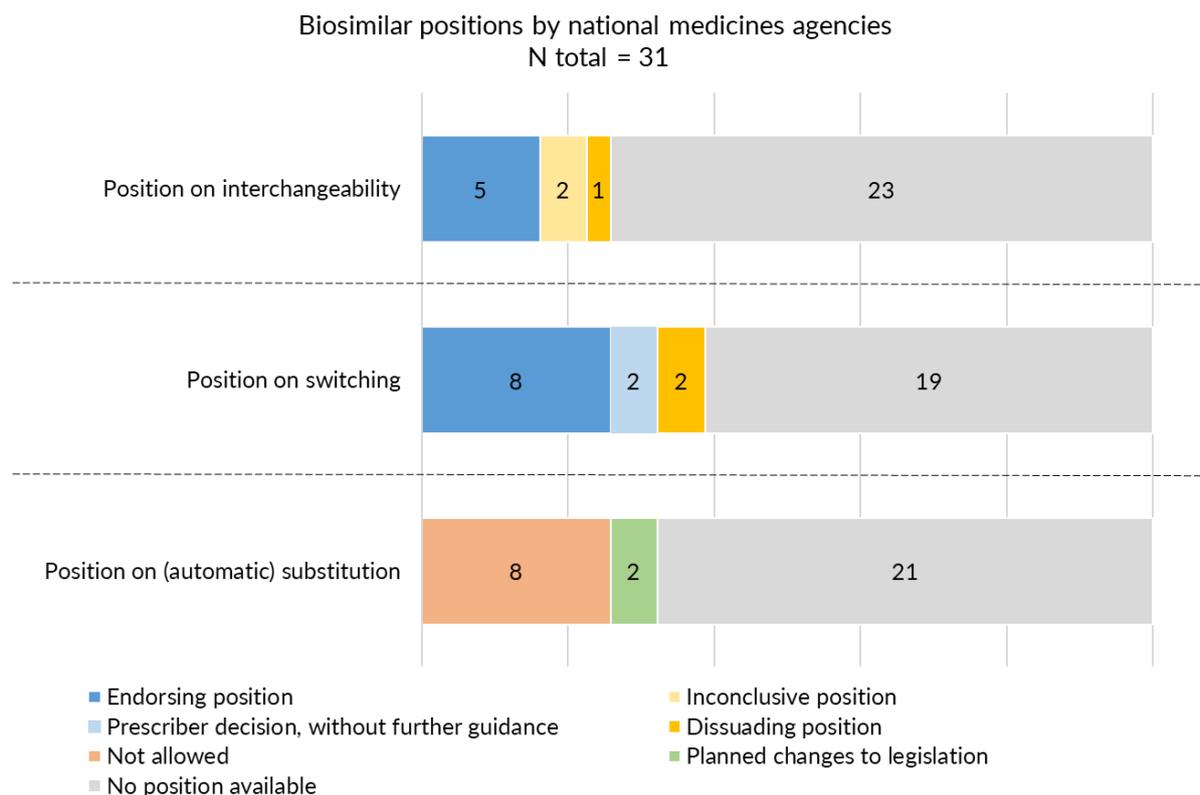
- “Because of the high similarity, there is no reason to believe that the body’s immune system would react differently to the biosimilar compared with the original biological upon a switch. This view is supported by the current experience with biosimilars on the market and by literature data. In our opinion, switching patients from the original to a biosimilar medicine or vice versa can be considered safe.”
- “Our conclusion is that biosimilars licensed in the EU are interchangeable.”

ICMRA (2019) (22), which includes EMA, EC DG SANTE and several national medicines agencies as members - statement about confidence in biosimilar products (for healthcare professionals)

- “Changing between originator and biosimilar (i.e., a prescribing healthcare professional transferring a patient on treatment from one medicine to another) is an accepted clinical practice in many countries.”
- “Some countries have regulatory frameworks that permit substitution at the pharmacy level (i.e., without intervention by the prescriber) under certain conditions.”

EC, European Commission, EMA: European Medicines Agency, HCP: healthcare professional, ICMRA: International Coalition of Medicines Regulatory Authorities, Q&A: Question & Answer

FIGURE 18. BIOSIMILAR POSITIONS BY NATIONAL MEDICINES AGENCIES



With regards to switching, twelve NCA websites provided an explicit position. In general, switching statements were comparable between NCA websites, commenting that relevant changes in treatment outcomes are not expected upon switching from the reference product to a biosimilar or *vice versa*. Despite being generally supportive, different nuances were made. Some agencies focussed mainly on reassuring the safety of switching by for example referring to the growing availability of clinical switch data. Others underlined the authority of the prescribing physician in making switch decisions without providing further guidance. Two agencies explicitly discouraged back and forth switching between biosimilars and their reference product. Only three national medicines agencies specifically made reference to biosimilar to biosimilar switching (Overview of positions on switching in Supplementary Table S6).

In the context of (automatic) substitution, only ten national medicines agencies provided a clear position of which most indicating automatic substitution to be not allowed. A few countries pointed towards foreseen changes in legislation to eventually permit automatic substitution of biologicals (of certain product types or under certain conditions) (Overview of position on substitution in Supplementary Table S7). In Germany, substitution of biosimilars was already possible, but limited to the substitution of “bioidenticals” or “duplicates”, i.e. biosimilars made by the same manufacturer, which have been licensed under a different brand name. More recently, a new legal framework has been introduced in the context of the “*Gesetz für mehr Sicherheit in der Arzneimittelversorgung* (GSAV)” or “law for more safety in the supply of pharmaceuticals”, broadening the application of automatic substitution of biologicals beyond bioidenticals (266). The German Statutory Health

Insurance (G-BA) is responsible of translating this into practice, with offering two sets of guidance: one towards physicians with details on how to switch and one towards pharmacists, providing a positive list of biosimilars eligible for automatic substitution. The change is planned to come into effect in 2022 (266). Also in Norway, the possibility for automatic substitution of biologicals is being considered, with the national medicines agency proposing the Pharmacy Act § 6-6, which forms the basis for generic pharmacy substitution, to be changed to allow automatic substitution for biologicals (267). Table 15 provides an overview of automatic substitution practices for biological medicines across Europe.

TABLE 15. (AUTOMATIC) SUBSTITUTION FOR BIOLOGICAL MEDICINES IN EUROPE: AN OVERVIEW OF PRACTICES

Allowed (under specific conditions)	(Planned) changes to legislation	Not allowed		No info
France ¹ Hungary ¹ Latvia Lithuania Poland ²	Germany ⁴ Norway ⁵	Austria Belgium Croatia Czech Republic Denmark Finland Greece Iceland Ireland	Italy Malta Netherlands ³ Portugal Romania Spain Sweden UK	Bulgaria Cyprus Estonia Liechtenstein Luxembourg Slovakia Slovenia

1. Authorized by law under specific conditions (e.g. only for treatment naïve patients), but not implemented in practice
2. Automatic substitution is not recommended, but due to a lack of regulation or specific guidance, automatic substitution may occur
3. For insulin biosimilars, insurance companies are increasingly forcing pharmacies to substitute to the biosimilar
4. New legislation planned (GSAV: Gesetz für mehr Sicherheit in der Arzneimittelversorgung), that will allow biologicals to be substituted at pharmacy level
5. Proposal to alter Pharmacy Act § 6-6 (basis for generic (automatic) substitution in pharmacies), eventually permitting automatic substitution of new classes of medicinal products, e.g. biological drugs

Status 2019, sources: consulted NCA websites, (35),(266),(267)

In general, regulatory medicines agencies from Western and Northern European countries appear to provide more elaborate biosimilar guidance. Strong representation of Member States in EU level regulatory activities for biosimilars such as involvement in EMA's BMWP (with members from Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Sweden, and the Netherlands (268), overview in [Table S2](#)) and rapporteur or co-rapporteurship ([Figure S1](#): Germany, UK, Finland, Austria and the Netherlands have been most frequently in the lead) in biosimilar evaluation seems to have translated in more elaborate and outspoken regulatory biosimilar guidance on a national level.

4.2 QUALITATIVE INSIGHTS FROM SEMI-STRUCTURED EXPERT INTERVIEWS

Fourteen expert stakeholders participated in a semi-structured interview. An overview of participant characteristics is shown in [Tables S8 and S9](#) in Supplementary material. The interview results are structured according to the five main themes (sections 4.2.1 – 4.2.5) derived from thematic analysis of interview transcripts.

4.2.1 EMA LEADING THE WAY IN GUIDANCE AND COMMUNICATION ABOUT BIOSIMILARS

EMA's efforts towards improving stakeholder understanding about biosimilars were recognized, with several interviewees underlining the positive evolution in terms of stakeholder outreach. Especially, the EMA/EC information guides for healthcare professionals and patients were perceived as reference documents in the field, which helped to inject trust in biosimilars and disseminate clear messages towards the medical community.

"In the past years, the way EMA is communicating and putting documents on their website, you see that they try to be as clear and explicit as possible also in some kind of lay language. They try to convert their regulatory text towards the audience of prescribers and patients. That is positive in my opinion." (HCP7)

"They [EMA] have been successfully convincing the physicians' community in general that the way the evaluations have been done is sufficiently efficacious. That was at the beginning the problem, because we were not familiar with the kind of investigation that the EMA proposed." (HCP4)

At large, EMA was considered to lead the way in terms of biosimilar regulatory science and communication: *"Once they make a decision or statement the rest will follow. So it is important that organizations such as EMA play their role in informing the general public."* (I2) Strong regulatory communication was considered especially important in the context of dispelling misinformation about the underlying science of biosimilars.

Also, the publication of scientific articles about biosimilars by European regulators was recognized to have been helpful to update the medical community. However, some interviewees mentioned that it was not always clear to them if these presented the position of the individual authors or that of the agency. EMA's website was considered to be a rich source of information on biosimilars. Yet, despite the fact that the website has a dedicated page on biosimilars, several interviewees cautioned that relevant information may not be easy to retrieve for healthcare professionals and patients. In addition, several interviewees argued that the role of EMA may not be well-known by all, recommending to increase awareness about the EMA and its activities in general.

Some interviewees mentioned that promoting biosimilars may go beyond the remit of the EMA, and considered it not to be the EMA's responsibility to take up an active role in stakeholder education. Others argued that consolidating efforts at central level in terms of developing stakeholder guidance may positively contribute to homogenous messaging across Member States. A few interviewees remarked that while information should be made available at EU level, its dissemination is the

responsibility of the NCA's and professional organizations, who should subsequently make use of the information to inform stakeholders more locally.

“EMA is the reference, and they have a role to be transparent, but I do not think it is up to them to insure dissemination of this information. ...They are doing more and more, but it is not their job to make sure that all HCPs and patients know and understand exactly what a biosimilar is. I think there is a lot to do at national level and in the professional organizations as well.” (17)

4.2.2 THE EUROPEAN PUBLIC ASSESSMENT REPORT AS TRANSPARENT TOOL ON BIOSIMILAR EVALUATION – IS IT FIT FOR PURPOSE?

Interviewees deemed the EPAR an important tool to transparently inform about the regulatory evaluation and decision-making to approve or refuse a market authorization for a given medicine. The EPAR was considered to be especially useful by pharmaceutical industry interviewees as an instrument for them to learn about competing products. Although interviewees agreed that the EPAR is important to provide insight in product evaluation, some remarks were made. First, interviewees noted that the level of transparency provided by the EPAR may depend on the time of publication of the EPAR, with newer EPARs being more detailed and structured than older ones. Second, enhancing the level of substantiation provided in the EPAR was noted as a point for improvement. Reading the EPAR was considered requiring the ability to “read between the lines”, and interviewees would like to see more justifications regarding the outlined decisions (e.g. providing more in depth reasoning why something was considered acceptable or not).

While the EPAR was generally considered fit for purpose for expert and industry stakeholders, the document was considered too complex and long to serve as informational or educational instrument to inform healthcare professionals with their daily practice. Most interviewees believed that individual physicians are not likely to use the document: *“Transparency is there, but it is not because you have a PDF online that people will read it. If you’re a prescribing physician, you won’t read the EPAR I think.” (14)* It was also mentioned that healthcare professionals are generally not aware about the existence of the EPAR. Several interviews argued that a shortened version, in addition to the full EPAR, should be made available. It was suggested that such summary should not only provide general information on the product (as is currently made available in the Medicine Overview document), but include a conclusion on why the biosimilarity assessment was concluded to be positive, equipping stakeholders with the rationale behind EMA’s evaluation and opinion. An interviewee pointed towards the structural change in EPARs of more recently approved biosimilars, which include a specific concluding section on biosimilarity: *“If you just want to grab the main points about biosimilarity, it is easy because you can go directly to the biosimilarity section” (HCP2).*

4.2.3 EUROPEAN VERSUS NATIONAL RESPONSIBILITIES

The provision of clear information and consensus papers at EU level was mentioned to be important to help steer and shape initiatives at national level. Clear EU-information and guidance may spur national agencies to action, and closer cooperation between EMA and the NCAs was advocated in

this regard. Filling the gap between the EMA and national medicines agencies and strengthening the guidance by the latter was considered important. NCA guidance was believed to have a more direct and tangible impact on activities at the national level, and NCA's may coordinate more easily with local stakeholders.

"I think that national competent authorities play a more important role because they have more visibility in their respective countries" (I1)

Interviewees argued that NCAs should explore ways to provide more dynamic information opposed to short, static information on the NCA's website: *"It should be more dynamic as opposed to the way it is put now on their website."* (HCP7). Suggestions included the establishment of a Q&A platform, and videos where patients, physicians, and heads of the medicines agency etc. could speak up on the use of biosimilars. Several interviewees pointed to the fact that information provided by NCAs appears to be difficult to retrieve in some cases, which may be especially hindering for non-experts in the field.

4.2.4 NATIONAL COMPETENT AUTHORITIES TO ADDRESS INTERCHANGEABILITY, SWITCHING AND SUBSTITUTION

Interviewees pointed towards the sometimes limited and variable guidance between NCAs regarding the use of biosimilars:

"NCAs have in general not been clear on how biosimilars could be integrated into the treatment of patients. No one had clearly communicated that it [interchangeable use] is a possibility. It is a maze for a non-expert to understand what they should do in their country. You have to go, like trying to find the Da Vinci code, through details, websites and try to figure out what the recommendations are." (I4)

"Some agencies in Europe were more pro-active in this regard. I think it is also linked to having a strong advocate in the country." (I4)

In addition, some interviewees found positions to be too implicit. In this context, it was mentioned that positions appear to largely address only a single switch from reference product to biosimilar:

"It is important to provide information more extensively and more precisely in the future. Especially more guidance is important for situations like multiple switching" (HCP5)

Another interviewee mentioned: *"NCAs could be more proactive on that, but we have many sources of information that we use to make our own decisions"* (HCP4).

Some interviewees argued for a more central coordination on biosimilar-related information and position statements, to ensure convergence. Some mentioned that EMA should publish guidance about interchangeability as the limited and heterogeneous guidance on Member State level may lead to confusion. Others anticipated it difficult to develop guidance that would be accepted across Europe.

4.2.5 INFORMING AND EDUCATING STAKEHOLDERS ABOUT BIOSIMILARS – A COLLABORATIVE EFFORT BETWEEN REGULATORS AND SCIENTIFIC STAKEHOLDER SOCIETIES

The collaboration between EMA and healthcare professional stakeholder organizations in the context of biosimilar information development was recognized as positive. Interviewees stressed the importance of joining forces, explaining that healthcare professional stakeholder organizations can help translate and tailor regulatory information to the needs of their members. Healthcare professional associations were considered to be crucial in conveying trust and should be considered as an active link between EMA and the healthcare professionals. A few interviewees mentioned that having information on EMA's website is especially important for scientific associations for them to disseminate it, rather than for the individual physician to consult EMA's website directly. Well informed physicians may then in turn inform their patients.

“It is crucial that these kinds of scientific associations endorse the regulatory approval and try to express that endorsement towards their members.” (HCP7)

5. DISCUSSION

Access to trustworthy and transparent information about biosimilars and clear guidance on their use is essential to improve understanding on biosimilars and appropriately inform healthcare professionals and patients regarding their implementation in clinical practice. This study aimed to assess how regulators, both on a central and national level in Europe, provide information and guidance about the evaluation and use of biosimilars, with a specific focus on guidance related to interchangeability, switching and substitution, and how this is perceived by external demand-side stakeholders. To this end, both a review and comparative analysis of publicly available information and position statements regarding biosimilar use by EMA and national medicines agencies and semi-structured expert interviews with healthcare and pharmaceutical industry professionals were conducted.

5.1 REGULATORY INFORMATION AND POSITIONS ON BIOSIMILARS AND THEIR USE: UNTAPPED OPPORTUNITIES AT THE NATIONAL LEVEL AND A NEED FOR HARMONIZATION

While biosimilar evaluation and approval relies on a solid centrally coordinated European regulatory pathway, with external stakeholder dissemination strategies to explain the underlying science underpinning their evaluation and use (109),(258),(97),(44),(114), this study found that at the national level the information and guidance available on biosimilars considerably varies between medicines agencies. Information on biosimilars, and positions on their use, i.e. on interchangeability, and the associated practices of switching and substitution, are not consistently available and vary in extent and content.

This gap in consistent information on biosimilars at the national level may be explained by the fact that providing guidance on interchangeability, switching, and substitution falls outside the otherwise centrally organized evaluation and approval of biosimilars, and is managed at Member State level.

These decentralized responsibilities appear to have been addressed to different degrees across Member States. Overall, regulatory information provision on biosimilars appears to have operated at different speeds between the EU and the national level. While prescriber practices across Member States are expected to show a certain degree of heterogeneity as these practices are shaped in the context of their respective healthcare systems and medical culture (i.e. frameworks to allow for physician-led switching and/or pharmacy-led substitution), a uniform position from a scientific viewpoint on the interchangeability is to be expected. The observed heterogeneity between positions of national regulatory agencies, together with the absence of a clear EU position on interchangeability, may suggest a lack of regulatory and scientific clarity on the safety of an exchange between reference product and biosimilar.

Besides clear regulatory guidance on biosimilar use, clear regulatory information regarding biosimilars and the science underpinning their evaluation and safe use is believed to be essential to build stakeholder confidence. Whilst the precise impact of regulatory information and guidance on biosimilar acceptance is hard to isolate from other drivers at play, its availability is essential to provide stakeholders with accurate and trustworthy facts, and dispel misinformation in the debate. Furthermore, regulatory information forms the basis for subsequent coherent and accurate information dissemination on biosimilars and their use more locally.

5.2 THE INTERCHANGEABLE USE OF BIOSIMILARS

The discussion on whether or not a biosimilar can be safely interchanged with the reference product or other biosimilars has persisted since their introduction (269),(270). This discussion touches upon how biosimilars can be used in clinical practice, especially so for biosimilars that are intended for used in a chronic treatment setting, and is as such essential to address. While concerns were raised that an interchange between non-identical biologicals might result in an increase in immunogenicity, this has not been observed in clinical practice and the theoretical basis that this would occur has been considered to be weak (97),(265). Based on the available clinical data from over a vast body of clinical switch studies, no apparent signals were detected to assume that switching would be associated with any major efficacy, safety or immunogenicity concerns (51),(112). For biosimilars that met EU regulatory requirements, it is considered unlikely that the body's immune system would react differently to the biosimilar upon a switch since comparable structure and immunogenicity has been demonstrated between the biosimilar and the reference product (97),(265). Clinical data continue to emerge, also on multiple switching, and switching has been routinely adopted in clinical practice in several healthcare settings across Europe (106). While the scientific discussion on switching from reference product to biosimilar has been largely settled, questions on multiple switching and switching between biosimilars of the same reference product emerged, and healthcare professionals advocate for more scientific and regulatory clarity in this regard to support them with the appropriate use of biosimilars in clinical practice.

Whereas in Europe switching generally takes place under supervision of the prescriber, some countries are planning to allow for substitution of biologicals at the pharmacy level (266),(271) The

translation of substitution of biologicals in practice would involve an assessment of substitutability on product-specific level by the national medicines agency, upon which the biosimilar could be included in an “exchange” or “substitution list” (266),(271). In this context, it will be essential that community pharmacists are well prepared and trained to appropriately counsel patients with such a transition. The pharmacist must be familiar and confident in biosimilar use to mitigate for possible nocebo effects, and trained to counsel the patient with a possibly new injection device that such an exchange may entail (153),(255),(269).

It is important to note that regulatory approaches for biosimilar interchangeability vary across the globe. Whereas interchangeability assessment is not part of regulatory biosimilar evaluation in Europe or in Australia, the US Food & Drug Administration (FDA) has a dedicated regulatory pathway for biosimilar interchangeability designation. This interchangeability designation regulates automatic substitution, i.e. biosimilars that receive interchangeability designation may subsequently be substituted by the pharmacist without intervention of the prescriber, if also in line with state law (see Box S1 in Supplementary information). Given these differences in regulatory approaches, it is important to consistently position the discussion in its correct geographical context to mitigate for possible misconceptions (45).

5.3 A CALL FOR STRENGTHENED BIOSIMILAR GUIDANCE ON THE NATIONAL LEVEL AND A UNIFIED EU SCIENTIFIC POSITION ON INTERCHANGEABILITY

The EMA has expressed its continued commitment in developing actions to reinforce trust and confidence in biosimilars (272). In EMA's *Regulatory Science 2025 Strategic reflection*, promoting the availability of biosimilars and supporting their uptake in healthcare systems was included as a core recommendation to advance patient-centred access to medicines. This point was again reiterated in the EMA and HMA Network Strategy to 2025 (272),(273).

Europe has been leading the way in the field of biosimilars since the introduction of the first regulatory pathway for biosimilars in 2005, and the strong scientific and stakeholder outreach track record in this regard should be continued at the national level.

Three main recommendations are advanced:

(i) The availability of consistent one-voice information about biosimilars should be strengthened across national medicines agencies. For the latter, national regulators can leverage existing, EU developed healthcare professional and patient information materials locally. These materials have been made available in all 23 EU languages for the purpose of supporting consistent messages and education on biosimilars throughout the EU, and can be easily made available on national websites. In addition, several national agencies developed detailed stakeholder information about biosimilars, which may serve as a basis for other national medicines agencies (274),(275).

The scientific and regulatory knowledge and expertise with biosimilars that is consolidated at EMA and BMWP level could be leveraged to further aid initiatives at the national level. A closer collaborative framework between the EMA (BMWP, EMA Biosimilar Matrix) and the national

medicines agencies could strengthen information dissemination from the central to the national level, and leverage and transfer EU level biosimilar expertise across the broader European regulatory network. Furthermore, closer collaboration between regulators may stimulate the exchange of biosimilar best practices among Member States, and result in coordinated action to respond to biosimilar misinformation and queries that emerge at the national level. In terms of concrete initiatives to foster this collaboration, the recently established Heads of Medicines Agencies (HMA) Biosimilar group, which is composed of representatives nominated by interested national medicines agencies and an EMA representative, is an important step and platform in this regard (276),(277).

(ii) Besides strengthening the availability of information and education on biosimilars at the national level, regulators should join forces and act swiftly to provide a unified and unambiguous scientific EU position on biosimilar interchangeability. The lack of EU-level guidance in this regard and the variation in positions from national medicines agencies across Member States might unintentionally suggest a lack of regulatory and scientific clarity on this. Guidance should include information on reference to biosimilar, biosimilar to reference and biosimilar to biosimilar switching

In 2018, individual members of the BMWP paved the way for a scientific position beyond national Member State boundaries by conveying the European perspective with regards to interchangeability and the safety of switching in the form of a scientific publication published under personal name (97). A next step is now needed to clearly address the discussion on biosimilar interchangeability and switching from a formal regulatory point of view, and unambiguously inform healthcare professionals who are confronted with questions related to this in clinical practice. While a clear regulatory position is needed to provide guidance on the population level, it is up to the prescriber to decide on the suitability of an exchange on the level of the individual patient. Furthermore, it should be made clear that such a unified scientific position has not the goal of intervening with the Member States' sovereignty regarding prescribing and dispensing practices. Policy decision regarding prescribing practices should be made in the context of the local healthcare system, and such a unified position may inform healthcare decision makers in the development of policy measures related to biosimilar use.

Such unified position requires central coordination and cooperation between national regulatory agencies (269),(115). Also here, the recently established HMA Biosimilar group may play a vital role (277).

(iii) To make reliable information on biosimilars more easily retrievable for stakeholders, a centralised, European-led online repository for healthcare professionals and patients on biosimilar medicines could serve as central go-to information hub, with one-voice, factual information on biosimilars that is in line with the latest scientific and regulatory experience. On a product-specific level, the EPAR may be leveraged more actively – and especially the dedicated discussion on biosimilarity which was part of a revision to increase more transparency on the assessment – by creating awareness on its existence (278),(279).

5.4 INFORMING STAKEHOLDERS REQUIRES A COORDINATED MULTI-STAKEHOLDER EFFORT

While regulators have an important role in providing clear information on biosimilars and the regulation and science underpinning their use, conveying trust in the use of biosimilars and effectively educating physicians and patients about biosimilars requires a multi-stakeholder effort. Besides regulatory authorities, professional stakeholder associations such as healthcare professional and patient organizations have an important role in informing and translating regulatory guidance to physicians, pharmacists, nurses and patients (119),(260).

The availability of clear regulatory information and guidance about biosimilars may form the basis of correct and unbiased stakeholder information, but – as also emphasized during the interviews - needs further active leveraging from stakeholder organizations to actually reach the healthcare professional and patient. Regulators should continue to seek collaboration with healthcare professional and patient organizations to effectively disseminate unbiased and correct information about biosimilars, on the European as well as on the national level (119),(260), (280).

5.5 STRENGTHS AND LIMITATIONS OF THE STUDY

Based on a structured mapping of the available information from European regulatory agencies and qualitative stakeholder interviews, this study offers new and important insights on the European landscape of regulatory information and guidance for biosimilars. However, some limitations need to be considered. The fact that some NCA websites offered information only or in part in the Member State's local language, made the retrieval and extraction of relevant information complex. Websites were thoroughly scanned for biosimilar information with both English and local language translated terminology, but certain omissions cannot be excluded. Non-English retrieved information was translated to English with the help of an online text translator. This may have led to small differences in nuances of wording between original and translated position statements. Furthermore, the web-based screening allows to only collect and review information that is publicly available on the websites of the regulatory agencies.

The qualitative component of the research allowed to gather stakeholder insights and proposals on regulatory information and guidance dissemination for biosimilars and the role European and national regulators have in this regard. Interview participants were purposefully selected based on their expertise and pan-European and/or national insights on the study topic. It should be noted that – as with qualitative research in general – the findings are bound to the participant sample. While the qualitative part of the study focussed on the perspective of healthcare and industry professionals, future research could explore the perspective and needs of other stakeholders such as policy makers and patients. In addition, a study with European regulators may further distil actionable avenues forward from the perspective of the regulator.

6. CONCLUSION

This study showed that regulatory information and guidance on biosimilars and their use, i.e. on interchangeability, and associated practices of switching and substitution, considerably varies across national medicines agencies in terms of availability, extent and content. Untapped opportunity exists at the national level to expand and harmonize regulatory information and guidance for biosimilars. Moreover, regulators should collaboratively strive for a unified, scientific EU position on the interchangeability of biosimilars.

1. ABSTRACT

To date, there is no consensus among stakeholders about switching between reference biological products (RPs) and biosimilars, which may have been curbing the implementation of biosimilars in clinical practice. This study synthesizes the available data on switching and assesses whether switching patients from a RP to its biosimilar or vice versa affects efficacy, safety or immunogenicity outcomes. A total of 178 studies, in which switch outcomes from a RP to a biosimilar were reported, was identified. Data were derived from both randomized controlled trials and real-world evidence. Despite the limitations stemming from a lack of a robust design for most of the studies, the available switching data do not indicate that switching from a RP to a biosimilar is associated with major efficacy, safety or immunogenicity issues. Involvement of the prescriber in any decision to switch should remain and attention should be paid to the mitigation of a potential nocebo effect.

2. INTRODUCTION

Following the expiry of exclusivity rights on original biological medicines (further called the reference products (RPs)) the market opens up for biosimilar versions. Due to the intrinsic variability that is inherent to biological medicines and the complex manufacturing process of these products, a biosimilar cannot be an exact copy to the RP, but needs to demonstrate that it is a highly similar version of the RP. As defined by the European Medicines Agency (EMA), a biosimilar is *“a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established”* (14).

Since the authorization of the first biosimilar in 2006 in Europe (somatropin, Omnitrope® by Sandoz GmbH), more than 50 biosimilars for a wide range of products and therapeutic areas have been approved in the European Union (EU) (169). The first wave of approved biosimilars included mainly relatively small therapeutic proteins, such as hormones (e.g. somatropin, insulin glargine) and growth factors (e.g. filgrastim, epoetin). Over the last years more complex biosimilars, such as monoclonal antibodies (mAbs) and fusion proteins used in rheumatology, gastroenterology and oncology, have been approved and entered the market in Europe (169). Since the first biosimilar approval in 2015 in the USA (filgrastim, Zarxio® by Sandoz Inc.), the FDA approved over 20 biosimilar products (281).

The market entry of biosimilars can play an important role in containing escalating healthcare expenditures, as they can be offered at a lower price than the RP and lead to price competition. The adoption of biosimilars can also lead to increased patient access to biological treatments and free healthcare budgets for the reimbursement of innovative medicines (171).

An approved biosimilar is similar in efficacy, safety and quality to the RP and any observed differences are deemed clinically irrelevant (14). Therefore biological treatment of a bio-naïve patient (i.e. a patient without previous treatment with a particular biological medicine) can be initiated with a corresponding biosimilar without any efficacy or safety concerns, other than those proclaimed for the RP. However, the case of switching patients under treatment with the RP to its biosimilar has been questioned and there are still concerns remaining among many healthcare professionals (HCPs) and patients (43),(66). Concerns have been raised that switching between highly similar, but not identical versions of a biological medicine may lead to an increase in immunogenicity, due to the subsequent exposure to potentially different sets of epitopes (for example due to differences in glycosylation between the products (282),(120) although this has never been observed in clinical studies. The formation of antidrug-antibodies (ADA), although these uncommonly result in a clinically harmful effect, could subsequently lead to safety issues or a loss of efficacy (LOE) to the treatment (283).

2.1 KEY CONCEPTS AND TERMINOLOGY

Switching is the act by the treating physician “to exchange one medicine for another with the same therapeutic intent” (6). Switching can refer to a change between two different molecules (with a different INN, e.g. infliximab to adalimumab) or a change between a RP and its biosimilar version (e.g. infliximab to CT-P13) or between biosimilars for the same RP. Switching from a RP to a biosimilar (or *vice versa*) or between biosimilars is also referred to as non-medical switching (i.e. switching merely for cost-saving reasons). Dörner and colleagues proposed the term transitioning for this type of switching (49), in an effort to delineate the different types of switches used in the literature. In this article, the term switching refers to the switch from a RP to a biosimilar (or *vice versa*). Automatic substitution is “the act of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber” (6). The practice of substitution is regulated on a member state level and for biological medicines prohibited or advised against in most European countries (142). Interchangeability is a characteristic of two medicines and “refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or *vice versa*) or replacing one biosimilar with another” (6), either prior to the start of a biological treatment or during (stable) treatment.

Switching and substitution practices and the designation of interchangeability are not regulated on a EU level as prescribing practices fall within the responsibilities of the different EU member states (6). In the United States (US), the US Food and Drug Administration (FDA) has created a regulatory designation pathway for the scientific evaluation of interchangeability. An interchangeable product needs to meet additional requirements in addition to being authorized as a biosimilar (284). For the proposed interchangeable product it needs to be shown that it “can be expected to produce the same clinical result as the RP in any given patient; and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its RP is not greater than the risk of using the RP without such alternation or switch” (284). According to the Biologics Price Competition and Innovation Act (BPCI Act) section 351(k)(4), the pharmacist would be allowed to substitute a prescribed biological RP with an interchangeable biosimilar without the involvement of the prescriber, if allowed by state laws (284). Thus far, no biosimilars have yet been deemed interchangeable by the FDA (281).

In 2012, Ebbers *et al.* investigated the safety of switching between therapeutic proteins, addressing the key question surrounding the use in practice of biosimilars. The study did not find evidence from clinical trial data or post marketing surveillance (PMS) data that switching to and from different biological medicines led to safety concerns (285). Since then, many more biosimilars have been approved and entered the market (169). Increasingly, national competent authorities and HCP organizations formulated guidelines about switching (286). However, switching remains a highly debated topic and the arrival of the more complex mAb biosimilars to the market only further sparked the discussion (120),(287). Various biological medicines, especially blockbuster mAbs, are used in a chronic setting, stressing the need to address these questions in an effort to aid (clinical)

decision making. Furthermore, the uncertainty about switching limits the competition potential of biosimilars to curb the increasing burden on healthcare budgets and to increase treatment access for patients.

This systematic literature review aims to synthesize the currently available data on switching and assesses the safety, immunogenicity and efficacy of switching between RP and its biosimilar version(s). This review broadens the scope of previous studies (241),(285) by reviewing switch data for biologicals of every therapeutic class for which a European market authorization has been granted, more specifically: (i) human recombinant growth hormones (hrGH), (ii) erythropoietins, (iii) granulocyte colony stimulating agents (G-CSFs), (iv) insulins, (v) tumor necrosis factor alpha inhibitors (anti-TNFs), (vi) gonadotropins, (vii) low molecular weight heparins, and (viii) mAbs in oncology. Further, we aim to provide a critical insight on the current state of the art related to switching. This overview can be useful for HCPs and other stakeholders in their (clinical practice) decision-making.

3. METHODS

A systematic literature review was carried out up to 19th of June 2018 in the biomedical databases Embase, Medline, Cochrane and Web of Science. Search results were manually screened based on predefined inclusion and exclusion criteria ([Table S2 Applied inclusion and exclusion criteria](#)). The search terms can be consulted in [Table S1 Applied search terms](#). Seen that many of the publications on switch data are recent and emerging, additional searches were performed in grey literature and congress proceedings. The inclusions were further supplemented by the systematic screening of the reference lists of included articles for other relevant inclusions (snowballing).

Studies describing a switch from a RP to a biosimilar (or *vice versa*) were searched and included for every biosimilar approved by the European Commission (EC) or under EMA evaluation at the time of the study, i.e. switch studies for somatotropin, epoetin, filgrastim, insulin, enoxaparin, follitropin, anti-TNFs (adalimumab, etanercept, infliximab) and mAbs used in oncology (rituximab, trastuzumab). Both randomized controlled trials (RCTs) and studies conducted in clinical practice (e.g. observational cohort studies and registries), i.e. real world evidence (RWE) were included in the systematic literature review.

For each identified study, parameters such as study and patient characteristics and the study design were systematically extracted. Further, the reported efficacy, safety and immunogenicity outcomes and the conclusion of the authors were systematically screened and extracted. Studies were subsequently evaluated on the reported (differences in) efficacy, safety and immunogenicity parameters, as well the conclusion (and if applicable the advice about switching) of the authors.

The search in the different biomedical databases resulted in 4517 articles. After removing duplicates of identified articles, 2972 articles remained and were considered for inclusion. [Figure S1 Flow Diagram](#) in the Online Supplementary Information provides a schematic overview of the different steps in the screening process and the according results. The flow diagram is based on the PRISMA

2009 Flow Diagram for reporting a systematic review (288). At the end of the selection process, 178 unique studies were identified and included in the systematic literature review. In the case of multiple publications (combination of full-text and abstracts or multiple full-texts for the same study) for the same group of patients that switched, only one publication was counted and withheld. Three identified studies included both a group of patients that switched from the infliximab RP to an infliximab biosimilar as patients that switched from the etanercept RP to an etanercept biosimilar. These were counted as separate results/studies.

4. SWITCH STUDIES BETWEEN BIOLOGICAL REFERENCE PRODUCTS AND BIOSIMILARS

In total, 178 studies were identified and included in the systematic literature review. Switch studies were identified for somatotropin, epoetin, filgrastim, insulin, anti-TNFs (adalimumab, etanercept, infliximab), follitropin biosimilars and mAbs used in oncology (rituximab, trastuzumab). No switch data were identified for patients treated with enoxaparin biosimilars. Figure 19 provides an overview of the number of identified studies across the product classes. The majority of the studies related to switching from an anti-TNF RP to a biosimilar (132/178), and more specifically most relate to switching from infliximab RP to CT-P13 (Remsima®/Inflectra®).

Different types of study designs were identified. Figure 20 illustrates the main different switch designs. Most of the studies consisted of a single switch, i.e. patients changed one time from the RP to a biosimilar. Only six studies with a multiple switch design (i.e. patients changed multiple times between the RP and the biosimilar, alternating back on forth) were identified (127),(128), (132),(289),(290),(291). No studies on switching between biosimilars were identified.

FIGURE 19. OVERVIEW OF NUMBER OF SWITCH STUDIES ACROSS PRODUCTS

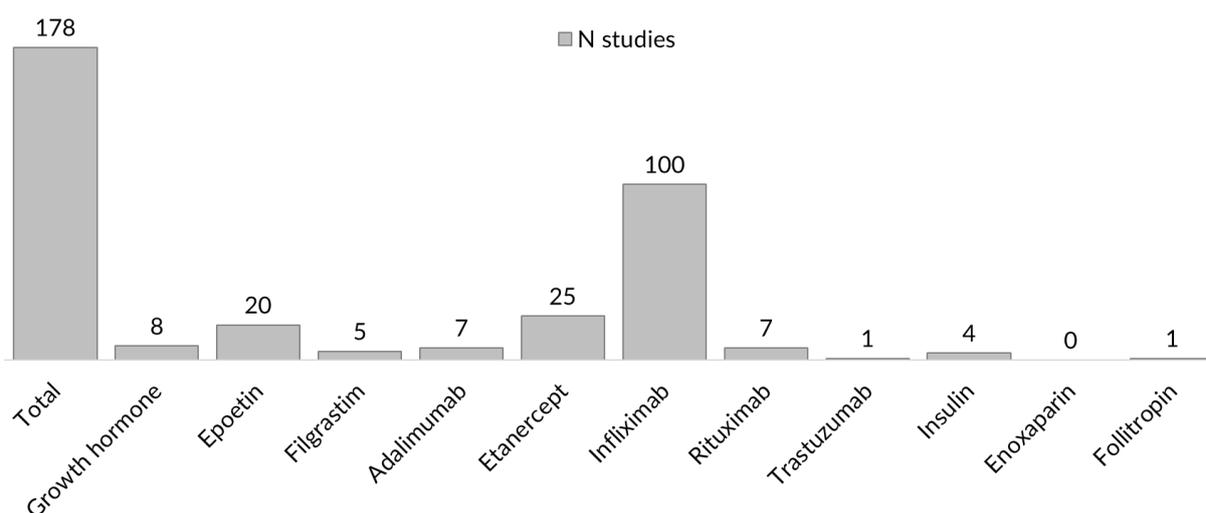
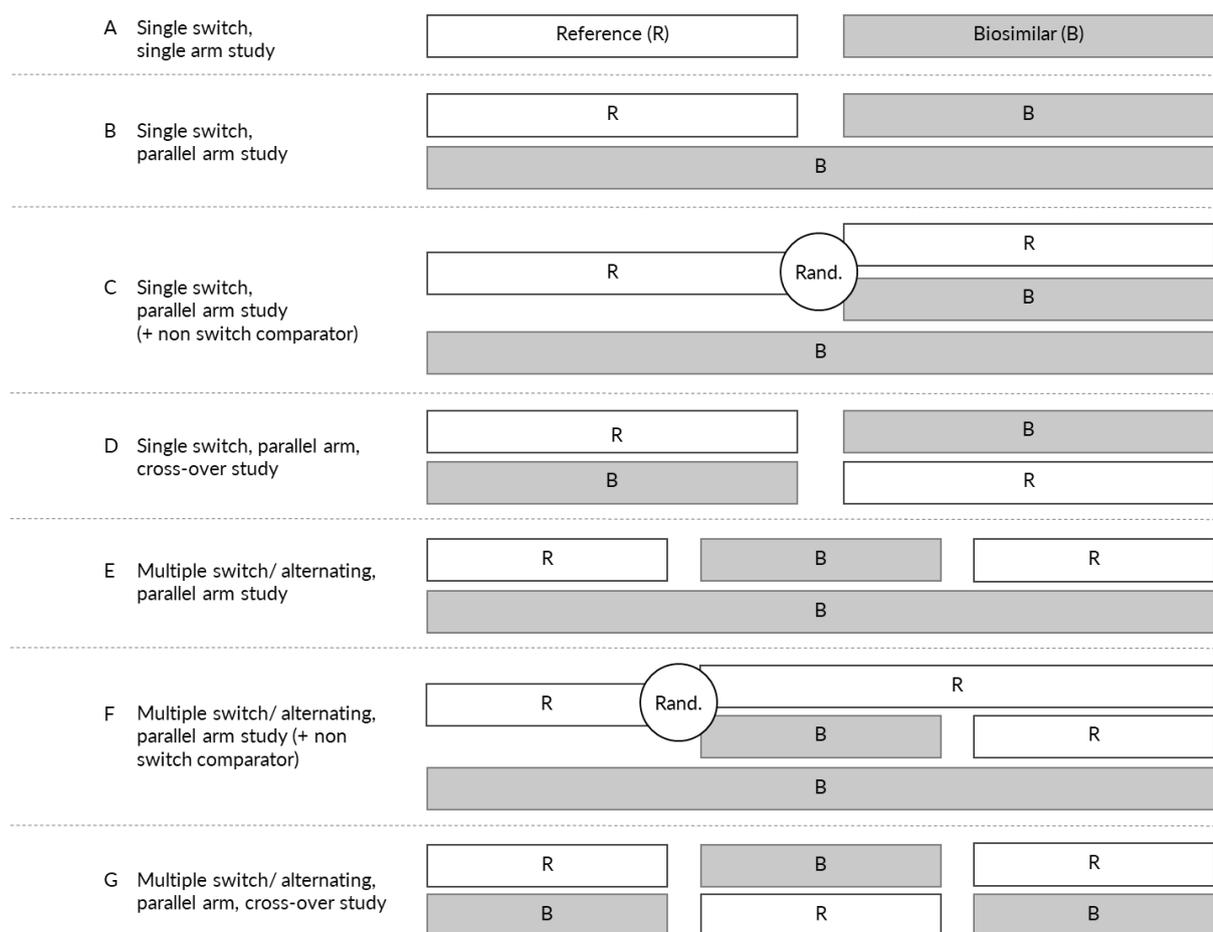


FIGURE 20. OVERVIEW OF DIFFERENT SWITCH STUDY DESIGNS



B: biosimilar, R: reference product, rand.: randomization

Data are originating from two main classes of studies. First, 38 studies (21%) can be categorized as RCT studies and open label extension studies (mostly these studies are part of the phase I/III clinical development of the proposed biosimilar, but also include for example the NOR-SWITCH trial) (103). An overview of the study design and switch results of this first class of switch studies, across products and disease area, can be found in Table 16. A full overview of parameters and main results for all switch studies identified is provided in [Tables S3-S11](#) in the Online Supplement. Second, the bulk of the data (N=140, 79%) is originating from studies conducted in the real world setting (i.e. RWE, defined as non-randomized studies outside the biosimilar candidate’s clinical development). RWE consists of either parallel arm, non-randomized, non-blinded studies or, and predominately, studies following a single arm design (i.e. the total patient cohort that (systematically, sometimes driven by procurement decisions) switches from the RP to the biosimilar, without a comparator arm). Further, registries, such as the DANBIO registry for the switch from the infliximab RP to CT-P13 and the switch from etanercept RP to SB4, were identified.

In addition to efficacy and safety outcomes, the measurement of trough levels (TL) and ADA upon switching was screened. TL and ADA were reported in 71 of 178 studies. Figure 21 shows the number of studies reporting on ADA and/or TL across products.

Based on the conclusion of the authors, the majority of the studies did not identify major efficacy, safety or immunogenicity issues due to switching from a RP to its biosimilar version.

Study specific results per product are further discussed below and shown in [Tables S3-S11](#) in the Online Supplementary Information.

4.1 SWITCH STUDIES FOR SOMATROPIN

One biosimilar (Omnitrope®) of somatropin (RP Genotropin®), a rhGH, has been authorized in the EU (169). Eight switch studies from the RP of somatropin (Genotropin®) to Omnitrope® have been identified ([Table S3](#) in the online supplementary information). Seven studies consisted of a single arm study design and one was a randomized open label phase III trial (292). All studies consisted of a single switch from the RP to the biosimilar. Overall, none of these studies indicated safety or efficacy issues related to switching.

4.2 SWITCH STUDIES FOR EPOETIN ALFA/ZETA

Five biosimilars (representing two unique products) of epoetin alfa (RP Eprex®) are EU approved (Epoetin Alfa Hexal®/Abseamed®/Binocrit® and Silapo®/Retacrit®) (169). The marketing authorization holder of Silapo®/Retacrit® requested another INN for their active substance, i.e. epoetin zeta (169). A total of 20 switch studies were identified for epoetin alfa and epoetin zeta ([Table S4](#) in the online supplementary information). Five switch RCTs were identified, of which one trial can be considered as a multiple switch study (127),(293),(294),(295),(296). Before enrolment, patients were treated with an originator. Upon the start of the trial, a part of these patients were switched to a biosimilar, followed by a second switch to the originator during the study duration (127). Further, fourteen single arm studies were identified. One of the studies, a retrospective matched control study in hemodialysis patients, demonstrated a dosing penalty (i.e. requiring higher doses to maintain Hb level) after switching (297). In this study 163 patients were switched and followed up during 24 weeks. Higher doses of 40% were reported to be required to maintain anaemia control (297).

4.3 SWITCH STUDIES FOR FILGRASTIM

Seven biosimilars (representing four unique products) of filgrastim (RP Neupogen®) have been approved in the EU, i.e. Zarzio®/Filgrastim Hexal®, Tevagrastim®/Ratiograstim®, Nivestim® and Grastofil®/Accofil® (169).

Five studies included a switch from the filgrastim RP to a filgrastim biosimilar ([Table S5](#) in the online supplementary information). Three of these consisted of a randomized phase III trial design, of which one study included a multiple switch (298),(299),(132). The other two studies consisted of a retrospective chart/database review. Overall, none of these studies indicated safety or efficacy issues related to switching. In all these studies, patients were treated with chemotherapy.

TABLE 16. OVERVIEW OF RCT AND OPEN LABEL EXTENSION SWITCH STUDIES

Authors	Product	Population	Study design	N patients switched	Follow-up*	Efficacy, safety, and immunogenicity outcomes	ADA rep.	Reported conclusion/switch advice
Single switch studies								
Adalimumab biosimilars								
Cohen, S et al. (2017)(300)	Adalimumab – ABP 501	RA	OLE of RCT phase III trial	237	46 w	Similar efficacy between switch and BS cont. arms. Rate of TEAEs and ADA similar between switch and BS cont. arms.	Yes	<i>Long-term safety, immunogenicity and efficacy results similar between switch and cont. arms.</i>
Cohen, S.B et al. (2018)(301)	Adalimumab – BI695501	RA	Randomized, double-blind, parallel arm, phase III trial (VOLTAIRE-RA)	147	34 w	ACR20/50/70 response rates, safety and immunogenicity (ADA, ADA titers, neutralizing antibodies) were similar across the 3 arms (RP-BS switch, RP cont., BS cont.).	Yes	<i>The switch had no impact on efficacy, safety, and immunogenicity.</i>
Hodge, J et al. (2017)(302)	Adalimumab – CHS-1420	Ps and PA	Double blind, randomized, parallel arm, phase III trial	124	8 w	PASI75 achieved in 84.6%, 81.6%, and 88.3% pts in BS cont., switch, and RP cont. arms. TEAE reported in 20.1%, 19.4% and 16.3% pts in BS cont., switch, and RP cont. arms. ADA reported in 4.0 %, 0.8% and 2.3% in BS cont., switch, and RP cont. arms.	Yes	<i>Similar safety and efficacy between switched and non-switched pts.</i>
Papp, K et al. (2017)(303)	Adalimumab – ABP 501	Ps	Randomized, double blind, parallel arm, phase III trial	77	36 w	PASI percentage improvements from baseline similar across arms (RP-BS switch, RP cont., BS cont.). No significant differences across arms in percentages of PASI 50, 75, 90 and 100 responders. No new safety signals detected. AEs balanced between arms. Incidence of overall ADA comparable across arms.	Yes	<i>Similar efficacy, safety and immunogenicity profiles after single switch between arms.</i>
Weinblatt, M et al. (2018)(304)	Adalimumab – SB5	RA	Extension, double blind, randomized, controlled phase III trial	125	28 w	ACR response rates comparable between switch and cont. arms. Comparable trends in DAS28, SDAI, and CDAI across arms. The safety profile was consistent across arms. Proportion of pts with ADA, neutralizing ADA and sustained ADA was similar between arms.	Yes	<i>Switching had no treatment-emergent issues such as increased AEs, increased immunogenicity, or loss of efficacy.</i>

Etanercept biosimilars

Emery, P et al. (2017)(305)	Etanercept – SB4	RA	OLE of randomized, double blind phase III trial	119	48 w	ACR response rates sustained and comparable between BS cont. and switch arms (ACR20 response rates at w 100 77.9% vs 79.1% respectively). TEAE rates 47.6% vs 48.7 respectively. One patient in each arm developed non-neutralizing ADA.	Yes	<i>Efficacy, safety and immunogenicity comparable between the cont. and switch arms. No risk associated with switching pts from RP to SB4.</i>
O'Dell, J et al. (2017)(306)	Etanercept – CHS-0214	RA	Randomized, double blind, parallel arm study	220	24 w	Response rates maintained in cont. and switch arms (93.8% vs. 92.7% for ACR20, 75.0% vs. 73.6% for ACR50, 49.6% vs. 51.4% for ACR70 respectively). AEs in 74.4% vs 76.6% pts, SAE in 4.6% vs 7.5% pts, SAEs related to study drug in 0.9% vs 1.9% pts. Treatment-emergent binding ADA in 1.4% pts receiving BS cont. and 0.7% of switched pts.	Yes	<i>No clinically meaningful differences in efficacy, safety, or immunogenicity between switch and BS cont. arms.</i>
Matucci-Cerinic, M et al. (2018)(307)	Etanercept – GP2015	RA	Randomized, double-blind, parallel arm, phase III study (EQUIRA)	166	24 w	The mean change in DAS28-CRP was comparable between the cont. and switch arms. EULAR and ACR 20/50/70 response rates were comparable between arms. TEAEs in 42.9% vs 38.0%, SAEs in 2.3% vs 2.4% pts, injection site reactions in 0% vs 3.6% pts in the cont. vs switch arm. 2.4% pts in the cont. arm had single-event, very low titer, non-neutralizing ADA.	Yes	<i>The switch did not affect efficacy and safety of etanercept treatment in pts with moderate-to-severe RA.</i>
Song, Y.W et al. (2018)(308)	Etanercept – LBEC0101	RA	OLE of randomized controlled double blind phase III trial	78	48 w	DAS28-ESR score maintained in cont. and switch arms. Response rates at w 100: 79.7% vs. 83.3% for ACR20, 65.2% VS 66.7% for ACR50% and 44.9% vs. 42.3% for ACR70 for cont. and switch arms, respectively. AE incidence comparable between arms (70.0% vs 70.5%). Proportion of pts with newly developed ADA similar between arms (1.4% vs 1.3%).	Yes	<i>Efficacy and safety comparable in both cont. and switch arms.</i>

Infliximab biosimilars

Alten, R et al. (2018)(309)	Infliximab – PF-06438179/ GP1111	RA	Randomized, double-blind, parallel arm phase III study	143	24 w	ACR20 rates and DAS28-CRP scores comparable between arms. Incidence of TEAE 36.8%, 33.6%, and 37.8%, SAEs (4.6%, 7.7% and 2.8%) and infusion-related reactions (3.2%, 8.4% and 4.2%) comparable between the cont. BS, cont. RP and switch arm.	Yes	<i>Study showed the absence of clinically meaningful differences in efficacy, safety and immunogenicity between switch and cont. arms.</i>
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Jørgensen, K.K et al. (2017)(310)	Infliximab – CT-P13	RA, CD, UC, Ps, PA, SpA	Randomized, double blind, parallel arm, single switch non-inferiority phase IV trial (NOR-SWITCH)	241	52 w	Disease worsening occurred in 26% and 30% of pts in the cont. and switch arms, respectively. The 95% CI of the adjusted treatment difference (-4.4%) was -12.7 – 3.9, fell within the pre-specified non-inferiority margin. The frequency of AEs was similar between arms. Trough drug concentrations similar in the two arms. Incidence of ADA detected during the study was 7% vs 8% for cont. and switch arm, respectively.	Yes	<i>NOR-SWITCH showed that switching to CT-P13 was not inferior to cont. treatment with the RP based on non-inferiority margin of 15%. No non-inferiority was shown in individual diseases (study not powered for this).</i>
Goll, et al. (2017)(311)	Infliximab – CT-P13	RA, CD, UC, Ps, PA, SpA	OLE, parallel arm NOR-SWITCH	183	26 w	Disease worsening occurred in 16.8% and 11.6% of pts in the cont. and switch arms, respectively. 3 and 5 pts in the cont. and switch arms, respectively, developed ADA. TLs and the frequencies of reported AEs comparable between arms.	Yes	<i>OLE of NOR-SWITCH trial did not show any difference between pts who maintained CT-P13 vs pts who switched.</i>
Kim, Y et al. (2017)(312)	Infliximab – CT-P13 or vice versa	CD	Randomized, controlled, single switch, parallel arm phase III trial	110	24 w	Clinical remission and CDAI-70 response rates maintained and similar among arms (BS cont., RP cont., RP-BS switch, BS-RP switch) after switching. One-year safety similar among arms. At Week 30, 1 IRR reported after switching (pt ADA positive at time of switch). No further IRR reported in switch arms after. No clinically meaningful differences in immunogenicity reported.	Yes	<i>The switch arm was comparable to RP and BS cont. arms in terms of efficacy and safety profiles.</i>
Park, W et al. (2017)(313)	Infliximab – CT-P13	AS	OLE study of double, blind RCT (PLANETAS extension)	86	48 w	ASAS20, ASAS40 and ASAS partial remission rates similar between arms. Proportion of pts with at least one TEAE was 48.9% vs 71.4% in the cont. and switch arms respectively. Proportion of pts with ADA similar in cont. and switch arms.	Yes	<i>Switching from RP to CT-P13 is possible without negative effects on safety or efficacy.</i>
Smolen, J.S et al. (2018)(314)	Infliximab – SB2	RA	Extension randomized controlled phase III trial	94	24 w	ACR20 was comparable across switch, RP cont., BS cont. arms. TEAEs in 36.2%, 35.6% and 40.3%, respectively. Newly developed ADAs in 14.6%, 14.9% and 14.1%, respectively.	Yes	<i>Efficacy, safety and immunogenicity comparable between switch and cont. arms. No treatment emergent issues or clinically relevant immunogenicity after switching.</i>

Tanaka, Y et al. (2017)(315)	Infliximab – CT-P13	RA	OLE of phase I/II trial	33	69.0 ± 29.5 w	The type and frequency of AE were similar between arms. Number of ADA-positive pts 48.5% vs 31.6% in switch and maintenance arm, respectively.	Yes	<i>CT-P13 was well tolerated in pts who switched.</i>
Kay, J et al. (2016)(316)	Infliximab – BOW015	RA	OLE of double blind RCT	53	32 w	No significant difference in proportion of pts achieving ACR20, 50, or 70 responses between arms. Mean improvements in CRP, ESR, and tender and swollen joint counts did not differ significantly between arms.	NR	<i>Durability of response to BOW015 has been demonstrated. No switch advice.</i>
Volkers, A et al. (2017)(317)	Infliximab – infliximab BS	IBD	Randomized, double blind, single switch, parallel arm, phase IV non-inferiority trial	15	30 w	One pt (switch arm) experienced relapse of IBD. Two pts experienced a SAE, not related to the study drug.	NR	<i>Preliminary results show that switching from infliximab RP to infliximab BS is feasible and safe.</i>
Yoo, D.H et al. (2017)(318)	Infliximab – CT-P13	RA	OLE of double blind RCT (PLANETRA extension)	144	48 w	Similar ACR20, ACR50 and ACR70 rates between the cont. and switch arms. Proportion of pts with at least one TEAE comparable between cont. and switch arm (53.5% and 53.8%, respectively). Proportion of pts developing ADA similar between arms.	Yes	<i>Switching not associated with any detrimental effects on efficacy, safety or immunogenicity.</i>
MAbs in oncology								
Von Minckwitz, G et al. (2018)(319)	Trastuzumab – ABP 980	Early breast cancer	Randomized, double-blind, phase III study	171	NR	Percent of pts with disease progression/recurrence/death was 5.3% vs 2.9% in the RP cont. and switch arm respectively. No increase in frequency or severity of AEs and no unexpected safety signals. No increase in cardiotoxicity. In adjuvant phase, 1 pt in the switch arm developed binding non neutralizing ADA. In neoadjuvant phase (pre-switch), 2 pts in the RP cont. and in the BS cont. arm developed binding non neutralizing ADA.	Yes	<i>Switching from trastuzumab to ABP 980 was. Switching did not increase the frequency or severity of AEs, no unexpected safety signals were noted, and it did not increase the incidence of developing ADAs. Event-free survival was also similar between treatment groups.</i>
Cohen, S.B et al. (2018)(320)	Rituximab – PF-05280586	RA	Randomized extension study (REFLECTIONS)	126	96 w	No notable differences in drug concentrations between groups, and no apparent relationship between IRR and ADA with or without switch. Long-term safety and tolerability of PF-05280586 acceptable in all groups. Percentage of subjects with a	Yes	<i>Tolerability and acceptable safety of a single switch was demonstrated. No increased immunogenicity</i>

						low disease activity score and disease activity score remission was similar across groups for all time points.		<i>due to switching based on either ADA or IRR reports.</i>
Park, W et al. (2017)(321)	Rituximab – CT-P10	RA	OLE phase I study	20	24 w	All efficacy endpoints (DAS28-ESR, DAS28-CRP, EULAR response) comparable between cont. and switch arms, no statistically significant differences. No significant differences in AEs. ADA incidence similar between cont. and switch arms.	Yes	<i>Switching had no notable impact on the efficacy or safety of treatment.</i>
Shim, S.C et al. (2017)(322)	Rituximab – CT-P10	RA	OLE phase III study	109	24 w	DAS28 and ACR response rate comparable between arms, B-cell depletion comparable after the first infusion and maintained until 24w in all arms. Safety profiles comparable between arms. No remarkable changes in immunogenicity profile followed the switch.	Yes	<i>Switch arms were comparable to BS and RP arms groups in efficacy, safety and immunogenicity.</i>
Tony, H.P et al. (2017)(323)	Rituximab – GP2013	RA	Randomized, double-blind, parallel-group trial (ASSIST-RT)	53	24 w	Hypersensitivity reactions, ADA and the rate of AEs were similar between arms.	Yes	<i>The safety of pts between switch and cont. arms was comparable.</i>
Nasonov, E et al. (2017)(324)	Rituximab – BCD-020	RA	Double blind RCT, parallel cross over switch	80	24 w	There were no significant differences in ACR20 after partial crossover at 48w (24w switch). AEs rates: 44.44% for cont. BS, 38.46% for cont. RP, 57.14% in RP-BS switch arm, 62.50% in BS-RP switch arm. Incidence of ADA was 3.85% in cont. BS arm, no binding ADA in other groups.	Yes	<i>One-year data show that switching between products does not affect treatment outcomes.</i>
Smaller biologics								
Romer, T et al. (2009)(292)	Somatropin – Omnitrope®	GHD in children	Randomized, open-label phase III clinical study	45	75 m	6.8% pts developed low ADA titers. At the final visit, no pts had detectable ADA.	Yes	<i>Switch between rhGH preparations was well tolerated and safe.</i>
Hadjiyianni, I et al. (2016)(325)	Insulin glargine – LY2963016	T1D & T2D	Randomized, controlled clinical study	362	24 w	TD1: no significant differences in efficacy parameters, but more weight gain in switch arm compared to cont. No significant differences in TEAEs and SAEs. TD2: no significant differences in efficacy parameters. No significant differences in TEAEs. Significantly, fewer pts in switch arm experienced ≥1SAE. Proportion of	Yes	<i>Pts who switched from RP to insulin BS have similar efficacy and safety outcomes compared to pts under con. RP treatment.</i>

						detectable ADA in switch arm statistically significantly higher compared to cont. arm (potentially due to baseline imbalances).		
Goh, B.L et al. (2007)(293)	Originator – GerEPO®	Haemo dialysis pts	Randomized, open label, parallel arm, single switch study	87	12 w	Both arms showed a similar decline in Hb. More pts in switch arm reported AEs due to subjective symptoms, more pts in switch arm were withdrawn due to AE or decrease in Hb (similar Hb decline in both arms).	NR	<i>Results are convincing with respect to efficacy measured in terms of Hb response, the duration of trial was only 3 m, which is insufficient for safety evaluation.</i>
Haag-Weber, M et al. (2009)(294)	Epoetin – HX575	CKD	Randomized, controlled, open label clinical trial.	314	54 w	Mean changes in Hb levels were 0.15 ± 0.09 g/dl and 0.06 ± 0.12 g/dl in switch and cont. arm respectively. Difference between arms: 0.08 g/dl (95% confidence interval: -0.17; 0.34). No antibody formation detected.	Yes	<i>No differences in safety, immunogenicity or efficacy profiles following the switch. The long-term safety profile of the BS was comparable to the RP.</i>
Harzallah, A et al. (2015)(295)	Epoetin Hemax® – BS epoetin Epomax®	Haemo dialysis pts	Phase III trial	53	43 days	No significant difference in mean Hb levels between arms. 5 pts discontinued after switch (2 due to unrelated abdominal pain, unclear for other 3).	NR	<i>Epomax® was effective at maintaining the Hb levels at target concentrations and was well tolerated.</i>
Krivoshiev, S et al. (2010)(296)	Epoetin zeta – RP	CKD	Randomized, observer blind, controlled phase III trial	230	28 w	Percentage of pts with infections and infestations was similar. No pts developed ADA.	Yes	<i>Epoetin zeta is equivalent to epoetin alfa in respect of its clinical efficacy. Safety profile is similar: no unexpected AEs, no pts developed anti-erythropoietin antibodies.</i> <i>No switch advice.</i>
Gatzemeier, U et al. (2009)(298)	Filgrastim – XM02	NP in pts under chemo-therapy	Randomized, controlled phase-III study	80	Max 6 chemo-therapy cycles	The AE profile was similar between cont. and switch arms.	NR	<i>XM02 is safe and well tolerated.</i> <i>No switch advice.</i>

Engert, A et al. (2009)(299)	Filgrastim – XMO2	NP in pts under chemotherapy	Randomized, controlled phase III trial	29	Max 6 chemotherapy cycles (3 w/cycle)	Incidence of observed/protocol defined FN was 31.7% and 41.4% in the cont. and switch arms, respectively. The AE profile was similar between switch and cont. arms.	Serum concentrations	<i>XM02 has a similar efficacy profile and does not appear to have different safety profiles as compared with the RP. XM02 is safe and well tolerated. No switch advice.</i>
Strowitzki, T et al. (2016)(326)	Follitropin – Ovaleap®	Assisted fertility	OLE phase III trial	67	Cycle 2 & 3 (treatment up to 20 d/cycle)	Safety and efficacy findings were comparable to the outcomes in the main phase III study, comparing Ovaleap® and Gonal-f®.	Yes	<i>Results in support of the safety and efficacy of a switch to Ovaleap®.</i>
Multiple switch studies								
Blauvelt, A et al. (2017)(289)	Adalimumab – GP2017 or vice versa	Ps	Parallel arm, randomized double blind phase III trial (ADACCESS) 4 x switch: at w17, w23, w29, and w35. Follow-up until w51	126	34 w	No clinically relevant differences in efficacy and safety between the cont. and switch arms (RP cont., BS cont., RP-BS switch, BS-RP switch) across the study duration. Overall, differences in the frequency of ADA detection were <11% among the arms.	Yes	<i>There were no clinically meaningful differences in long-term efficacy between the cont. and multiple RP-GP2017 switch groups. Switching was well tolerated.</i>
Genovese, M.C et al. (2017)(290)	Adalimumab –FKB327	RA	Randomized OLE of RCT phase III trial (ARABESC-OLE) 2 x switch: at w0 (start OLE) and w28. Follow up until w76	216	48-76 w	Interim analysis: ACR20 response rate at w 30 comparable between cont. (BS-BS 82.5%; RP-RP 84.3%) and switch (BS-RP 86.5%; RP-BS 89.1%) arms. Safety profiles comparable for all treatment sequences (group sizes reduced after switching). No consistent differences in ADA profiles between cont. and switch arms.	Yes	<i>Interim OLE results indicate that long-term safety, efficacy, and immunogenicity were comparable between cont. and switch arms.</i>

Gerdes, S et al. (2017)(128)	Etanercept – GP2015	Ps	Randomized, double-blind, parallel arm, multiple switch phase III study (EGALITY) 3 x switch: at w12, w18, w24. Follow up until w52	196	40 w (6w interval)	PASI 50, PASI 75 and PASI 90 response rates, percent change from baseline in PASI scores and all other efficacy parameters similar between switch and cont. arms. Incidence of TEAEs, including injection site reactions comparable between arms. No pts positive for binding ADA.	Yes	Similar efficacy between cont. and switch arm. No clinically relevant differences in safety or immunogenicity between arms, indicating no impact of repeated switches between GP2015 and RP.
Wizemann, V et al. (2008)(127)	Epoetin alfa – epoetin zeta or vice versa	CKD, anaemia	Double blind cross-over phase III trial 2 x switch: at w0, at w12	239	12 w	Hb levels were equivalent. Pts underwent minor dose adjustments during treatment crossover. AE profile was similar. No pts developed neutralizing ADA.	Yes	Epoetin zeta is therapeutically equivalent to epoetin alfa in the maintenance of target Hb levels in pts with renal anaemia. No unexpected AEs were seen.
Blackwell, K et al. (2015)(132)	Filgrastim – EP2006	NP in pts under chemotherapy	Randomized, phase III trial 5 x switch: at each chemo cycle every 3 w	109	4 treatment cycles	Alternating between biosimilar and RP or vice versa showed no clinically meaningful differences regarding efficacy and safety. No increased risk of developing ADA under repeated alternating.	Yes	Alternating between BS and RP or vice versa showed no clinically meaningful differences regarding efficacy and safety. The immunogenic response to filgrastim assessed under conditions of repeated alternating and non-alternating showed no increased risk of developing anti-G-CSF antibodies.

*Follow-up after switch, ADA rep.= ADA measurements reported

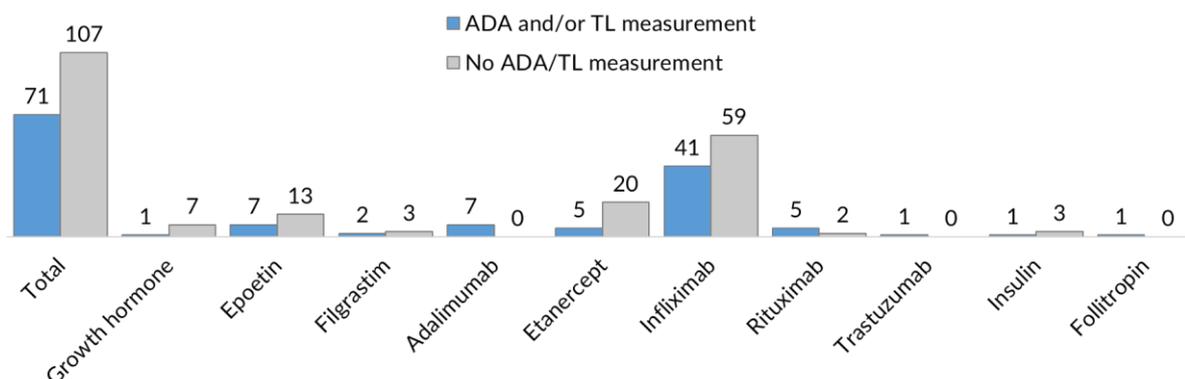
ACR: American College of Rheumatology, ADA: anti-drug antibody, ADRs: adverse drug reactions, AS: ankylosing spondylitis, BS: biosimilar, CI: confidence interval, CD: crohn's disease, cont: continuous, CRP: C reactive protein, d: days, DAS: Disease Activity Score, ESR: Erythrocyte Sedimentation Rate, FN: febrile neutropenia, GHD: growth hormone deficiency, Hb: haemoglobin, IBD: inflammatory bowel disease, m: months, IRR: infusion-related reaction, m: months, N: number, NR: not reported, OLE: open label extension, PA: psoriatic arthritis, PASI: Psoriasis Area and Severity Index, PMS: post marketing study, Ps: chronic plaque psoriasis, pts: patients, RA: rheumatoid arthritis, rhGH: recombinant human growth hormone, RP: reference product, SAE: serious adverse event, SpA: Spondyloarthritis, T1D: type 1 diabetes, T2D: type 2 diabetes, TEAE: treatment-emergent adverse event, UC: ulcerative colitis, w: weeks, y: year

4.4 SWITCH STUDIES FOR INSULIN GLARGINE/LISPRO

Two unique biosimilars of insulin glargine (RP Lantus®) are approved in the EU, i.e. Abasaglar® and Semglee® (169). Insulin lispro Sanofi® is an EU-approved biosimilar of the insulin lispro RP (Humalog®) (169).

Four studies incorporating a switch between the insulin glargine RP and a biosimilar were identified (Table S6 in the online supplementary information). One of these studies, based on a retrospective chart review, indicated an increase in insulin dosage by 2.4 units after switching 24 patients to the biosimilar (327). The results of another retrospective chart review, of 73 patients switched from Basalin® to Lantus® showed further reductions in blood glucose although the insulin glargine dose did not increase (328). The incidence hypoglycemia was low during both Basalin® and Lantus® treatment (2.4% vs 1.2%, respectively), with no cases of severe hypoglycemia. Authors concluded that further studies are needed to verify these findings (328). Basalin® is not approved in the EU or the US, thus not to be considered a true biosimilar evaluated by a stringent regulatory framework. A lack of true biosimilarity could thus potentially explain the observed pre- and post-switch differences. The retrospective design poses further a limitation to the interpretation of the results. No insulin lispro switch studies were identified.

FIGURE 21. NUMBER OF STUDIES WITH ADA AND/OR TROUGH LEVEL MEASUREMENTS



ADA: antidrug antibody, TL: trough level

4.5 SWITCH STUDIES FOR ANTI-TNFs

The study parameters and results of the RCT and open label switch studies for infliximab, adalimumab and etanercept are shown in Table 16. A complete overview of all the anti-TNF switch studies can be found in [Tables S7-S9](#) in the online supplementary information.

4.5.1 INFLIXIMAB

Four biosimilars (representing three unique products) of infliximab (RP Remicade®) have been EU-approved, i.e. Remsima®/Inflectra®, Flixabi® and Zessly® (169). One hundred studies incorporating a switch between the RP and one of its biosimilars have been identified. The study parameters and results of the switch studies for infliximab can be consulted in [Table S6](#) in the online supplementary information.

4.5.1.1 RESULTS OF RCTS AND PHASE I/III (EXTENSION) TRIALS INVESTIGATING THE SWITCH FROM THE INFLIXIMAB RP TO A BIOSIMILAR

Most RCTs investigating switching from the infliximab RP to one of its biosimilars incorporated a switch after the assessment of the primary trial endpoint in a clinical trial, i.e. an extension trial. Extension studies of the pivotal PLANETAS and PLANETRA trials, investigating the switch from infliximab RP to CT-P13, the first infliximab biosimilar, showed no reduced efficacy nor an increase in AEs between the maintenance and the switch group (318),(313). However, during the second year of the PLANETAS extension study, the incidence of more than one treatment emergent adverse events (TEAE) was 48.9% versus 71.4% patients in the maintenance CT-P13 and the RP-CT-P13 switch group, respectively (313). ADA incidence and hypersensitivity reactions observed in both extension trials (PLANETRA and PLANETAS) did not significantly differ between maintenance and switch group (318),(313). Further, a phase III double-blind RCT investigating the single switch from infliximab RP to SB2 (Flixabi®) has been conducted in rheumatoid arthritis (RA) patients (94 patients switched) (314). The efficacy, safety and immunogenicity profiles were reported to remain comparable between groups up to the end of 24 weeks of follow-up, indicating that there were no TEAEs or clinically relevant differences after switching from the RP to SB2 (314). The landmark NOR-SWITCH study, financially supported by the Norwegian government, is an independent randomized, double blind, non-inferiority (NI) study with 52 weeks of follow-up (310). NOR-SWITCH aimed to evaluate maintenance of efficacy and the monitoring of AEs in patients after the switch from infliximab RP to CT-P13 in comparison with the efficacy and AEs in patients under continued treatment with the RP. Patients across the six therapeutic indications of infliximab were included, i.e. patients with RA, spondyloarthritis (SpA), psoriatic arthritis (PsA), chronic plaque psoriasis (Ps), Crohn's disease (CD), ulcerative colitis (UC). The primary endpoint of the study was disease worsening (determined by worsening in disease-specific composite measures or a consensus about disease worsening between the investigator and the patient, which lead to a major change in the treatment). The NI margin set at 15% at 52 weeks, assuming 30% disease worsening in each group. Almost 500 adult patients on stable treatment with the RP for at least six months were 1:1 randomized to switch to CT-P13 or to continue treatment with the RP. Disease worsening

occurred in 26% of patients in the RP group and in 30% of patients in the CT-P13 group. The lower limit of the 95% CI of the adjusted risk difference fell within the predefined NI margin of 15% (-4.4%, 95% CI -12.7, 3.9), showing that switching from the RP to CT-P13 was not inferior to continued treatment with the RP. Further, the frequency of serious AEs, overall AEs and AEs leading to discontinuation was similar between groups. Serum trough concentrations and the incidence of ADA were also similar between groups. A drawback of this study is the fact that it was not powered to show NI in the individual therapeutic indications (310). The patients that completed the 12-month treatment were asked to enter in an open-label follow up study in which all patients received CT-P13 for 26 weeks. The extension study did not show any difference between patients who maintained CT-P13 compared to patients who switched from the RP to CT-P13 (311). Further, the single switch from the infliximab RP to BOW015 was investigated in an open-label extension phase III trial in patients with RA (316). The impact of a single switch from the RP to PF-06438179/GP1111 (Zessly®) was investigated in a RCT phase III trial (309), and the single switch from RP to CT-P13 was investigated in an open label extension phase I/II trial (315), and in a RCT phase III trial (312). Overall, the switch did not negatively affect efficacy, safety or immunogenicity of treatment in these studies.

4.5.1.2 REAL WORLD CLINICAL STUDIES INVESTIGATING THE SWITCH FROM THE INFlixIMAB RP TO A BIOSIMILAR

Several studies (91/100) have aimed to collect real-world data for the switch from the infliximab RP to one of its biosimilars, mostly for CT-P13 (first approved infliximab biosimilar). An overview of the study design and results of these studies is available in [Table S6](#) in the online supplementary information. A study based on the data from the DANBIO registry reported outcomes of a systematic, nationwide switch from the infliximab RP to CT-P13 of Danish RA, SpA and PsA patients under infliximab treatment (329). Investigators reported that the disease activities were similar three months pre- and post-switch. After one year of follow-up, approximately 84% of patients were still under CT-P13 treatment, which was lower than in NOR-SWITCH (96%). Authors indicated that this difference could be explained by the real-life setting of the study. The one-year retention rate was slightly lower (3.4%) compared to patients treated with the RP in a historic cohort (329).

Some infliximab switch studies reported a difference in efficacy, safety, immunogenicity, retention rate or product dosage before and after switching or between the switch and maintenance group in their final conclusion (330),(331),(332),(333),(334). Multiple studies reported a high number of discontinued treatment, mainly driven by worsening in patient reported outcomes (PROs), without changes in objective parameters (e.g. in TL, ADA, CRP). Mostly, authors concluded that this was probably driven by placebo effects (i.e. patients' negative expectations leading to experienced AEs or a perceived decrease in response (122),(330),(331),(332),(333)).

4.5.2 ADALIMUMAB

Eight biosimilars (representing five unique products) of adalimumab (RP Humira®), have been approved in the EU, i.e. Imraldi®, Solymbic®/Amgevita®, Halimatoz®/Hefiya®/Hyrimoz®, Cyltezo® and Hulio® (169). Seven switch studies from the RP to one of its biosimilars were identified (Table S5 in the online supplementary information). These are all double blind or open label extension studies of phase III trials as part of the biosimilar development program. Two studies investigated switching from the RP to ABP 501 (Amgevita®/Solymbic®), in two different patient settings (RA and plaque psoriasis) (300),(303) The trial in RA was a phase III open-label extension trial, incorporating a single switch from the RP to ABP 501 in 237 patients with a follow up of 46 weeks (300). The trial by Papp and colleagues investigated the single switch from the RP to ABP 501 in 77 patients with moderate to severe plaque psoriasis, during a phase III RCT (303). Data from both trials indicated that safety, including immunogenicity, was similar among groups after a single switch (300),(303). One phase III RCT trial investigated the single switch from the RP to SB5 (Imraldi®) in 125 patients with RA. Efficacy, safety and immunogenicity profiles were reported to be comparable between groups. It was stated that no TEAEs or clinically relevant immunogenicity arose by switching (304). The trial by Blauvelt and colleagues consisted of a sequence of four switches (multiple switch design; switch at week 17, 23, 29 and 35) between the RP and GP2017 (126 patients switched, 34 weeks follow-up after initial switch at week 17). Efficacy, safety and immunogenicity were reported to be similar among the switch and non-switch groups (289). A randomized open label extension study investigated the impact of a second switch at week 48, after the first switch at week 24 during the double blinded part of the study, between the RP and FKB327 in RA patients. The interim results suggest that safety, efficacy, and immunogenicity were comparable between the maintenance and switch groups (290). Further, for both CHS-1420 and BI695501 a randomized double blind RCT investigated a single switch from the RP. Overall, no efficacy, safety or immunogenicity issues were reported (302),(301).

4.5.3 ETANERCEPT

Benepali® and Erelzi® are two unique EU-approved biosimilar versions of etanercept (RP Enbrel®) (169). In total, 25 etanercept biosimilar switch studies have been identified. Five of these consist of a double-blind or open label RCT of which four were conducted in rheumatology indications (305),(306),(307),(308). The other study consisted of a multiple switch double blind RCT (EGALITY) investigating switching between the etanercept RP and GP2015 in patients with plaque psoriasis (128). Patients were switched at week 12, 18, 24 and 30 and followed up to 52 weeks. It was concluded that the repeated switches between the RP and GP2015 had no negative impact on safety or immunogenicity outcomes (128). Out of 20 RWE studies, 18 were conducted in rheumatology and two in dermatology. A multiple switch was performed between the RP and SB4 with patients with rheumatic disease in clinical practice, switching from RP to SB4 and back again after approximately a year and half (291). It was reported that the multiple switch did not negatively impact the disease activity. However, a high proportion of patients discontinued SB4 after the first

switch. The authors attributed this to placebo effects, as no worsening in disease activity measures was observed (291). In a single switch study from etanercept RP to SB4 in patient with rheumatic disease, 39% of patients experienced side effects (335). The authors underlined the need to improve the patients' experience of switching as a way to decrease side effects (335). This need was echoed in a single switch from etanercept RP to SB4 in patients with rheumatic disease in a single centre in France (336). Approximately 17% of patients discontinued the biosimilar, while no objective parameter concluded a lower efficacy or a decreased safety profile. The authors suggested that this could be explained by the open study design (i.e. patients were aware of the switch) (336). The study parameters and results of the switch studies for etanercept can be consulted in [Table S6](#) in the online supplementary information.

4.6 SWITCH STUDIES FOR FOLLITROPIN ALFA

Two biosimilars (representing two unique products) of follitropin alfa (RP GONAL-f®) have been authorized in the EU, i.e. Ovaleap® and Bemfola® (169). One open label extension phase III single switch study from follitropin alfa RP (GONAL-f®) to Ovaleap® has been reported, which can be consulted in Table 16 or [Table S10](#) in the online supplementary information. The study results were overall in support of the safety and efficacy of the switch (326).

4.7 SWITCH STUDIES FOR LOW MOLECULAR WEIGHT HEPARINS

Two biosimilars (representing one unique product) of enoxaparin (RP Clexane®) have been authorized in the EU, i.e. Inhixa® and Thorinane® (169). No switch studies between the RP of enoxaparin and an enoxaparin biosimilar have been identified.

4.8 SWITCH STUDIES FOR MONOCLONAL ANTIBODIES IN ONCOLOGY

The study parameters and results of the RCT and open label switch studies for rituximab and trastuzumab are shown in Table 16. A complete overview of all rituximab and trastuzumab biosimilar switch studies is shown in [Table S11](#) in the online supplementary information.

4.8.1 RITUXIMAB

Six biosimilars (representing two unique products) of rituximab (RP Mabthera®) have been approved in the EU, i.e. Truxima®/Ritemvia®/Blitzima®/Rituzena® (CT-P10) and Riximyo®/Rixathon® (GP2013) (169). Seven switch studies have been identified. Five studies were conducted in the scope of the clinical biosimilar development i.e. the single partial cross-over switch to BCD-020 (324) (a Russian product, not approved in the EU or US, thus not to be considered a true biosimilar evaluated by a stringent regulatory framework), an open-label extension phase I study for CT-P10 (321), an open-label extension phase III study for CT-P10 (322), a double, blind RCT for GP2013 (323) and a randomized extension phase I study for PF-05280586 (320). All were performed in patients with RA. None of these studies detected safety, efficacy or immunogenicity issues related to switching. In addition, results of two RWE rituximab switch studies were reported, of which one was conducted in non- Hodgkin's B cell lymphoma and one in RA (337),(338). The

study of Nisar *et al.* (2018) switched 29 RA patients to CT-P10 (338). It was reported in abstract that 20% of these patients had severe serum sickness with loss of efficacy and loss of confidence in the treatment. Authors concluded that they support routine switching to the rituximab biosimilar, however close monitoring needs to be applied (338).

4.8.2 TRASTUZUMAB

Five unique biosimilars of trastuzumab (RP Herceptin®) have been approved in the EU: Herzuma®, Kajinti®, Ogivri®, Ontruzant®, Trazimera® (169). For one biosimilar (Kanjinti®) a single switch was incorporated during the phase III trial in early breast cancer (EBC) (319). Efficacy, safety and immunogenicity was reported to be comparable between the maintenance and switch group (319). No RWE was identified.

5. CURRENT SWITCH EVIDENCE – LEARNINGS AND CONSIDERATIONS

This article provides a systematic overview and a critical insight in the currently available evidence about switching from a biological RP to its biosimilar(s).

Several reviews of switching studies from biological RPs to biosimilars have been published. The first review in 2012 by Ebbers and colleagues investigated switching for erythropoietins, hrGHs and G-CSFs (285), products for which at that time a biosimilar was approved. Since then many other biosimilars, for different RPs across several therapeutic classes, have been approved, including the more complex mAb biosimilars (169). Further, other reviews have been conducted but these mostly focussed on one specific product class or therapeutic area (241),(339),(340). Recently, two other systematic literature reviews (McKinnon *et al.* and Cohen *et al.*) have been published that included switch studies derived from multiple product classes and disease areas (341),(342). Studies were included until June of 2017. Although both reviews, with the exemption of some data points (e.g. the paper of McKinnon excluded studies in which fewer than 20 patients were switched), include similar data, the conclusion of the authors on the safety of switching was divergent (341),(342). Unsurprisingly, as the topic of switching is heavily debated, and the heterogeneity of study designs leaves some room for interpretation. Cohen and colleagues concluded that the body of evidence provides reassurance that switching is not associated with immunogenicity-related safety concerns or decreased efficacy (342). The review by McKinnon and colleagues concluded that there are important evidence gaps around the safety of switching, underlining the need for further, more robust studies (341).

This article aims to provide a systematic and exhaustive review of all switch studies between biological RPs and their respective biosimilars, and this across therapeutic classes and products for which the EC has approved a biosimilar, updating and adding to the existing literature studies. This review provides a complete overview of existing switch studies from biological RP to biosimilars until June 2018.

This systematic literature review applied a holistic approach, meaning every study describing a switch from a RP to a biosimilar was included. This was done in an effort to give a complete and unselected/unbiased overview of the existing studies. This can be seen as a strength but also as a limitation of the review, as regardless of the sometimes very limited sample size or incomplete methodology and its associated low(er) level of evidence, studies were included. Further, studies that only reported data in abstract and/or in poster were included too. This to capture the most recent and most complete data about switching since many data are recent and still emerging. Data from abstracts and posters should be considered as preliminary until published in full-text in a peer-reviewed journal. A major limitation of this study was the heterogeneous character of the individual studies, limiting the comparability between studies and making a formal meta-analysis impossible. Most of the studies and data were descriptive in nature. Only a few studies, mostly (extension) clinical studies in the development program of a biosimilar, were powered or designed to detect differences in efficacy. Other limitations include potential publication bias of individual switch studies.

5.1 THE DESIGN OF SWITCH STUDIES AND THEIR QUALITY

Based on the currently available data there are no robust data that indicate that switching from a RP to its biosimilar leads to major safety issues. However, the design of many studies is not sufficiently sensitive or not methodologically robust enough to identify and thus exclude differences in the occurrence of rare safety events or differences in efficacy.

LOE during maintenance treatment is quite common for certain therapeutic products and disease fields. For example, between 23-46% of patients treated with an anti-TNF in IBD lose response to treatment over time (343). Juillerat and colleagues identified a dropout rate of 18% during the first year of treatment, followed by 8% and 10% during year two and three for IBD patients treated with infliximab (344). In the case of an experienced or observed decrease or loss in response during a single arm switch study, it is hard to determine if this is due to (i) the mere “normal” decrease in treatment response over time, (ii) due to placebo effects of the patient (experienced inefficacy or decreased efficacy) or (iii) due to increased immunogenicity. The evidence derived from single arm studies is thus limited. The use of objective endpoints, such as the measurement of ADA or TL can partially address the interpretative limitation of single arm studies in case of identified efficacy or safety signals. The same argument can be made for registries. Registries, although informative of nature, can be difficult to interpret as they lack such a comparator arm and may not be able to adjust for all confounding variables.

Not only studies without a parallel arm have limitations for the interpretation of data, well-designed clinical trials can also be insufficiently sensitive to detect small differences in efficacy (345). Louis and colleagues investigated the risk of relapse of CD patients in prolonged remission after the discontinuation of infliximab treatment (345). After a follow-up period of 28 months, more than half of the patients were still in remission. The one-year relapse rate was $43.9\% \pm 5.0\%$ (345). A potential decrease in response after switching could thus potentially go undetected in some cases, due to

sustained remission of treatment on the RP in some patients. Further, most switch trials have a relatively short follow-up period, mostly too short to identify rare immunological events. Further, the sample size of the identified switch studies and RCTs was mostly too small to identify rare AEs.

The bulk of the switch data in the real world setting consists of monitored switches from the infliximab RP to CT-P13, explained by the fact that CT-P13 was the first infliximab biosimilar, and mAb biosimilar in general, to be introduced on the market. Most of these studies were conducted in IBD. This could be interpreted as an effort of individual hospitals and pharmaceutical companies to gather clinical evidence about the use of infliximab biosimilars in gastro-enterology, given that the product received approval for CD and UC based on the principle of extrapolation of indications.

The body of identified switch studies is heterogeneous in their design, and, by consequence, in the quality of the generated evidence, and cannot exclude every potential risk. On the one hand, the gathered data may provide a general indication that switching seems not to be associated with major efficacy, safety or immunogenicity issues. On the other hand, findings with respect to switching should be product-specifically and disease-specifically interpreted and cannot be generalised to other products or other diseases, given different immunological complexities of the different products, different disease states and different concomitant treatments.

5.2 CROSS-REACTIVITY OF ADAS BETWEEN THE RP AND ITS BIOSIMILAR

Several studies have investigated the immunogenic profile of the infliximab RP and one of its biosimilars CT-P13 (Remsima®/Inflectra®) and the cross-reactivity of ADAs between both products (282),(346),(347),(348). These studies provided similar results in support of the immunogenic similarity between infliximab RP and CT-P13 in IBD (348),(346) or rheumatic diseases (282),(347). It was shown that ADAs against the RP recognized and reacted to the biosimilar in a similar way, indicating that these products share similar immunodominant epitopes. Additional epitopes (due to e.g. differences in the glycosylation pattern, impurities or aggregations) may not be excluded, but data suggest that the epitopes that are involved in the immune response to the RP are also present for CT-P13 (282). Further, the regulatory quality standards applied for biosimilar candidates preclude meaningful impurities or aggregations. It is obvious that patients showing an immunogenic response under treatment with the RP (or biosimilar) should not be switched to the biosimilar (or RP), as the existing ADAs will cross-react with both versions. Likewise, ADA-negative patients under treatment with the RP, are not expected to assert an immune response to the biosimilar when switched (348).

5.3 ADDRESSING THE QUESTION OF SWITCHING IN EUROPE

Different from the FDA in the US, there is no regulatory pathway considering a designation of interchangeability in Europe. Further, there is no official position of EMA about switching, interchangeability or substitution, as this falls within the responsibilities of the individual member states. The information guide for HCPs, prepared jointly by EMA and the EC, indicates “*there is no reason to believe that harmful immunogenicity should be expected after switching between highly similar*

biological medicines" (349), referring to an article by a group of European regulators and members of the biosimilar medicinal products working party (BMWP) (350). This group of regulators argues that switching patients from a RP to a biosimilar or *vice versa* can be considered safe, as there is in their opinion no reason to believe that the immune system would react differently to the biosimilar compared to the RP, given the fact that they are highly similar (350). It is concluded that the demonstration of biosimilarity, together with adequate PMS, sufficiently and realistically ensures interchangeability of biosimilars in the EU (350). Increasingly, guidance about the use of biosimilars in practice and switching is provided by national competent authorities and professional HCP organizations (286). Several national regulators indicate that switching from a RP to a biosimilar is deemed appropriate, provided that it is done under the supervision of the prescriber, the patient is properly informed, the patient is clinically followed-up and traceability of the products is ensured (286). Despite an increase in guidelines among certain authorities and organizations, the confidence among many stakeholders remains low and continues to lead to questions. Harmonisation of (national) regulatory guidance and/or scientific recommendations on the use of biosimilars and switching may aid the decision-making of HCPs and other decision makers.

5.4 DISCONTINUATION RATES AND THE NOCEBO EFFECT

In several studies (330),(331),(332),(333),(334), authors concluded that patients experienced subjective AEs or LOE, potentially explaining the high dropout rate and the need to switch back to the RP. The experienced AEs or LOE were not linked to objective safety signals and investigators ascribed this to attribution or nocebo effects; i.e. patients' negative expectations leading to experienced AEs or a perceived decrease in response (122).

Several studies investigating the perspectives of stakeholders identified uncertainty among patients and HCPs about biosimilars and the act of switching from a RP to a biosimilar (351),(352). The potential nocebo effect upon switching highlights the importance of a good knowledge and understanding of physicians and patients about biosimilars. Potentially, the information provided to patients may play a role in the perceived outcome of the treatment. Well-informed HCPs should inform patients about the product they receive in an evidence-based manner. The nocebo effects further highlight the importance of shared, evidence-based decision-making between the physician and the patient. Strategies mitigating the nocebo effect may improve patient outcomes and discontinuation rates (122).

5.5 FURTHER CONSIDERATIONS: MULTIPLE SWITCHING, SWITCHING BETWEEN BIOSIMILARS OF THE SAME REFERENCE PRODUCT AND TRACEABILITY

Until now, a limited number of studies report about multiple switching (127),(289),(290),(128),(291),(132). Some studies were not designed to investigate multiple switching, but did report on switching back from the biosimilar to the RP for some patients. The question about multiple switching among HCPs is increasingly raised, indicating the need for information in this field. Following the FDA interchangeability guidance (284), multiple switch

studies evaluating two or more alternating exposures may emerge in the future. Since multiple, independently developed biosimilars of the same RP have been approved and are on the market, switching between biosimilars of the same RP, is a possibility as well. However, not every biosimilar of the same RP is a distinct product. Indeed, some biosimilars are licensed under different brand names but contain exactly the same product, e.g. Remsima® and Inflectra® contain both the active substance CT-P13, and Blitzima®, Ritemvia®, Rituzena® and Truxima® contain CT-P10. So far, no data about switching between biosimilars of the same RP was identified.

To ensure adequate traceability, it is of importance to document the specific biological product that is prescribed, including brand name, INN and batch number when prescribing biologicals or when reporting any adverse events. Post-marketing pharmacovigilance remains key for both RPs and biosimilars to track ongoing safety and immunogenicity and detect potential safety signals. PMS is particularly important to identify rare immunological events that can only be detected after a long follow-up period in large patient numbers. To ensure an optimal use and value of the registries, it is important to include brand names and batch numbers to correctly identify the medicine if any product-specific efficacy, safety or immunogenicity concern should arise (349),(353).

5.6 RESIDUAL UNCERTAINTY

It has been argued that switching could lead to increased immunogenicity, due to potential differences in epitopes between the biosimilar and the RP. Relevant differences in this regard, such as quality differences in terms of high molecular weight aggregates or impurities, would however be excluded by the robust regulatory evaluation of biosimilars, i.e. such differences would preclude biosimilar approval.

The scientific principles underpinning the biosimilarity exercise are in fact based on the comparability concept, a well-established scientific principle which is used to evaluate the differences of a biological product before and after a manufacturing change (biologicals frequently undergo manufacturing changes after approval (24),(350),(354),(355)). Demonstrating comparability ensures that the products pre-and post-manufacturing change are highly similar and allows regulators to conclude that any observed differences have no adverse impact on efficacy or safety of the product. Demonstrating biosimilarity generally requires a more comprehensive comparison than manufacturing changes. The latter rarely require clinical data, but for major changes such as a change of cell-line large scale clinical studies may be required (350). Overall, the extensive experience gathered in regulating manufacturing changes of reference products has provided assurance to regulators about the risks associated with switching from one highly similar version of a biological to another (350).

Although the switch studies presented in this review cannot exclude every potential risk associated with switching from a RP to a biosimilar, as clinical studies are variable and insensitive to assess the impact of minute differences, they do not corroborate the voiced concerns of increased immunogenicity due to switching. Therefore, discouraging a single switch from a RP to a biosimilar

may be deemed disproportional compared to the residual uncertainty associated with such a switch. Further, residual uncertainty, to a certain extent inherently associated with the use of any biological medicine or any medicine in general, can never be fully excluded. The current body of switch data, together with the robust biosimilar approval pathway, however help to limit the residual uncertainty to an acceptable level.

6. CONCLUSION

Based on the currently available switch data of over 170 studies, there are no robust data that indicate that switching from a reference biological to a biosimilar is related to major efficacy, safety or immunogenicity issues. The switch studies cover different molecules across different therapeutic classes. Most of the currently available data refer to switching for anti-TNFs and more specifically, from the infliximab RP to CT-P13 (Remsima/Inflectra®). Due to a small sample size and generally short follow-up period, most of the identified studies are however insufficiently sensitive to detect and thus exclude rare adverse events. Data on multiple switching and switching between biosimilars for the same RP is so far scarce or not present. Although the decision to switch must be made on an individual and product specific level, this review on switching between biological RPs and biosimilars supports that for the products studied, a single switch is not intrinsically linked to an increase in immunogenicity, safety or efficacy issues. Any decision to switch should involve the prescriber and attention must be paid to the mitigation of potential nocebo effects

PART 4
BIOSIMILAR PROCUREMENT &
POLICY MAKING

1. ABSTRACT

Background: In Europe, off-patent biologicals and biosimilars are largely procured by means of tender procedures. The organization and design of tenders may play a key role in the evolving biosimilar market, and currently it is not fully elucidated how tenders for off-patent biologicals and biosimilars are designed and if approaches are aligned with sustaining market competition and societal savings for healthcare systems over the long term.

Objectives: This study aims to (i) explore the design and implementation of tender procedures for off-patent biologicals and biosimilars in Europe, (ii) identify learnings for sustainable tender approaches from purchasers and suppliers, and (iii) formulate recommendations in support of competitive and sustainable tender practices in the off-patent biologicals market.

Methods: A mixed methods design was applied. A quantitative web-survey was conducted with hospital pharmacists and purchasers (N=60, of which 47 completed the survey in full), and qualitative expert-interviews with purchasers and suppliers (N=28) were carried out.

Results: The websurvey results showed that the organization and design of tenders for off-patent biologicals and biosimilars, and the experience of hospital pharmacists and purchasers with this, considerably varies on several elements across European countries. From the qualitative interviews, signals emerged across the board that some of the current tender approaches might negatively affect market dynamics for off-patent biologicals and biosimilars. The focus on generating short-term savings and existence of originator favouring tender practices were identified as elements that may limit timely competition from and market opportunity for biosimilar suppliers. The need to optimize tender processes, considering a more long-term strategic and sustainable view, was expressed. In addition, challenges appear to exist with differentiating between products beyond price, showing the need and opportunity to guide stakeholders with the (appropriate) inclusion of award criteria beyond price. Due to the variety in tender organization in Europe, a 'one size fits all' tendering framework is not possible. However, on an overarching level, it was argued that tender procedures must aim to: (i) ensure market plurality and (ii) include award criteria beyond price (warranted that criteria are objectively and transparently defined, scored and competitively rewarded). Depending on the market (maturity), additional actions may be needed.

Conclusions: Findings suggest the need to adjust tender procedures for off-patent biologicals and biosimilars, considering a more long-term strategic and market sustainable view. Five main avenues for optimization were identified: (i) safeguarding a transparent, equal opportunity setting for all suppliers with an appropriate use of award criteria, (ii) fostering a timely opening of tender procedures, ensuring on-set competition, (iii) ensuring and stimulating adherence to laws on public procurement, (iv) securing an efficient process, improving plannability and ensuring timely product supply and (v) safeguarding long-term sustainable competition by stimulating market plurality.

2. INTRODUCTION

Biological medicines represent a growing share of the total pharmaceutical spend, primarily driven by their high prices and increasing use and as such place a growing pressure on healthcare budgets (8). In Europe in 2018, over 30% of pharmaceutical expenditure was on biological medicines, totalling approximately EUR 53 billion (117).

With the expiration of patents and other exclusivity rights for numerous block-buster biological medicines, interest in the development and commercialization of biosimilars rose (10). Biosimilars are products that are similar to an already authorized biological product, the originator product, with regards to quality, safety and efficacy (14). The EU has the most mature biosimilar market at present, with 57 biosimilars approved for 16 distinct molecules across various therapeutic areas such as rheumatology, gastroenterology and oncology (116). The biosimilar market is rapidly evolving and the number of approved biosimilars is expected to grow over the following years (356). Biosimilars pose an opportunity for healthcare systems to foster competition following the originator's loss of market exclusivity and lower spending on biological medicines while safeguarding safe and effective treatment. Of the total spend on biological medicines in the EU, 21% is now exposed to biosimilar competition (EUR 12 billion yearly) (117). Biosimilar market entry has shown to lead to significant price reductions and increased patient access to biological therapies (10),(39). The 2020 IQVIA *The Impact of Biosimilar Competition in Europe* report showed that, based on list-price changes, biosimilar market entry has led to an overall 5% reduction in the total EU drug budget spending since 2014 (11).

On a pan-European level, moderate biosimilar uptake and considerable price reductions have been achieved. The experience of individual countries, regions and hospitals with biosimilars differs however considerably, which might be partly explained by the differences in biosimilar policies between and within countries (10),(35).

To face budgetary pressures, cost-containment measures have been introduced by European payers to reduce pharmaceutical spending (54). Tender practices are of specific interest as cost-containment measure in the context of off-patent biological and biosimilar procurement as they make use of supplier competition. Tendering is defined as a formal and predefined procedure in which multiple suppliers enter a contract competition, with the aim to select a best value for money medicine or medicines (55),(54),(53). A tender procedure is generally applied to procure medicines when alternatives or equivalents for a specific medicine are available, which is the case for off-patent (originator) biological medicines and biosimilars. Hospital medicines, including most biologicals, should generally be procured by means of tenders in Europe. Public hospitals or non-public hospitals that are considered as bodies governed by public law should in principle organise tenders according to the harmonised EU rules on public procurement (357). The EU rules are transposed into national legislation and apply to tenders whose monetary value exceeds a certain amount (358),(359). In tender procedures, price reductions beyond (mandatory) decreases at list-price level can be achieved. Together, these allow healthcare systems to optimize spending on off-

patent biologicals and biosimilars. In addition to stimulating price competition, tenders may incentivize suppliers to compete on product or service differentiation, creating additional value for the patient and/or the care process.

When organized and applied in an appropriate way, tendering can be an efficient procurement mechanism, providing equal access to the different suppliers on the market and fostering competition between them, creating an opportunity for healthcare systems to contain expenditure and/or achieve savings that can be invested in other areas of care while possibly creating additional value for patients and care processes (53). However, questions exist around the effective organization and application of tender procedures and significant variation exists in the organization of such tenders across European Member States, regions and purchasing groups (54),(118),(360),(361),(362). The way how tender procedures are designed may have important implications on pharmaceutical market competition over the longer term (53),(363),(364),(365). Tender design elements such as the level on which tenders are organized, the number of winners, the tender duration and selection-and award criteria are important in this.

The importance of effective biosimilar competition for healthcare systems, together with emerging questions regarding the sustainability of tender approaches, the application of award criteria beyond price and the long-term viability of biosimilar commercialization (366),(117), poses a timely opportunity to assess current tender practices for off-patent biologics and biosimilars and considerations regarding its possible influence on dynamics in the off-patent biologics market in Europe.

This study aims to (i) explore the design and implementation of tender procedures by contracting authorities for off-patent biologicals and biosimilar and (ii) identify stakeholders learnings and components for sustainable tender approaches, to in the end (iii) formulate proposals in support of competitive and sustainable tendering practices, supporting long-term presence of different competitors and accompanying benefits for healthcare systems. Table 17 provides study highlights.

TABLE 17. STUDY HIGHLIGHTS

<p>What is already known about the topic?</p> <ul style="list-style-type: none"> ▪ The organization and implementation of tendering of off-patent biologicals and biosimilars varies across European Member States, regions and purchasing groups. ▪ The organization and design of tenders may play a key role in the evolving biosimilar market. It is not fully elucidated how tenders for off-patent biologicals and biosimilars are designed, and if approaches are aligned with sustaining market competition and societal savings for healthcare systems over the long term.
<p>What does the study add to existing knowledge?</p> <ul style="list-style-type: none"> ▪ This mixed methods study reports quantitative results derived from a survey among purchasers and hospital pharmacists regarding the application of tenders and qualitative insights from expert-interviews with suppliers and purchasers. ▪ This paper puts forth an actionable framework with proposals that could contribute towards a more sustainable organization and application of tenders for off-patent biological medicines and biosimilars in Europe.
<p>What insights does the study provide for informing health care-related decision-making</p> <ul style="list-style-type: none"> ▪ Findings may inform and support purchasers, suppliers and policymakers regarding the organization and optimization of tender procedures for off-patent biologicals and biosimilars. ▪ Tender procedures must aim to (i) ensure market plurality and (ii) include award criteria beyond price (warranted that criteria are objectively and transparently defined, scored and competitively rewarded). Depending on the market (maturity), additional actions are considered needed.

Terminology: the term “off-patent biologicals” refers to reference biologicals that lost patent protection and are exposed to competition from biosimilar alternatives.

3. METHODS

The study follows a mixed methods design, consisting of a survey and semi-structured interviews, gathering both quantitative and qualitative data. The study concentrates on tender procedures organised by contracting authorities. Tenders that are organized by private entities are not bound to organise public procurement procedures and are therefore out of scope. Ethics approval of the study was granted by the Research Ethics Committee UZ/KU Leuven.

3.1 QUANTITATIVE WEB-SURVEY

3.1.1 RECRUITMENT

A quantitative, anonymous web-questionnaire was developed to survey purchasers and hospital pharmacists about the organisation of tenders for off-patent biologicals and biosimilars. The survey was disseminated to hospital pharmacists and purchasers across Europe, via professional associations such as the European Association of Hospital Pharmacists, by contacting procurement entities and the network of the research group.

3.1.2 SURVEY DEVELOPMENT

The survey was developed based on a study of the literature and consisted of questions about (i) the experience of participants with tender procedures for off-patent biologicals and biosimilars and perceived challenges, (ii) the design of tender procedures (number of winners, average tender duration, reopening of tenders, physician involvement), (iii) the application of selection-and award criteria and (iv) considerations about interchangeability and switching, as tenders may result in an exchange of products. The survey questions were refined based on comments from both a hospital pharmacist and a supplier. The survey was developed online in the KU Leuven Websurvey-server and gathered anonymous data. The survey consisted of closed multiple choice, ranking or Likert-scale questions. Participants were given the possibility to add additional information in an open text field for certain questions and answer options such as “Other”. The first window of the websurvey provided participants with information about the study, the voluntary nature of participation and a statement regarding agreement to participate. The survey was anonymous, and no personal data were collected.

3.1.3 ANALYSIS

Responses were gathered between October 2018 and February 2019. The survey answers were analysed descriptively on an overall group level.

3.2 QUALITATIVE SEMI-STRUCTURED INTERVIEWS

3.2.1 RECRUITMENT

To gather qualitative, in-depth expert insights regarding the organization of tenders for off-patent biologicals and biosimilars, semi-structured interviews were conducted with hospital pharmacists, purchasers and pharmaceutical industry employees. The sampling was purposeful to obtain a range of experiences and perspectives, reflecting both the purchaser and supply side perspective, from individuals that are knowledgeable about and experienced with tender processes for off-patent biologicals and biosimilars.

Eligible participants worked currently or formerly as (i) medicine purchaser or hospital pharmacist, (ii) in, or as consultant to, a pharmaceutical company with at least one EMA-approved originator biological or biosimilar (or having both originator and biosimilar products) or for a pharmaceutical industry trade organization. Employees from both legacy originator and legacy generic companies were recruited. Participants were selected for their experience with and knowledge about tender practices for off-patent biologics and biosimilars (263).

To capture diverse and comprehensive insights, both participants with insights on a pan-European level (e.g. from European professional associations, European pharmaceutical company headquarters or trade organizations) and participants with country specific insights were invited. For the latter, participants were recruited from a purposive selection of seven European countries, representing different tender organizational systems (central purchasing: Denmark and Norway,

regional purchasing: England and Italy, buying group/hospital individual purchasing: France, the Netherlands and Belgium). The choice to capture the insights of both purchaser- and supply (industry)-side participants was made to obtain views from the two principal stakeholder groups in the tender process.

Participant recruitment was carried out by screening relevant websites, scientific and professional stakeholder associations, relevant conferences and publications and the network of the research group for eligible participants.

While different sampling strategies were applied for the survey and the interviews (broad *versus* purposeful sampling), a certain overlap in participants may theoretically have been possible. The impact of having a respondent possibly participating in the survey and a subsequent interview is considered negligible on interview results since the survey and interviews served distinct purposes.

3.2.2 INTERVIEW GUIDE AND INTERVIEWS

Interviews were carried out in English, with the exception of a few interviews in Dutch, in person, via telephone or teleconference between March 2019 and February 2020. All participants provided written informed consent prior to the start of their interview. Consent was given by all participants for using the encoded and anonymized data from their interview for scientific publication. Interviews were conducted using an interview guide based on topics identified from scientific literature, policy documents, position statements related to the procurement of off-patent biologics and biosimilars and the quantitative survey results. Interviewees were asked to share their insights on challenges, best practices and learnings regarding tender practices for off-patent biologicals and biosimilars, as well as proposals towards long-term sustainable tender practices. An overview of discussed topics is shown in Supplementary Information [Table S9](#). All interviews were audio-recorded and transcribed *ad verbatim*. Interviews were carried out until saturation of the data (263).

3.2.3 ANALYSIS

Interview transcripts were pseudonymised and analysed according to the thematic framework method, using Nvivo® data analysis software (59).

4. RESULTS

4.1 SURVEY RESULTS - ORGANIZATION AND DESIGN OF TENDERS FOR OFF-PATENT BIOLOGICALS AND BIOSIMILARS

In total, 60 hospital pharmacists and purchasers participated in the web-survey. The number of participants varied throughout the survey due to survey logic and participant drop-out. Forty-seven respondents completed the survey in full. Survey participants' characteristics are shown in [Table S1](#) in Supplementary Information. In general, survey results showed that the implementation and design of tenders for off-patent biologicals varied on several elements.

4.1.1 PERCEPTIONS ABOUT THE TENDER ORGANIZATION

The majority of participants (61%) indicated their organisation to have moderate to extensive *experience* with tendering for biological medicines. Hospital pharmacists (88%), physicians (68%) and a procurement office (67%) were indicated to generally participate in formulating the tender conditions and subsequent product selection. A similar proportion of participants mentioned that differences (44%) and no differences (46%) exist between tender procedures applied for biologicals and small molecule medicines.

When tendering for biological medicines, 60% of participants identified *questions* about interchangeability and switching between biological reference products and biosimilars as challenging. Participants also identified the formulation of appropriate award criteria (25%), supply chain reliability (23%) and the formulation of criteria to select viable suppliers (19%) as challenges when tendering for biologicals. About one fifth of participants indicated to not identify specific challenges with tendering for biological medicines, different from those experienced with tendering for medicines in general. Full survey results are shown in [Table S2](#) in Supplementary Information.

4.1.2 THE TENDER DESIGN

The reported *average tender duration* varied substantially. Over one quarter of participants (27%) indicated that tender agreements are made for one up to two years. Approximately 20% of participants indicated that tender agreements last between six months and one year, and a similar number indicated tenders to last between two and three years. Tenders shorter than 6 months (12,5%) or longer, between 3 and 4 years (12,5%) appear less common. Approximately half of participants (55%) indicated that contracts can be *reopened after loss of exclusivity* of the tendered originator product.

Almost half of participants (46%) indicated that tenders are generally awarded to a single *winner*. The same proportion of participants indicated that both single and multiple winner constructs are possible. Only 9% indicated to organize tenders with multiple winning suppliers.

Over half of participants (56%) indicated that the *physician's voice* is incorporated in the tender procedure as being part of the tendering committee. According to 68% of participants, physicians can request a motivated exception to prescribe a different product than the tendered product. Only 10.5% indicated that physicians *maintain therapeutic freedom* to prescribe a different product than the tendered product. Full survey results are shown in [Table S3](#) in Supplementary Information.

4.1.3 APPLICATION OF SELECTION- AND AWARD CRITERIA

According to 68% of participants, no meaningful *differences* exist in the selection criteria applied in tender procedures for small molecule and biological medicines. Similarly, 60% of participants indicated that there are no differences in the award criteria for biological medicines and those for small molecule medicines while 33% made a distinction.

In terms of applied *selection criteria* (when applicable), 27% indicated to consider the financial viability of the supplier. One fifth of participants indicated to consider the supplier's reputation and the supplier's production capacity. To a lesser extent, participants indicated to consider the supplier's track record of previous tenders (16%), previous collaboration (12%), the duration that the supplier already markets the product (8%), the market share of the product (6%) and the supplier's investment in academic research (4%).

In terms of applied *award criteria besides price*, the product's registered indications (49%), the product's stability/shelf life (45%), the product's delivery device (35%) and the packaging (35%) were indicated to be generally considered. In terms of award criteria related to supply, 41% of participants indicated to consider the supply conditions and 29% the emergency delivery and 24/7 reachability of the supplier. Almost a quarter (22%) of participants indicated to award on additional efficacy and/or safety data (in addition to the data required for regulatory approval, such as clinical data in an additional patient population, or switching data). Value added services (e.g. supporting educational activities, product training programs, information brochures for HCPs or patients about the product, support with switching from the medicinal product previously used) (18%), customer support (14%) and expenses incurred from switching from the previous winner (6%) were considered to a lesser extent.

The *relative weight given to price* when awarding the tender varied among participants. The majority of participants indicated that a certain weight was given to award criteria besides price (predominately awarded on price (38%), a 50/50 distribution between price and other criteria (19%), predominately on other criteria besides price (19%)). Approximately 20% of participants indicated tenders to be awarded entirely on price.

When formulating *award criteria*, a large number of participants indicated to do so in collaboration with or advice from experts within their own organization (70%). Over half of participants indicated to base themselves on previous experience and almost half to base themselves on national or European guidelines. Thirteen percent of participants indicated to formulate award criteria in collaboration with or advice from (one of) the suppliers. Full survey results are shown in [Table S4](#) in Supplementary Information.

4.1.4 INTERCHANGEABILITY AND SWITCHING CONSIDERATIONS IN THE CONTEXT OF TENDERS

For the formulation of the tender, over half of participants deemed biosimilars interchangeable with their reference product, while 28% believed this depends on the product class and 13% indicated that biosimilars and their reference product are not interchangeable. The majority of participants (68%) indicated that biosimilars and the reference product are grouped in the same lot. According to 43% of participants, no *difference* is made between bio-naïve patients and patients already under treatment with the biological medicine when tendering for biological medicines, with 36% indicating that a difference is made. When the patient already undergoes treatment with the previous winner, approximately half of participants indicated that the option is foreseen to keep patients on therapy with the previous winner. This was indicated to be realized via a multiple winner tender, *i.e.* there

are multiple winners, and one of them is the previous winner (29%), direct procurement of the previous winner (42%) or via an existing contract with the previous winner (21%). Full survey results are shown in [Table S5](#) in Supplementary Information.

4.2 INTERVIEW RESULTS - CONSIDERATIONS REGARDING THE DESIGN AND ORGANISATION OF TENDER PROCEDURES

In total, 28 expert-interviews were conducted. [Table S6](#) and [Table S7](#) in Supplementary Information provide an overview of interview participants' characteristics.

4.2.1 CONSIDERATIONS REGARDING TENDER DESIGN ELEMENTS

4.2.1.1 DIVIDING PRODUCT VOLUME AMONG SUPPLIERS – ENSURING MARKET PLURALITY

Presently, tenders are often organised on a single-winner basis, in which the total tendered volume is awarded to one supplier. A *single-winner tender design* generally leads to significant discounts, certainly if the product volume is significant such as in national single-winner tenders. The generated initial price pressure has proven advantageous for healthcare systems to realize immediate large savings. However, awarding total market volume to a single winner excludes non-winning competitors from the market for the duration of the tender contract. While price-driven, single winner tenders generally translate in welcomed large initial savings for healthcare systems, these might decrease supplier plurality in the market. A proliferation and continuation of the single winner-takes-all approach may as such lead to reduced levels of competition. In addition, relying on a single or limited number of suppliers may impact the continuity of patientcare in case of product shortages. Large volume, single-winner tenders may in addition imply a potentially large time and product write-off for contenders who did not win.

Dividing the market among multiple suppliers, providing a commercial opportunity for several suppliers and ensuring *plurality in the market*, was the single most recommended intervention by interviewees towards creating more sustainable tender practices. Some hesitations were expressed by purchasers, as the organization of multiple winner tenders increases the complexity of tenders and product management in the hospital. Healthcare systems and purchaser authorities need to be equipped to accommodate and effectively organize such a multi-winner tender structure. Besides this remark, both purchasers and suppliers broadly voiced their support. Awarding tenders to multiple winners may also contribute to lower price pressure due to the smaller product volumes. In addition, it provides price reductions on all tendered products and may possibly increase the physician's therapeutic freedom to choose between different products, as such avoiding physicians using a higher-priced non-tendered product. The availability of multiple commercial products on the market may further help to mitigate supply chain issues.

Various scenarios could be explored and applied to ensure market plurality, depending on the market size and product volume. Multi-winner tenders (*i.e.* the tender is awarded to multiple bidders) can

be organized or markets can be divided into multiple commercial single-winner opportunities (e.g. on hospital network or regional level).

To effectively organize a multi-winner tender, interviewees argued that some *conditions* need to be fulfilled. First, the tendered volume on purchaser level needs to be large enough to be divided among multiple bidders. Second, from the perspective of the purchaser, purchasing capacity would need to be consolidated to increase the feasibility of organizing multi-winner tenders, as this may add to complexity and workload. Third, suppliers should be provided with a guarantee regarding the allocation of volume per supplier. A clear volume estimation per winner is needed to allow them to manage their supply chain and formulate a competitive bid. Multi-winner scenarios in which the first winner is the utilized product and other winners serve as back-up in case supply issues would occur with the first-ranked winner are to be avoided.

In countries where tendering takes place on hospital (group) level (typified by small volumes and generally small procurement teams), single-winner tender structures may be a more efficient route while still stimulating competition as multiple opportunities to win volume exist across the market.

Dividing the market volume among multiple winners on a central or regional purchasing level should not necessarily translate in the availability of multiple products on an individual hospital level. The different winners may be allocated to certain regions or hospitals, which is for example the case in England.

The advantages and conditions related to the organization of multi-winner tenders are outlined in Table 18.

TABLE 18. ORGANIZING MULTI-WINNER TENDERS: CONSIDERATIONS

Advantages	Conditions
<ul style="list-style-type: none"> ▪ Stimulating market presence of multiple suppliers over the longer term 	<ul style="list-style-type: none"> ▪ Volume at purchaser level needs to be sufficiently large to be divided among different suppliers. Alternatively, multiple single-winner opportunities can be organized in a given market to ensure supplier plurality (i.e., the approach and number of winners should be adjusted to market purchasing characteristics.)
<ul style="list-style-type: none"> ▪ Offering commercial opportunity to multiple suppliers 	<ul style="list-style-type: none"> ▪ The purchaser's capacity needs to be sufficiently consolidated to accommodate the increased complexity and workload
<ul style="list-style-type: none"> ▪ Lowering immediate steep price pressure (avoid one winner takes all), which may lead to more sustainable price dynamics over the longer term 	<ul style="list-style-type: none"> ▪ The allocation of volume between suppliers needs to be clear and guaranteed
<ul style="list-style-type: none"> ▪ Providing price reductions on all tendered products 	
<ul style="list-style-type: none"> ▪ Possibly increasing physician's product choice 	
<ul style="list-style-type: none"> ▪ The availability of multiple commercial products on the market may help to mitigate supply issues in case shortages would occur 	

4.2.1.2 TENDER AWARD CRITERIA – ENSURING A FAIR DESIGN AND APPLICATION

Purchasers are encouraged to award a tender based on the Most Economically Advantageous Tender (MEAT) principle, including qualitative elements linked to the tender-subject beyond price, as outlined in the EU Procurement Directive 2014/24/EU (357),(367),(368). Tender procedures that solely or mainly focus on price, while delivering savings in the short term, may lead to price erosion and lower the number of competitors over the longer term. Interviewees cautioned that this could ultimately result in *de novo* market consolidation and increased prices in a given market.

Lowest bid procedures should be avoided and suppliers should aim to compete sustainably *on additional elements*. Multiple European trade organizations (both originator and biosimilar oriented associations) and also the European Association of Hospital Pharmacists (EAHP) underwrite the practice to include criteria beyond price in tender procedures (369),(370),(363),(371),(364), as such awarding the best-value biological(s). An overview of position statements of these organizations is made available in [Table S8](#) in Supplementary Information. The inclusion of award criteria beyond price can lead to benefits for the patient (e.g. less painful injection) or the broader organization of care (e.g. facilitating efficient handling by means of ready-to-use preparation or pre-filled syringes). Including additional criteria besides price can furthermore contribute to countering steep price

erosion identified in price-only tenders, as this would stimulate to suppliers to innovate and sustainably compete on value-adding criteria.

Four main *challenges* related to including additional award criteria emerged from the interviews. First, the inclusion of award criteria besides price appears not to be routinely included in tenders for off-patent biologicals and biosimilars. According to interviewees, price remains often the sole or dominant differentiator in tender decisions.

Second, stakeholders appear to have questions on how to exactly formulate and apply these criteria. Both purchasers and suppliers mentioned difficulties with translating the MEAT principle to applicable award criteria for off-patent biologicals and biosimilars. As stipulated in the EU Public Procurement Directive, criteria should be compliant with the principles of transparency, non-discrimination and equal treatment to allow an objective comparative assessment (357). Any criteria that could be perceived as anti-competitive or introduce bias should be excluded from inclusion. Further, only criteria that are related and proportionate to the subject matter of the tender should be included. Caution should be exerted regarding requesting or offering additional services or benefits. In case these are not directly related to the subject matter, these should be strictly avoided. Some interviewees mentioned for example the offering or requesting of research funding. This leads to the third identified challenge related to the application of award criteria.

It appears that in some cases where additional criteria are included; these may *a priori* favour the reference product or disadvantage the biosimilar. For example, including an award criterion on the length of product market presence would structurally disadvantage recently launched products, *i.e.* biosimilar alternatives, compared to the reference product. Including such an award criterion could therefore be considered as an unreasonable expulsion of competition. Moreover, criteria that are not directly related to the subject-matter can steer the decision-making on non-product related factors, and especially when these are disproportionately weighted in the decision. Additional product-related services are mentioned to be interpreted broadly in some instances. Requesting or offering bonuses or benefits beyond the scope of the product, such as research grants and conference support, should be strictly excluded. In Table 19, an overview of the types of criteria that should be avoided is shown. In Belgium, it was mentioned by stakeholders that the possibility to provide free goods via medical need programs might also disadvantage biosimilars, as these cannot be applied for if already been granted for the reference product.

Fourth, suppliers expressed difficulty in terms of determining award criteria that would allow to truly differentiate and compete on. It was mentioned that the applied award criteria beyond price often can be relatively easily fulfilled by all suppliers. In such case, including additional criteria increases the effort and cost for the supplier, without playing a differentiating role in the allotment. Interviewees also mentioned that most criteria only temporarily offer a certain differentiation. With the increasing experience with biosimilars, the need for services in terms of educational switch support may for example wane. Moreover, competitors will prepare to meet differentiating additional award criteria in the subsequent tender rounds. Due to the comparable nature of

reference biologicals and biosimilars, it may prove challenging to develop criteria on a product level that could offer differentiation over a longer term. Purchasers also alluded to the fact that the inclusion of additional award criteria should serve to drive actual added value rather than complicating interchangeability of products. To allow for appropriate evaluation of possible differentiating elements such as injection pain of the product, appropriate supporting data are needed.

From both the supplier and purchaser perspective, there is a strong request for a *framework* with general principles regarding the structuring and application of award criteria. In order to stimulate the inclusion of criteria besides price and ensure a correct application, guidance should be drafted to support involved stakeholders, especially purchasers with formulating their tenders. The EU Public Procurement Directive has set out a frame in which Member States and purchasers can operate. Further action may be needed to ensure proper translation and application of MEAT in practice on Member State and purchaser level. Relevant experts should be integrated to identify appropriate award criteria. In countries where procurement is organized on a local or individual hospital level, it may be useful for governments to provide such guidance to purchasers. Here, a flexible or semi-structured tender template could be designed to guide purchasers. Room for flexibility should be foreseen, to allow tailoring based on product-specific considerations and strategic differentiation. Such an award criteria template could be piloted with collaboration from tender authorities and governments.

Only additional criteria that drive *meaningful product differentiation*, leading to an advantage for the organization of care and/or the patient should be included. Criteria could include considerations related to various elements such as supply, packaging, product presentation, storage, reconstitution and easiness of use, licensing and product-related services. To give an example, several purchasers deemed data from stability studies a possible important differentiator for products that require reconstitution. An overview of criteria that can be taken into account is shown in Table 19. Award criteria besides price should also be *proportionally rewarded* based on the additional value created. This should enable criteria besides price to truly play a role in the allotment. Suppliers mentioned that actions are needed to include these additional criteria in the tender, otherwise potential differentiation strategies could be done in vain from the supplier perspective.

TABLE 19. A SELECTION OF CRITERIA TO CONSIDER AND AVOID IN TENDER PROCEDURES

A selection of possible criteria to consider beyond price
<p>1. Quality and technical related criteria</p> <ul style="list-style-type: none"> ▪ Presentation: vial size, available concentrations/dosages strengths, vial protection, etc. ▪ Packaging: labelling, storage volume, etc. ▪ Storage conditions: shelf life, stability pre-post-reconstitution, stability in/out of refrigeration, etc. ▪ Reconstitution and product administration: reconstitution time, efficient use/handling, e.g., ready to use formulation, pre-filled syringe, etc. ▪ Indications: authorization and reimbursement status
<p>2. Service-related criteria</p>

- Supply: (number of) manufacturing, packing and storage location(s), logistics arrangements, urgent delivery modalities, customer support, policy on returns/expired products, policy on strategic stocks
- Value added services related to the subject matter: home delivery, nurse service at home, therapeutic drug monitoring support, training and educational support for HCPs, etc.
- Environmental and sustainability criteria: sustainability/environmental company policy (production, transport), sustainability/environmental policy of subcontractors, packaging material

3. Patient-related criteria

- Product administration: (easiness of use of) device, injection pain (needle size, buffer, volume, etc.)
- Patient-driven services related to the subject matter: patient support program (online disease education, device training, adherence program, etc.), patient information material

A selection of less desirable criteria to consider

Only criteria that drive actual benefits (meaningful product differentiation, advantage for purchaser and/or patient) and are related to the subject matter should be included. The below criteria may be considered to impact the level playing field between products, to be misaligned with the biosimilarity principle and/or to be of limited value.

1. Criteria that require the product **to be already on the market for a certain period of time**, as these would naturally advantage products with longer market presence, i.e., the originator product, and disadvantage recently launched biosimilars
 - E.g., requiring product sales references of the previous 3 years
2. **Broad application of benefits or extra services that are not directly related to the subject matter**
E.g., financial resources/grants for research or financial support to attend conferences or trainings
3. Award criteria related to the **efficacy, safety or quality profile of the biosimilar product**
 - EMA evaluates the biosimilar candidate, once licensed there is no need to reassess the work of the regulator. Criteria should be formulated based on a full understanding of the biosimilarity principle (e.g., rewards on the extensiveness of the clinical development, although these might be convincing for clinicians, are less desirable).
4. Request for **clinical switch data** or financial support to conduct a **switch study**
 - This would generate an additional evidence generation hurdle beyond biosimilar licensing requirements
 - The national competent authority provides guidance in this regard
5. **Contract linkage via conditional discount offerings** or other price structuring beyond product price could limit competition
 - E.g., between linkage between SC and IV products, where only the IV segment is open to biosimilar competition

EMA: European Medicines Agency, HCPs: healthcare professionals, IV: intravenous, SC: subcutaneous. Consulted reference materials, besides interview transcripts: tender contracts, (372), (373)

Finally, award criteria need to be *transparently formulated*, and it must be clear to participants how these will be evaluated, i.e. which weight will be given to the criteria in the decision-making, and how will they be scored.

Arguments were made that a shift to the inclusion of additional decision-making criteria may gain more attention in future tenders. As first tenders focussed on steep discounts, further discounting

opportunities are finite. Including other award criteria may increasingly help differentiate between products.

4.2.1.3 TENDER FREQUENCY AND (RE-) OPENING OF CONTRACTS – ENSURING TIMELY COMPETITION

The time between the first possible use of a biosimilar after loss of exclusivity of the corresponding originator product and its actual use should be minimized. In addition to streamlining pricing and reimbursement procedures, a *timely opening* of tender procedures is essential to avoid delays in competition and ensure swift market opportunity for biosimilar alternatives. In addition to ensuring commercial opportunity, a timely opening of tenders should be stimulated to generate savings for healthcare systems as soon as possible.

Several interviewees mentioned that in some cases tenders are opened with a *significant and unnecessary delay*. Contracts with the supplier of the reference product that still apply at the time of biosimilar market entry could possibly explain a delayed tender opening. It was hypothesized that in some cases these contracts were strategically agreed prior to biosimilar market entry to as such extend the originator's market exclusivity artificially. Another possible explanation, which was also mentioned by purchasers, links to the fact that an overview of upcoming loss of exclusivities of reference products and biosimilar market entry dates on governmental and/or purchasing level lacks.

To ensure timely competition, healthcare systems and purchasers should *anticipate and prepare* for biosimilar market entry well in advance. Horizon scanning should be performed to identify the upcoming loss of exclusivity of reference products and anticipated biosimilar market entry dates. In addition to early preparation for the opening of tenders upon loss of exclusivity of the reference product, purchasers should coordinate contracts with the originator prior to its loss of exclusivity, taking the future entry of biosimilars into account. The length of the contract with the originator prior to biosimilar market entry should thus be set accordingly and preferably/compulsory include a clause that allows reopening if a biosimilar alternative enters the market, to avoid such blocking contracts at the time of biosimilar market entry.

In essence, competition should be realized as soon as possible, providing commercial opportunity, onset savings and possibly additional benefits. Below, different *approaches* are suggested that could be suitable to translate the timely opening of tenders into practice. First, healthcare systems and purchasers could set a certain term in which for existing public contracts a new tender procedure would need to be organised. This term could be included in legislation and made mandatory, such as is the case in Italy (374). Here, regional authorities are obliged to re-open supply agreements within 60 days after entrance of the biosimilar medicine to the market (374). A few interviewees mentioned that it should be made (more) clear if reopening is expected with every new entrant. Opening a tender upon market entry of the first biosimilar(s) could challenge market opportunity for subsequent biosimilar entrants for the same product. On the other hand, launching a new tender upon market entry of each subsequent biosimilar should be avoided as a reopening would increase workload, possibly involve repeated switching and increase uncertainty related to the product

volume. The latter may prove especially challenging for suppliers. Installing a shorter-term tender (e.g. 6 months) immediately upon market entry of the first biosimilar competitor(s), combined with a longer subsequent tender duration agreement (12-24 months) once the market has further matured in the number of competitors, could be an appropriate alternative when multiple biosimilars are expected to arrive to market in a staggered way. The combination of an on-set short term tender with a subsequent longer one, would allow direct competition, leading to immediate savings for the payer and commercial opportunity for the first biosimilar supplier(s), while avoiding a closed market for subsequent suppliers for a considerable length of time. Once the market has further crystalized in terms of number of available products (e.g. in 6 months or a year depending on estimated market entry dates), tenders for existing public contracts could be reopened. Such a combined approach is for example applied by the central purchasing body Amgros in Denmark.

The appropriate approach in terms of tender timing and frequency could be determined based on the *market-specific circumstances of the product*, such as the expected number of competitors and their anticipated dates of market entry. Tenders that are organized on a quarterly basis might create a high administrative burden for both purchasers and suppliers in addition to being undesirable from the switch perspective. On the other hand, tenders with a duration beyond two years may restrict competition from other suppliers over the longer term. Generally, a tender duration between 12 and 24 months is considered desirable in terms of stimulating market dynamics, while considering feasibility and avoiding a regular switch of patients by interviewees.

In countries where tendering is organized on a regional, purchasing group or hospital level, tender procedures could open up at varying times throughout the year, to spread commercial opportunity for suppliers and accommodate manufacturing capacity. Such a *rolling system* is in place in England, with the Tranche frameworks opening every six months in another one of the four regions (375). A *specialist procurement office* can play an important role in organizing and coordinating the timing and duration of tender procedures for products with biosimilar competition.

A *financial stimulus* (positive or negative) could also be considered to motivate purchasing bodies/hospitals to timely organize tenders, aligning the incentives of the purchaser with these of the overall healthcare system (savings for healthcare budgets, and/or premium payers/patients). For example, in Belgium the reimbursement agency lowered the reimbursement for biologicals for which a biosimilar alternative exists with 15% to hospitals (144),(376). As margins on the negotiated price difference between the tendered price and reimbursement limit can be retained by hospitals, hospitals are motivated to organize competitive tenders to procure medicines at low net prices (377). A similar construct exists in the Netherlands, where health insurers reimburse hospitals the list price of biologics with biosimilar competition only in part, anticipating savings based on discounts that hospitals negotiate in tender procedures (378).

4.2.1.4 SUPPLY CONDITIONS - INCREASING VOLUME AND PREDICTABILITY TO ENSURE CONTINUITY OF SUPPLY

Tender procedures need to be *efficiently managed*, to increase predictability and plannability for the supplier, which can in turn guarantee timely product supply for the purchaser. Special attention needs to be paid to the setting of product volume, lead time and supply agreements.

First, *increasing predictability* regarding the tendered volume is of benefit for both the purchaser and the supplier. It provides suppliers the ability to accurately assess the economies of scale in their bid, increase the ability of suppliers to participate in tender bidding, and manage production. The latter may help to avoid undue pressures on the supply chain. This includes *setting of reliable estimates of the volume* to be supplied, with guaranteeing a minimum volume and defining a maximum cap. Moreover, in the context of multi-winner tender structures, a clear and guaranteed (division of) volume was considered a prerequisite to allow participating bidders to plan accordingly. In addition, *clinical use guidelines* should be reviewed and revised, if needed in this context, following introduction of biosimilars to allow purchasers to correctly estimate (potentially increased) volumes for tenders. Covering an unexpected increase in demand may be difficult, as it is complex and lengthy to increase the production scale due to the complex manufacturing process of biologicals. In case no minimum volumes would be guaranteed, tenders could lead to a risk of unused stock and issues with scaling (379). Suppliers with overstock may go for highly competitive offers in pending or subsequent tender procedures, which may lead to unsustainable market dynamics.

Second, the time between the announcement of the winner(s) and the start of the contract (first delivery), also called *lead time*, is in some instances (deemed too) short, making the first supply deadline challenging. Lead times between minimum three to six months should be respected to support the supplier's supply chain management (taking into account that decisions regarding for example packaging cannot be easily re-allocated to other markets), as such reducing the risk of delayed deliveries and shortages. In general, *early communication* regarding the timing of tender procedures and expected volumes should be promoted.

Third, although fortunately no interviewees reported supply inabilities having occurred (yet) in the context of off-patent biologicals and biosimilars, the *hedging agreements for possible supply problems* are a point of consideration. By contract, suppliers are generally obliged to compensate the difference between the tendered price and the price at which the alternative product is offered by a competing supplier, often the list price, to remediate the supply issue. Although the burden of securing and financing an alternative product should naturally not be placed on the purchaser, the supply conditions should be set in such a way that they are manageable for suppliers to achieve, *i.e.* based on early and accurate communication regarding timing and volume of tender. Moreover, penalties should be proportionate to the contract value and the cause of the inability to supply (force majeure/external reasons for which could not be controlled), ensuring a fair balance of risk and reward for the supplier. For example, in France, penalties are based on list price and not net price, which might lead to an unbalanced risk and reward (379). Suppliers might decide not to

participate in tenders where penalties are disproportionate, leading to reduced competition. *Dialogue* between purchasers and industry should be stimulated to establish manageable supply conditions and balanced penalties.

In the case of a supply issue in a single winner tender market, other manufacturers might not be able to cover the sudden demand and remedy a potential shortage as their production may be reduced or discontinued (379). *Multi-winner tenders* might thus also be preferred in the context of mitigating the risk of possible medicine shortages, increasing the opportunity to source the product with another supplier. Purchasing strategies that result in steep and perhaps over the longer term unsustainable price reductions may also impact supply, as companies might economize on services such as the presence of strategic stocks. It was argued that focussing on price only may impact additional services and as such the quality of the supply chain.

A *joint tendering initiative* was set up between Norway, Iceland and Denmark in 2019 in response to the growing challenges with regard to supply security, especially for older medicines (380). Such contracts with large volumes are likely to be prioritized by pharmaceutical companies because of the potential large gain. Such evolution may however be less advantageous on a broader level as it further consolidates the market. Cross border procurement should be reserved to situations where purchasing and supply of products can alternatively not be ensured.

4.2.2 CONSIDERATIONS REGARDING THE ORGANIZATION OF TENDERS

4.2.2.1 CONSIDERATIONS REGARDING TRANSPARENCY ABOUT THE TENDER PROCEDURE AND PRICE

Transparency in tenders should be stimulated *throughout the procedure*. Prior to the start of the procedure, at the time of publishing, the tender format, including the eligibility and award criteria and the relative weight that is awarded to these, should be clearly communicated. Upon awarding the contract, feedback should be foreseen to the participating supplier regarding the allocation decision and their scoring. Moreover, the obligation to publish the contract award notice for contracts for which prior announcement is not needed, e.g. for exclusivity contracts (negotiated procedure without prior call for competition) with the incumbent/patent holder prior to biosimilar market entry, should be complied to increase transparency towards the biosimilar entrants. Managed entry agreements (MEAs) ask for specific attention in this regard. The confidential and opaque nature of MEAs, with also the concealment of the patent expiration date of the reference biological, hampers the market entry of biosimilar alternatives. Confidentiality provisions should be addressed to improve the design and transparency of such agreements (381).

A few interviewees argued that a *Best and Final Offer (BAFO) procedure*, which involves a negotiation or clarification on a first written offer, after which bidders are invited to submit a final offer, or any route that would provide a certain supplier to submit a second (informal) bid to surpass the offer of competitors, should be avoided. This practice may provide leeway for suppliers and purchasers to include offers or request elements that are outside the scope of the tender subject matter, as transparency lacks during the final offer made, and impact the equal opportunity setting.

The size of rebates in tender procedures is noted to vary considerably (depending on market maturity and tender volume), ranging between 10% and 90% of the list price (11). In terms of *price transparency*, actual contract prices are seldom publicly available, hampering the insight in the size of actual rebates (11). In Norway, where prices were made public from 1995 until 2017, prices from tender procedures are no longer made public (382). Industry might be willing to provide larger discounts when tender prices remain confidential and list prices un-impacted. *Providing confidential discounts in tenders* is likely to be preferred over pricing strategies that lower the medicine's list price. List prices are often included in external reference pricing systems, acting as benchmark in terms of list price regulation in other European countries. Confidential tender discounts avoid such leverage in price negotiations in other jurisdictions.

4.2.2.2 SWITCHING CONSIDERATIONS IN THE CONTEXT OF TENDERS - CLINICAL DATA, COST, PHYSICIAN FREEDOM AND GUIDANCE

Increasingly, guidance statements from EU Member States support that prescribers can safely switch patients from a reference biological to its biosimilar (98). Requesting *additional switching studies* could create an extra barrier for biosimilar developers and may advantage the incumbent, who does not need to gather such data, in tender procedures.

Similarly, determining and including *a switch fee per patient* in tender procedures would disadvantage the biosimilar competitor, as an additional price lowering of for example 5% would be needed to offset the switch fee. Most purchasers argue that the *cost of switching* is marginal compared to the savings that are generally generated in a tender and will as such not play a decisive role in tender decisions. Originator companies may have however some leverage in the broader procurement context, as the price of the originator product that may needed to be purchased to treat the rest population (patients that remain under treatment with the reference product) can be raised by the company in case they lose the tender contract. This could limit or offset the discount realized in the tender procedure, where the originator competes with its biosimilar (alternatives).

In addition to *guidance* regarding interchangeability and switching by authorities (98), purchasers and hospitals should receive *practical support* regarding the use of biosimilars and switching in clinical practice. Practical barriers associated with biosimilar use and uncertainty among stakeholders should be lowered. For example, in England, the NHS set-up different initiatives to educate stakeholders about biosimilars and provide guidance, with the aim of supporting safe, effective and consistent use of biologicals, including biosimilars (113),(383). In the Netherlands, some health insurers have applied a differential reimbursement, reimbursing hospitals at a premium for using biosimilars, as a benefit share between insurers and hospitals, with the aim of compensating hospitals for the time and cost investment associated with a switch (378).

4.2.2.3 COLLABORATION AND COMMUNICATION IN THE CONTEXT OF TENDERS

Collaboration among stakeholders could be stimulated to ensure the development of more sustainable tender practices. First, early involvement and agreement between the internal

stakeholders at the purchasing side (*i.e.* dialogue between purchasers, hospital pharmacists, physicians, nurses, etc.) regarding the modalities of the tender is believed to be essential. In hospitals, this is generally organized in a Drug and Therapeutics Committee. In countries with a centrally organized procurement such as Denmark and Norway, procurement bodies work together with specialist groups or expert committees. This approach is argued to result in good agreement of physicians to prescribe the tendered medicine.

Second, collaboration *among purchaser(s) (groups)* can increase negotiating strength and add to the consolidation of expertise, professionalism and capacity which is needed to conduct efficient and high-quality tenders. Third, *communication between industry and purchasers* should be stimulated. Increased dialogue could reduce supplier uncertainties and increase efficiency for the different stakeholders involved, establishing a balanced shared risk and reward between suppliers and purchasers. This could be pursued both on the supplier and purchaser level, in the context of specific procedures (preliminary market consultations, with the prerequisite that every supplier is treated equally and receives the same information) and by stimulating dialogue between umbrella industry and purchaser associations. Position statements on the organisation of tenders for off-patent biologicals and biosimilars have been published by these associations. [Table S8](#) in Supplementary Information provides an overview of the main viewpoints outlined in the position statements.

In terms of optimizing communication in the tender itself, multiple supplier interviewees mentioned that the information requested in a tender procedure should be streamlined. Only information that would be essential to the tender should be included. Continuing the digitalization of tender procedures will contribute towards increasing efficiency in this regard.

4.2.2.4 HEALTHCARE PROFESSIONAL INVOLVEMENT AND MOTIVATION

Involving physicians in the procurement process, avoiding top-down organized tenders, may help to increase physician adherence to the tender outcome. In Norway, the high adherence among physicians to prescribe the recommended medicine may be explained by the voluntary nature of and the involvement of stakeholders throughout the tender process (384). Informing and educating healthcare professionals about biosimilar medicines and related concepts can also help to increase acceptance of the tender outcome.

In some countries, *benefit sharing models* - in which savings generated by tender procedures and or biosimilar use are shared between purchasing bodies or payers and the hospital - are applied to incentivize stakeholders. In England, such benefit sharing is in place between the Clinical Commissioning Groups and the trust providers. The example of the University Hospital Southampton NHS, in which a 3-year benefit sharing model was applied, reported significant cost savings and investment in clinical services (such as increasing the capacity of the nurse-led service) while maintaining similar patient-reported outcomes as result of their managed switch programme from infliximab reference product to biosimilar in inflammatory bowel patients (385).

Instead of providing a positive benefit share incentive, other approaches have been reported such as the above mentioned lowering of the reimbursement level for biological medicines for which a biosimilar alternative is available in Belgian hospitals (377).

Interviewees were in favour of organizing stakeholder incentives to increase motivation among stakeholders and support them in their work, but cautioned regarding implementing rewards or quota to drive biosimilar uptake in particular. Establishing quota and incentives for the *use of best-value biologicals*, which could be either the originator or one of its biosimilars, was generally deemed more appropriate in terms of establishing a level playing field.

4.2.3 CONSIDERATIONS REGARDING THE SUSTAINABILITY OF TENDER PROCEDURES AND THEIR IMPACT ON MARKET DYNAMICS

Several interviewees considered that current tender designs often focus on *maximizing short-term savings*, which they argued resulted in higher than originally anticipated price erosions. Several interviewees mentioned that the publicly reported discounts up to 70% in the Nordics established a certain precedent for subsequent price competition (366),(382),(386). Although tender procedures should aim to obtain the most advantageous offer, a race to the bottom should be avoided. The majority of participants indicated that the *sustainability of current practices* should be reconsidered to ensure benefits to society and patients over the longer term.

The steep price erosion was in part attributed to the fact that companies appear to be willing to fiercely *compete on price* due to important advantages associated with winning first product volumes (“first in the market”). This would allow the supplier to gather real-world data and accustom stakeholders with their product. Early winners may also be successful in retaining the market, as the incentive to reopen soon could be low if subsequent additional savings are low and would for example not outweigh the costs (although estimated to be minimal by interviewees) and work associated with a second switch.

Moreover, originator companies appear to apply *strong defensive tactics* to maintain market share by significant price dropping. This was recognized to limit biosimilar market entry in several markets. Originator suppliers may have more leeway for pronounced discounts compared to their biosimilar counterparts due to the different stage in recuperation of development cost in the lifecycle of the product. Where biosimilar developers need to earn back biosimilar development investments upon market entry, investments are generally recouped at this stage for the originator product. Additionally, it was hypothesized that some companies lower prices to such an extent that other suppliers start to drop out. This was believed to have been the case with tender practices for adalimumab, where the originator company offered especially steep discounts in some markets. In cases where the originator swiftly dropped originator prices, originators have mostly been able to maintain a significant portion of the market.

A balance between realizing short-term savings *versus* avoiding possible unintended consequences in terms of decreased competition over the mid-long term should be considered. Some markets

could be more at risk than others for reduced competition, depending on the commercial opportunity in terms of volume and expected prices in the given market. Multiple suppliers believed that action is essential to prevent this evolution and cautioned that hesitations exist among developers regarding the continuation of their biosimilar programs. As counterargument, it was reasoned that not all suppliers need to remain on the market for some products, as three to four suppliers would suffice for a sustainable market environment.

In markets with high price pressure, suppliers may economize by for example reducing their emergency stock available, which adds vulnerability to the product supply chain. A race to the bottom in terms of price should be avoided. Several interviewees argued that the shortage sensitive dynamics in the off-patent small molecule market should be avoided for off-patent biologicals and biosimilars.

The development of a longer-term vision is argued to be needed, to avoid competition loss and to ensure sustainable dynamics and benefits for the healthcare system over the longer term. It was mentioned that there is a need to act now, to ensure healthcare systems and tender practices are prepared for the anticipated next wave of biosimilars reaching European markets. Collaboration between the public sector and manufacturers (umbrella organizations) is believed needed to establish such common ground and exchange of perspective. Willingness appears to exist from different parties to work towards a more sustainable framework. As several manufacturers invest in both originator and biosimilars products, consideration for sustainable tender approaches may be increasingly supported.

4.2.4 CONSIDERATIONS REGARDING COMPETITION DYNAMICS – ENSURING A LEVEL PLAYING FIELD

As noted earlier, some tender processes appear to advantage the reference product over its biosimilar (alternatives). Suppliers can attempt to steer the structuring of the tender in their favour. Competition-limiting elements (such as considering research financing) are also reported to be proactively requested by purchasers, which may be explained by loyalty to and (financial) ties with the incumbent. In addition to a possible deliberate steering of tender structures to favour a certain outcome/bidder, purchasers may in some cases introduce unintentional biases due to limited (procurement) expertise, questions around the structuring or hesitations regarding biosimilars.

Examples of dynamics that favour the originator product include the delayed opening of tenders due to ongoing contracts with the originator at the time of biosimilar market entry, the application of originator favouring award criteria or offering of conditional discounts. The latter could be for example linked to the length of the contract, the ranking of the product or the offering of services that are unrelated with the subject matter of the tender, such as research financing. In the Netherlands, 20-50% of contracts were reported to include such a conditional discount structure in 2018 by a sector enquiry of the anti-Tumour Necrosis Factor product market (387),(378). Clauses that stipulate that the discounts of the competitor will be matched or renegotiated, matching the lowest offer or guaranteeing lowest price, can impact biosimilar market entry and also distort price competition, as the originator is likely to match the offer. Adding a Best and Final Offer (BAFO)

round may lead to similar distortions. Contract linkage, in which offers or requests are made to provide rebates for previously delivered or contracted medicines or on a related product, in case the tender contract is won, is also reported to occur.

In case the level of price reductions offered would force biosimilar developers to compete with a price below cost of goods due to a dominant position of the originator, these can also be considered anti-competitive.

The existence of anti-competitive procurement practices warrants action. Awareness should be raised about the public procurement integrity rules, a culture of integrity should be promoted, and a better collection and analysis of data should be ensured to improve governance. Fostering the uptake of e-procurement and supporting procurers with the appropriate tools and exchange of best practice can contribute in this regard. The appropriate application of tenders should be monitored by the EU national Competition Authorities and the European Commission must support actions of EU countries in this regard (388).

4.2.5 FUTURE OUTLOOK OF INTERVIEWEES: POSSIBLE EVOLUTIONS IN TENDER ORGANIZATION

To contain costs, competition could be further opened up by *tendering beyond the international non-proprietary name (INN)* for biologicals, which is already applied in certain cases or settings, such as in some hospital groups in the Netherlands. Including products in a same therapeutic class, which may include in some cases branded medicines, will allow to further increase competition and could be considered as option to contain spending (389).

Tender procedures may also evolve from focussing exclusively on the product's price, to taking a more holistic approach, including the overall cost of treatment, which includes but is not limited to the medicine price. Procurement, which takes total cost of care delivery into account, also called *value-based procurement*, aims to focus on patient outcomes the product should have an impact on. Where traditional procurement may often focus on the technical specifications of the product, price and short-term benefits, value-based procurement focusses on getting a maximum patient outcome against total cost of care (390). For instance, the total cost of the in-hospital infusion of an intravenous medicine could be compared to the cost of the patient's self-administering of an oral medicine, or to the home-administration of a subcutaneous alternative.

Another possible foreseen development in tender practices includes *subscription-model tendering*, where for well-defined patient profiles, medicine packages focussing on the broader therapeutic needs of the patient could be tendered. Some countries and regions (US, Australia, UK) are testing such subscription-based procurement models, also called the Netflix-model (391),(392). In this type of procurement model, purchasers pay a pre-agreed flat amount to the supplier, irrespective of the volume of medicines used (391). Such approach could provide substantial benefits as it includes a capping of costs for the payer and 'de-risked' revenue for the supplier. It however also increases volume uncertainty for the supplier, which could result in supply chain management challenges (393).

5. DISCUSSION

Tender procedures warrant a careful organization, design, execution, and evaluation and if needed readjustment, to ensure that they are aligned with sustainable outcomes for patients, industry and society at large over the longer term. It is a delicate balancing act between ensuring the most efficient use of public financial resources and safeguarding sustainable competition over the longer term. In addition to optimizing the spending of public funds, public procurement and the effective use of tender criteria beyond price may also achieve other benefits for society, healthcare systems and patients (359).

In this mixed methods study, we sought to assess the experience with tendering procedures for off-patent biologicals and biosimilars in Europe and identify learnings from current practices. We did this by drawing from a quantitative web-survey targeted at European purchasers and qualitative expert-interviews with both purchasers and suppliers.

5.1 CHALLENGES IN THE ORGANIZATION OF TENDERS FOR OFF-PATENT BIOLOGICS AND BIOSIMILARS

During the qualitative analysis, three main challenges arose with the organization of tenders for off-patent biological medicines and biosimilars. First, current tender practices appear to focus on realizing short-term savings. This may be explained in part by the design of the tender, which often considers only price and rewards to one single winner. Moreover, changing originator competition strategies may play a part. Whereas originator manufacturers originally appeared to protect market shares via the development of second generation or reformulated products (e.g. Humira[®]'s new formulation launch aimed for less injection pain, or the subcutaneous versions of Herceptin[®] and MabThera[®]), strategies have shifted and include increased competition on price (117). From the payer's perspective, one could argue that cost savings are realized in such a scenario, regardless of any biosimilar uptake. Considering biosimilar market entry as leverage to encourage a price cut from the incumbent (via a mandated list price decrease or discounts in tender procedures) may be a successful strategy in the short-term in terms of realizing savings. However, over the mid-long term, this is likely to lead to opposite effects due to market impoverishment.

The second main identified challenge pertains to the fact that tender processes were in some cases argued to advantage the reference product over its biosimilar (alternatives). This could be both deliberately or unintentionally driven, possibly because of stakeholder preference to continue with the reference product due to brand loyalty and/or additional benefits, and/or issues with the design of the tender due to limited expertise with procurement of off-patent biologicals and biosimilars. While including additional award criteria provides the opportunity to compete more sustainably on value-adding elements besides price, it also gives room for possible steering.

Third, including award criteria beyond price appears to be challenging in practice. Purchasers expressed difficulties to find the right balance between award criteria which allow to differentiate and which are non-discriminatory. From both the survey and expert-interviews, guidance appears

to be needed on how to design tenders for off-patent biologicals and biosimilars and especially how to formulate appropriate award criteria. Only when truly differentiating and value-adding criteria are identified, included, objectively assessed and proportionally rewarded in the tender, the concept of MEAT can be successfully implemented and play a role in the allotment.

5.2 FIVE MAIN AVENUES FOR OPTIMIZATION

Based on the stakeholder insights from this study, we conclude with proposals on five identified main avenues for optimization of public procurement processes for off-patent biologicals and biosimilars (Figure 22): (i) safeguarding a transparent, equal opportunity setting for all suppliers; (ii) fostering a timely opening of tender procedures, ensuring on-set competition; (iii) ensuring and stimulating adherence to laws on public procurement; (iv) securing an efficient process, improving plannability and ensuring timely product supply and (v) safeguarding long-term sustainable competition by stimulating market plurality.

FIGURE 22. OFF-PATENT BIOLOGICALS AND BIOSIMILARS TENDERING: FIVE MAIN AVENUES FOR OPTIMIZATION

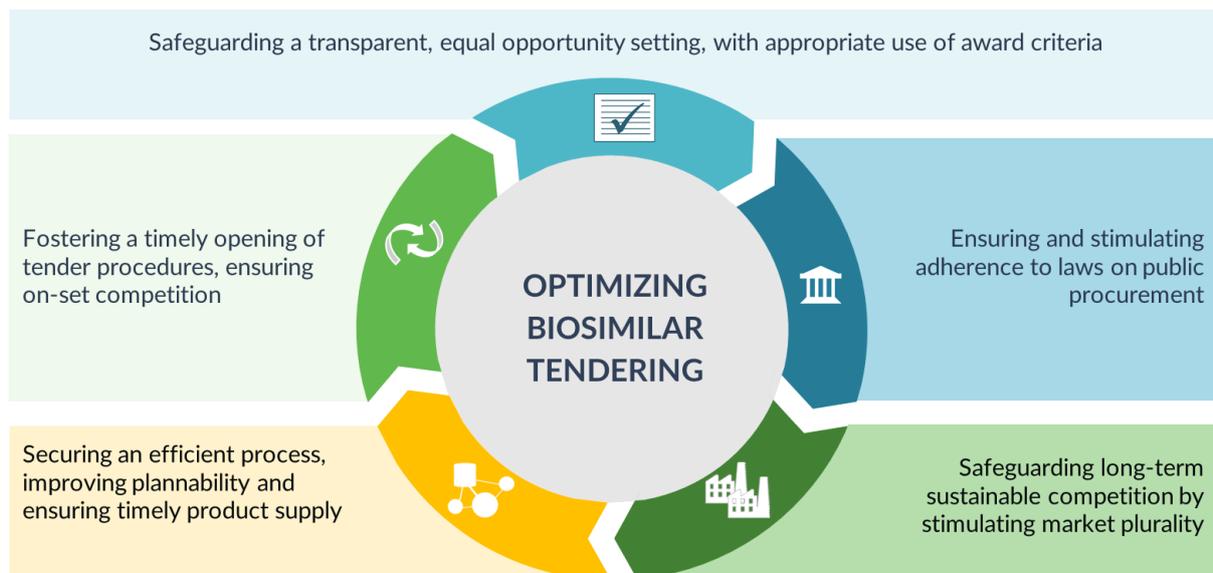


TABLE 20. PROPOSALS ON HOW TO OPTIMIZE TENDER PROCEDURES FOR OFF-PATENT BIOLOGICALS AND BIOSIMILARS

Ensuring sustainable competition and associated savings in the long-term in the off-patent biologicals segment - five main avenues for optimization

Tender practices should abide with the European Union and Member State rules on tendering. The involved actors, suppliers, purchaser bodies, payers, government and competition authorities, have a role to fulfil to ensure efficient, fair and transparent tender procedures for off-patent biologicals and biosimilars.

- Purchasers (hospital or procurement body): securing a transparent and efficiently managed process
- Industry/suppliers: ensuring timely, non-disrupted and high-quality supply
- Payers: establishing adequate incentives and resolving any counterproductive motivational schemes
Government: enabling sustainable market competition, by implementing policies and tender structures with a long-term perspective. Stimulating market plurality and providing guidance to purchasers
- Competition Authority: monitoring the correct application of tenders, by performing audits and following up purchaser adherence with laws on public procurement

The proposals outlined below can be considered as a general set of principles that can inform the different actors involved on possible improvements. Depending on the tender organization and maturity of the respective country or setting, measures should be selected and tailored to the country's context. Some of the proposed recommendations are based on existing best practices. Several countries, regions or hospitals have implemented already one or multiple of the proposed practices as outlined here.

1. Safeguarding a transparent, equal opportunity setting for all suppliers, with an appropriate use of award criteria

The tender procedure needs to be **transparent and non-discriminatory** with **predefined rules and pathway**, which are **adhered to** throughout the process

- Contracts should be awarded on the basis of **objective criteria that are compliant with the principles of transparency, non-discrimination and equal treatment** (as stipulated in the EU Directive (§ 90)) (357), allowing an objective comparative assessment.
- **Other award criteria besides price** that add value to the contract should be included, **applying the Most Economically Advantageous Tender (MEAT)** procedure as stimulated in the EU Public Procurement Directive (357), avoiding lowest bid procedures and stimulating suppliers to compete sustainably on more criteria.
- **A clear framework regarding selection—and award criteria** should be implemented and adhered to:
 - Selection and award criteria should be carefully formulated, to avoid that participants are excluded a priori or certain products are disadvantaged on improper grounds. **Criteria for which longer market presence is required or would be advantageous should be avoided**, as these could lead to unreasonable competition expulsion, disadvantaging recently launched products.
 - Only criteria that are **related and proportionate** to the subject matter should be included. Any criteria that could unreasonably limit competition or introduce bias should be excluded. The link with the subject matter should be clear. Caution should be exerted regarding requesting or offering additional services or benefits, and this should be strictly avoided if not directly related to the subject matter.

- Only additional criteria that **drive actual benefits** (meaningful product differentiation, advantage for purchaser and/or patient) should be included.
- Award criteria besides price should be **proportionally rewarded** based on the additional value created, as the provision of additional services increases investment for suppliers. This will also enable these criteria to truly play a role in the allotment.
- **Relevant experts** should be integrated to identify appropriate award criteria. In countries where procurement is organized on a local or individual hospital level, **governments** should provide **guidance** to purchasers regarding the structuring of the tender and application of selection and award criteria. Here, a **flexible/semi-structured tender template** could be designed to guide purchasers but also allowing room for tailoring based on product-specific considerations and strategic differentiation.
- Contracting authorities should **timely and transparently inform** possible competitors about the criteria that will be applied in the contract, by **specifying the award criteria** as well as **the relative weight or the allocation of points** given to each of those criteria in advance.
- **Linkage between contracts** (e.g., offer of or request to supplier to provide rebates for previously delivered or contracted medicines or rebates on a related product, in case the tender contract is won) can impact the equal opportunity setting and limit competition. Offering extensive conditional rebates with dominant position of the originator can be considered as anti-competitive exclusion.
- Avenues that provide **anonymity throughout the procedure**, such as requesting that bids are filed anonymously with coding identifier, should be applied where possible to avoid incumbent advantages (394).
- In the case of **preliminary market consultations**, these should guarantee that every supplier is **treated equally** and receives the **same information**. Although dialogue between purchasers and suppliers should generally be fostered to improve understanding of each other's needs on an overarching level, no direct input should be sought on the structuring of the tender from a supplier, as this could introduce steering of the structure of the tender.

2. Fostering a timely opening of tender procedures, ensuring on-set competition

Tender procedures should be opened as soon as possible, to avoid delays in competition and market opportunity for biosimilar competitors:

- Tender procedures should be prepared to **timely open**:
 - Systems should be **prepared** to organize tenders upon biosimilar market entry to reduce barriers to entry. A continuous re-opening of procedures with every new competitor entering the market should however be avoided, as this could introduce uncertainty in terms of volume and tender duration for the first tender winner(s) (lowering volume predictability) and also be burdensome for contracting authorities and industry.
 - Installing a shorter-term tender (e.g., 6 months) immediately upon market entry of the first biosimilar competitor(s), combined with a longer subsequent tender agreement, would allow immediate competition and market opportunity for the different competitors once the market has further crystalized in terms of number of available products.
 - Alternatively, a differentiated, product-specific approach in determining the appropriate term for opening a tender, taking into account the number of expected competitors, could be appropriate.
- **A specialist procurement office** involving the appropriate expertise fields could play an important role in organizing and coordinating the timing and duration of tender procedures for products with biosimilar competition. Moreover, such expert coordination office, should apply a long-term view, taking future biosimilar market entry into account to advice on

negotiated contract duration, avoiding **blocking contracts** at the time of biosimilar market entry. Such an expert procurement office should perform **horizon scanning** to identify the upcoming loss of exclusivity of reference products and anticipated biosimilar market entry dates. (cfr. infra, bullet D). Such expert procurement office or payers could also strategically set out incentive schemes to stimulate a timely opening of procedures, as needed.

- A **financial stimulus** should be put in place to stimulate purchasing bodies/hospitals to organize tenders, aligning the incentives of the purchaser with these of the overall healthcare system (savings for healthcare budgets).
- A tender **duration between 12 and maximum 24 months** would be desirable to stimulate market dynamics, while considering feasibility and avoiding frequent switching.

3. Ensuring and stimulating adherence to laws on public procurement

The rules on public procurement should be correctly applied:

- **Competition authorities should monitor and audit** the correct, timely and transparent implementation of and adherence to the laws on public procurement by purchasers and **investigate signals of anti-competitive conduct** (e.g., conditional rebates). If needed, they should take **appropriate measures**, ensuring a timely opening of tenders and the application of appropriate award criteria.
 - Governments should provide **feedback** to purchasing bodies on **performance** and apply **steering measures** where needed.
 - For decentralized purchasing systems, the route of establishing a dedicated, independent and centrally coordinated expert panel (involving lawyers, physicians, pharmacists), to conduct the assessment, could be explored. The transferring of assessment to an independent central organ could improve objectivity of and ensure the appropriate expertise in the evaluation.
 - Stakeholders should be stimulated to **actively report** any signals of anti-competitive conduct to the competition authority.
 - **Financing streams/structures** of purchaser bodies and involved stakeholders should be **reviewed, removing existing disincentives and introducing new incentives** that are aligned with the overall healthcare system
 - **Disincentives** to organize competitive tenders or **incentives that favour a specific product/preference for the originator/more expensive product** should be removed.
 - **Financial incentives schemes or other policies** should be put in place:
 - **Top-down:** such as **lowering the reimbursement level** of products that are open to competition to stimulate purchasers to timely organize competitive tender procedures.
 - **Stakeholder-involved:** Savings from tender procedures could be allocated in part to remunerate HCPs for their time investment in switching, as part of a gain-sharing model. Such a **gain-sharing model** could motivate and involve stakeholders, increasing adherence to the tendered winner(s) and countering possible financial incentives and preferences to use the originator product.
 - In addition to motivating stakeholders via above mentioned incentive schemes, **multi-winner tenders** or tenders with a ranking of preferred products can help to increase physician adherence to the tender outcome (avoiding physicians' use of the higher priced non-preferred product), as it may increase **physicians' freedom** to choose between available products. **Involving physicians in the tender procedures**, e.g., in the Drug & Therapeutic committee is also considered important in this regard.
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- Authorities and governments should also support stakeholders with **up-to-date guidelines for biosimilar use** (e.g., on (multiple) switching) and develop **policies and information campaigns to improve stakeholder confidence** in biosimilars and **increase awareness on their benefits**. This may help lowering practical barriers associated with biosimilar use and uncertainty among stakeholders.

4. Securing an efficient process, improving plannability and ensuring timely product supply

The tender procedure needs to be efficiently managed, optimizing and reducing the administrative and time burden for both suppliers and purchasers, as well as increasing predictability and plannability for the supplier—supporting timely product supply.

- The **predictability and plannability of tender procedures** and associated **volumes** to be supplied should be **improved** towards suppliers:
 - This includes setting of **reliable estimates of volume to be supplied** (with guaranteeing minimum volumes and a maximum cap), **timely communication regarding the timing** of tender procedures and making use of **acceptable lead times** to support suppliers to better forecast and anticipate on demand, as such reducing the risk of shortages.
 - In case of supply issues, **penalties** should be **proportionate** to the contract value and the cause of the inability to supply (force majeure/external reasons for which could not be controlled), ensuring a fair balance of risk and reward. In case of inability to supply volumes that are higher than estimated (e.g., not specified in procurement contract), the supplier should bear no (disproportionate) financial risk.
 - In some cases, a good strategy could be that tender procedures **open up throughout the year**, to spread commercial opportunity for suppliers and accommodate manufacturing capacity.
 - **Expertise on procurement** should be **consolidated** to actively **guide purchasers in timely and efficiently** setting up tender procedures
 - A **dedicated, expert procurement office** that consolidates knowledge, skill and experience with tender procedures should be available to **support purchasers/procurement bodies with the timely planning and efficient organization** of tender procedures.
 - Such a specialized procurement office should **set out strategy, coordinate** purchasers and tender procedures, **perform horizon scanning** to inform stakeholders on the upcoming loss of exclusivity of reference products and anticipated biosimilar market entry dates, **prepare stakeholder guidance** documents and monitor the number of competitors on the market.
 - Beyond coordinating the procurement strategy for products with anticipated biosimilar competition, the expert office should apply a long-term view and advice on contract length of new contracts, **considering future market entries, avoiding “blocking” contracts** at the time of biosimilar market entry, which would delay market competition.
 - **Specific measures** or a **tailored approach** could be applied to prepare for biosimilar market entry of a specific product (or product category) (as was done in several countries to prepare for adalimumab biosimilar market entry) or could be adjusted based on specific market dynamics.
 - Such an overarching expert office would also be beneficial in terms of **consolidating efforts, avoiding duplication and professionalising** the processes, as required by the increasingly complex structure of tender procedures.
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- Depending on the country, such expert centre could be established **at national or regional level**.
 - **Tender procedures and documentation requests should be harmonized, simplified and made leaner** to mitigate the administrative workload and increase efficiency, also reducing the possible sunk cost of participating suppliers. E-procurement should be wider used to allow information to be easily accessible throughout the tender procedure for both purchasers and suppliers. Beyond reducing the administrative burden, this will allow a higher traceability and transparency of procedures (367). The process should also be streamlined in terms of the **information** which is believed to be **essential**. **Operating on a larger scale** by grouping purchaser bodies and the existence of an expert procurement office guiding procedures could benefit purchasers and suppliers in this regard.

5. Safeguarding long-term sustainable competition by stimulating market plurality

The tender procedures and overall procurement strategy need to take a long-term view into account, tailored to supporting long-term sustainability, providing commercial opportunity for multiple suppliers

- **Stimulating market plurality and multiple commercial opportunities for suppliers**
 - Single-winner tenders can exclude non-winning competitors from the market for the duration for the tender contract, and long-term lead to reduced levels of competition. **Ensuring market plurality is a cornerstone for a sustainable and competitive tender market and should be part of tendering strategy**. Depending on market size and specific context (product volume), different scenarios can be appropriate and applied. **Multi-winner tender** can be organized on national level or regional level (if there is a **sufficiently large scale**), or markets could be divided into **multiple commercial single-winner opportunities** (e.g., on hospital network or regional level).
 - In the case of the scenario of multiple single or multi-winner opportunities across the market, a **rotating system** between regions or hospitals could be set up to increase dynamics and opening of commercial opportunities for suppliers over time.
 - Multi-winner tenders also provide price reductions on all tendered products and may increase the physician's **therapeutic freedom** to choose between different products, as such avoiding physicians using a higher-priced non-preferred product.
 - The availability of multiple commercial products on the market may also help to mitigate possible **supply issues**.
 - **Regular evaluation of the market situation and if needed revision of procurement and tendering mechanisms**
 - Market dynamics such as the numbers of competitors and associated manufacturers should be reviewed on an annual basis and tendering policies should be reviewed in this context, avoiding market concentration and de novo monopolies.
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Generally, stimulating market plurality, enabling market opportunity for multiple products, is considered to be the cornerstone towards creating a more sustainable and competitive tender market by stakeholders. This is in line with the findings of the KPMG cross-country analysis into the delivery of healthcare in hospitals by optimized utilization of medicines (379) and is supported by position statements of various industry umbrella organizations ([Table S8](#)). To realize the objective of sustained product plurality, several Member States and regions have been actively pursuing new

approaches from which best practices can be derived, such as the Commissioning Framework for biological medicines in England and the changes in the Italian legal framework related to biosimilars (395),(396),(374).

Overall, a combined action of all actors; suppliers, pharmaceutical industry associations, purchasers, payers, governments and competition authorities, is required to promote and strengthen the competition between off-patent biological medicines and biosimilars via tenders, and by extension establishing effective, healthy market dynamics. This requires a combination of practical and policy changes, involving alterations at purchaser level but also in the policy framework. Policymakers should set out a tender policy strategy, with appropriate organizational structures and stakeholder management to ensure adherence to public procurement rules. In addition to changes to the policy framework, any perverse incentives in the financing structure of purchaser bodies should be revised to ensure a level playing field. A combination of guidance (with initiatives such as horizon scanning, a tender template, award criteria framework and feedback systems), transparent reporting on the structuring and evaluation of tender procedures, and monitoring and feedback from governments or competition authorities will be necessary to sensitize stakeholders in this regard.

In general, monitoring the application of the tendering policy and subsequent changes in market dynamics is warranted, together with adapting its design if needed. National authorities should actively support purchasers with the appropriate application of tender procedures and introduction of award criteria, by providing the necessary guidance and feedback. Policy makers, purchasers and pharmaceutical industry associations should take action to collaboratively develop tender frameworks that include award criteria beyond price. For example, medical devices industry associations were successful in stimulating dialogue and collaborating with contracting authorities in order to develop a methodology to encourage the uptake of value-based procurement throughout the EU (397),(398).

Moreover, guidelines for biosimilar use to increase confidence and lower hurdles with the use of biosimilars (119) and an active promotion of best-value biological use by developing proper stakeholder incentivization schemes are warranted (396),(35),(115),(399).

As exemplified by both the survey and interview data, the design and execution of tenders for off-patent biologicals and biosimilars varies across European countries, regions and hospitals. As the tender landscape is variable across Europe, measures need to be adapted to country, region and setting specific needs. The results from the expert-interviews suggest that countries in which procurement is organized on a more local or hospital individual level, where there is more flexibility and individual purchaser freedom in the design and structuring of the tender, would especially benefit from increased guidance on tender and award criteria design. European regions, where tenders are organized with a central or regionally coordinated approach, such as for example England, were generally considered to have a well thought out procurement strategy and high level of tender expertise by interviewees. In addition to a consolidation of expertise, a more central or

coordinated organization of tenders aggregates purchasing needs, as such freeing up resources and time while increasing buying power.

The diverse approaches and outcomes with relation to the market entry of adalimumab biosimilars in the European countries included in the study illustrates again the diversity in healthcare systems and procurement practices across Europe. For example, NHS England and Amgros (the Danish procurement body) sought strategies to ensure rapid biosimilar adoption and generate immediate savings (400),(395). In Norway and the Netherlands, the originator manufacturer was able to retain market share by offering steep discounts (401). Although the biosimilar market entry of adalimumab biosimilars may have been a unique casus, as a multitude of competitors were lined up to enter simultaneously the market to compete with the number one blockbuster drug worldwide, lessons can be derived, such as the importance of well in advance preparing and planning for biosimilar market entry (395),(396).

5.3 STRENGTHS AND LIMITATIONS

The organisation of tenders for off-patent biologicals and biosimilars has been previously investigated in the context of a KPMG study on improving healthcare delivery in hospitals (379). Here, authors identify the following elements to foster biosimilar utilization in the hospital environment: swiftly reopening of tenders, organizing multi-winner tenders, implementing benefit sharing methods and switching towards MEAT criteria. These elements are considered relatively easy to implement with a potential high impact on the system (379). Also the law firm Baker McKenzie performed a multi-jurisdictional European study, identifying key legal and practical aspects of the biosimilars market, in particular with regard to public tendering (402). To the knowledge of the authors, this paper is the first scientific publication to assess in-depth stakeholder experiences with tender practices for off-patent biologicals and biosimilars and explore the sustainability of current practices.

The study presents both quantitative and qualitative data and is based on both purchaser and supplier experience. The qualitative survey data provide a snapshot of the heterogeneity of procurement practices and experiences of purchasers with the procurement of off-patent biologicals and biosimilars, across European countries. Participants from 23 different European countries, with varying levels of procurement organization (central, regional, local level) were queried. Overall, the quantitative data exemplify varying experiences across countries and provide a general overview of attitudes and challenges towards procurement of off-patent biologicals and biosimilars.

For the qualitative study part, interviews were conducted with experts in a selection of European countries that represent different tender structures, which enabled gathering information from various European contexts. In addition, interviews on a pan-European level were conducted to strengthen both country-specific and European-broad insights. Interviews were conducted with both purchaser- and supply (industry)-side participants, reflecting the insights of the two principal

stakeholder groups in the tender process. The choice of qualitative interviews permitted to gain detailed insight in current practices and gather proposals for improvement from experts in the field. Experts from a purposive sample of European countries were invited, to capture a broad range of insights from countries with varying practices. However, no interview insights were obtained from Eastern-European countries. It may be useful for future research to expand on in-depth country analyses, assess perspectives of policy makers on proposed measures and conduct a systematic analysis on tenders in the EU database on tenders.

The general set of principles and proposals as outlined in Table 20, based on pan-European and country specific expert insights, could be applied *mutatis mutandis* to specific countries and settings. It is important to note that not all findings are generalizable to the whole off-patent biologicals segment across Europe, as some are product, country, setting or time related. Depending on the tender organization and maturity of the respective country or setting, measures on different levels may be needed and these should be tailored to country context. Some of the proposed recommendations are based on existing best practices. Several countries, regions or hospitals implement at present one or multiple of the proposed practices as outlined in Table 20. Some learnings may not be limited to tender practices for originator biologicals and biosimilar and might apply to tender practices in general. The fact that discounts in tender procedures are generally confidential prevents to properly mirror the gathered qualitative insights on price competition with actual price data beyond list-price level. As estimated by IQVIA, confidential discounts range between 10 and 90% on list price and could offer a 5 to 10% saving to the overall drug budget (11).

5.4 BALANCING SHORT AND LONG TERM BENEFITS

It is clear from this study that it is a delicate balance between optimizing efficient spending of public funds, addressing patient needs and preserving competition over the longer term. When designed efficiently and conducted appropriately, tenders can stimulate competition and as such form a cornerstone for sustainable market dynamics. As ensuring the most efficient use of public resources and broad access to medicines is a common societal goal, actions to ensure that tender processes are effective and motivate suppliers to participate over the longer-term are essential. Starting in the next five years, the number of biological loss of exclusivities will increase substantially (11). Healthcare systems across Europe need to be prepared to facilitate and optimize market access for and competition from the next wave of biosimilar market entries, drawing from earlier experiences. This will allow healthcare systems to maximize the benefit of biological competition efficiently over the long term.

6. CONCLUSIONS

This study found that opportunity exists to improve tender practices for off-patent biologicals and biosimilars in Europe. In order to realise the competition potential of biosimilars and benefits from appropriate tender procedures for healthcare systems and patients, policymakers and purchasers, in dialogue with industry associations, need to take concerted actions with a long-term strategic view to optimize tender frameworks. Depending on the country's policy environment and the maturity of the procurement body, different sets of policy and practical measures are needed. In general, measures should aim to ensure supplier market plurality, establish a transparent and objective process, and include award criteria beyond price. This may contribute to creating a sustainable climate, with long-term competition in the off-patent biologicals market.

1. ABSTRACT

Objectives: With the growing availability of biosimilars on the European market, clinicians and pharmacists have multiple off-patent biological products to choose from. Besides the competitiveness of the product's price, other criteria should be considered when selecting a best-value biological. This article aims to provide a model to facilitate transparent best-value biological selection in the off-patent biological medicines segment.

Methods: The presented model was developed based on established Multi-Criteria Decision Analysis (MCDA) tools for rational and transparent medicine selection, i.e. the System of Objectified Judgement Analysis (SOJA) and InforMatrix. Criteria for the model were informed by earlier research, a literature search and evaluation by the authors.

Results: The developed model includes up-to-date guidance on the criteria that can be considered in the selection and provides background on the allocation of weights and the scoring that may aid hospital pharmacists and clinicians with decision-making in practice. Three main categories of criteria besides price were identified and included in the model: (1) product-driven criteria, (2) service-driven criteria and (3) patient-driven criteria. Product-driven criteria include technical product features and licensed therapeutic indications. Service-driven criteria consist of supply conditions, value-added services, and environment and sustainability criteria. Patient-driven criteria contain product administration elements such as ease of use and service elements such as patient support programs. The relative weighting of the criteria is largely context-dependent, and should in a given setting be determined at the beginning of the process, as well as how the criteria will be evaluated (i.e. the scoring system) to allow for a transparent selection.

Conclusions: The practical model may support hospital pharmacists and clinicians with transparent and evidence-based best-value biological selection in clinical practice. While the model may facilitate informed and transparent decision-making, the overview of criteria and the allocated weights need to be adapted to the local and product-specific context.

2. INTRODUCTION

Since the first biosimilar approval in Europe in 2006, more than 65 biosimilars across multiple therapeutic areas have been licensed and considerable experience has been gathered with biosimilar use in clinical practice (116). Despite the initial hesitance from some stakeholders to use them, which could largely be explained by a lack of understanding about biological medicines and misinformation in the debate (47),(119),(45), biosimilars are an integrated part of clinical care in many European countries today. The number of approved biosimilars is expected to grow substantially, with twice as many originator biologicals losing protection in the next ten years (11).

Healthcare providers should have a good knowledge and understanding of biosimilars, and the scientific principles underpinning their development and evaluation. Especially the (hospital) pharmacist, as a medicines expert, has an essential role in guiding biosimilar introduction in clinical care and informing clinicians and other healthcare providers about them. The remit and responsibility of hospital pharmacists may vary between countries and healthcare systems (403), but in general they take the lead in the clinical, economic and practical considerations related to pharmaceuticals and their introduction in the hospital therapeutic formulary (364). Effective and well-thought-out product selection is crucial to ensure the availability of safe, effective, high quality and cost-effective medicines (364). Hospital pharmacists have the expertise to integrate criteria in the product selection beyond the product's price (364), allowing selection based on the broader value of the product, in other words the selection of a best-value medicine.

The selection of a best-value biological, which can be either the originator biological or its biosimilar(s), which considers criteria beyond price in the decision-making, is a challenging and evolving topic. In response to the market entry of biosimilars, several articles have been published in the *European Journal of Hospital Pharmacists* over time with the aim to offer guidance on how to select a biosimilar in clinical practice (404),(405),(406). The biosimilar landscape has considerably progressed since the papers published in 2005, 2008 and 2013 (404),(405),(406), which asks for a reassessment and further development of guidance in this regard. First, insights in the evaluation of biosimilars and their use in practice consolidated, making the need for certain earlier proposed criteria obsolete. For example, earlier publications suggested to evaluate elements related to the biosimilar's efficacy and safety. However, the robust European regulatory framework related to the evaluation of biosimilars and the evidence acquired over 15 years of clinical experience with biosimilars clearly demonstrates that there is no need to reassess elements that are part of regulatory evaluation once licensed (6),(19). Second, selecting a best-value biological has evolved from making a choice between reference product and biosimilar, to a choice between the reference product and multiple biosimilars and/or between biosimilars, as for almost all reference products multiple biosimilars are available on the market today. Third, companies have increasingly made efforts to differentiate their products (both originator and biosimilars) on the basis of value-adding criteria within the margins of biosimilarity, instead of focussing exclusively on competition on price (117). Fourth and finally, a recent research study on biosimilar tender practices in the EU found that

purchasers, including hospital pharmacists, experience difficulties with identifying criteria besides price to select between available off-patent biologicals and biosimilars, and with their appropriate formulation (56). This demonstrates a clear need for guidance development on how to formulate selection criteria in the context of off-patent biologicals and biosimilars.

In this article, we provide an up-to-date model to aid hospital pharmacists and clinicians with best-value biological selection making in the off-patent context, including guidance on the criteria that can be considered and background on the allocation of weights and the scoring. Table 21 provides an overview of the study highlights.

TABLE 21. STUDY HIGHLIGHTS

What is already known about the topic?
<ul style="list-style-type: none"> ▪ With a growing number of biosimilar products coming available on the European market, hospital pharmacists have a wide range of off-patent biological products to choose from. Besides price, additional criteria may be considered when selecting a best-value biological (or multiple best-value biologicals). ▪ Taking the broader product value into account may lead, besides savings, to benefits for the patient, hospital and or the healthcare system. ▪ However, earlier research pointed out that hospital pharmacists experience difficulties with formulating and applying criteria besides price in the context of off-patent biologicals and biosimilars selection making, highlighting the need for guidance.
What does the study add to existing knowledge?
<ul style="list-style-type: none"> ▪ This article provides an up-to-date and transparent model, which attempts to guide hospital pharmacists regarding possible criteria to consider in the selection making of a best-value biological, or best-value biologicals, in clinical practice. ▪ Possible criteria to consider, besides price, when selecting a best-value biological can be categorized into three groups: product-driven, service-driven, and patient-driven criteria. The relevance and weighting of the proposed criteria should be adapted to the local and product specific context.

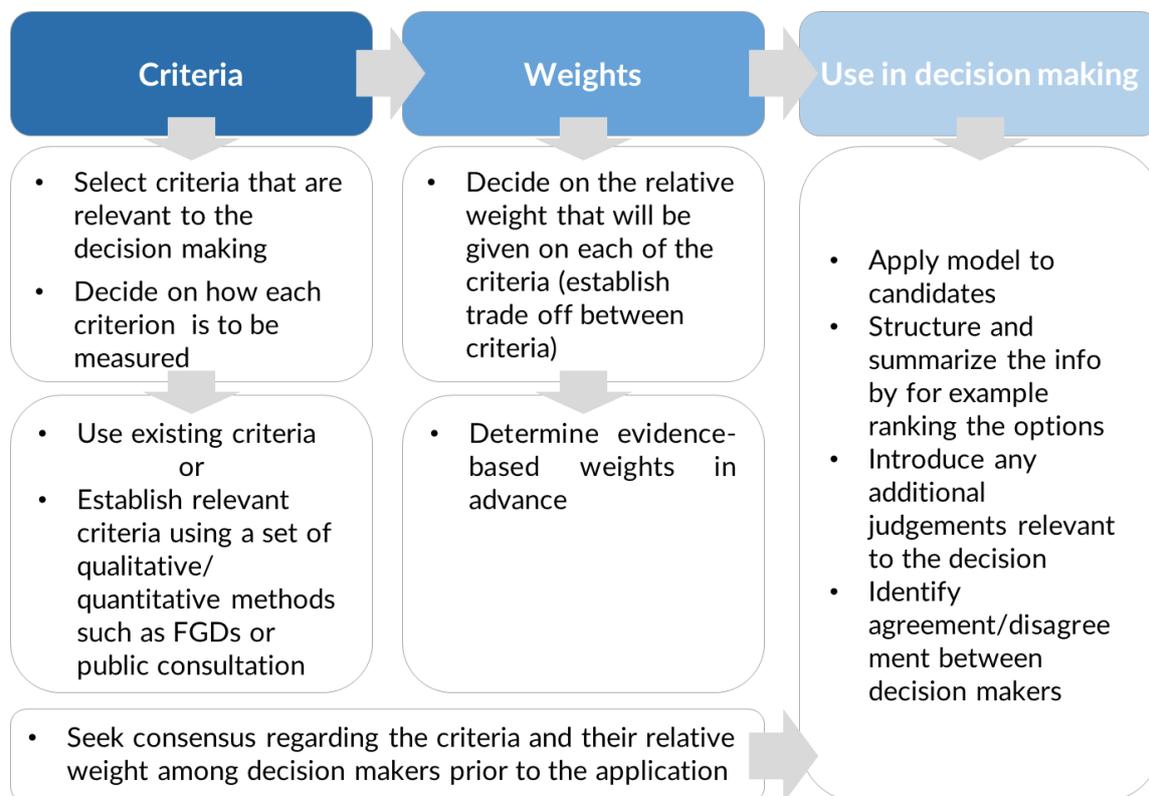
3. METHODS

This study presents a model for the selection of best-value biologicals in the off-patent context based on the System of Objectified Judgement Analysis (SOJA) and InforMatrix, two established assessment tools in rational and transparent drug-decision making (407),(408). SOJA and InforMatrix are examples of Multi-Criteria Decision Analysis (MCDA) tools. MCDA is defined as “a set of methods and approaches to aid decision-making, where decisions are based on more than one criterion, which makes explicit the impact on the decision of all the criteria applied and the relative importance attached to them” (409).

The decision-making model presented includes three consecutive steps: (i) identifying the criteria to apply in the decision-making, (ii) deciding on their relative weights and scoring system (iii) evaluating the possible candidates. Figure 23 depicts a schematic overview of the model.

FIGURE 23. SCHEMATIC OVERVIEW OF THE MCDA BASED DECISION-MAKING MODEL

Figure adapted from Devlin, N, Sussex J, *Incorporating multiple criteria in HTA. Methods and processes. Office of Health Economics. 2011(408). FGDs: Focus Group Discussions, MCDA: Multi-Criteria Decision Analysis*

**3.1 IDENTIFICATION AND ASSESSMENT OF SELECTION CRITERIA**

Selection criteria can be determined by making use of existing criteria or by establishing *de novo* relevant criteria. For the latter, qualitative and or quantitative methods, such as for example focus group discussions or a public consultation, have been applied in the past (409).

For the selection of off-patent biologicals, criteria are available from earlier research to build on (56),(404),(405),(406). To inform the model, hand searches of the published scientific (in PubMed, Embase) and grey literature were performed. Search terms were related to biosimilars, biologicals, procurement, tendering. No formal inclusion or exclusion criteria were established. Identified articles were reviewed qualitatively by the researchers. More specifically, the identified criteria were compiled, compared and evaluated based on the SOJA and InforMatrix model criteria and discussion among the authors. In particular, criteria were assessed for their compatibility with the biosimilarity principle and their relevance today. An overview of previous articles, drawing criteria from different methodologies, is provided in Table 22. The criteria were compiled, compared and evaluated based on the SOJA and InforMatrix model criteria and discussion among the authors. Specifically, criteria were assessed for their compatibility with the biosimilarity principle and relevance in the current context (*i.e.* vast clinical experience that has been gathered with biosimilars). During the selection, no elements that are part of regulatory assessment should be opened up to reassessment (56). As such, criteria that are adequately covered during the evaluation by the EMA (*e.g.* criteria related to

demonstration of comparable efficacy and safety of a biosimilar to its reference product) were omitted (406),(56).

Based on this, we present an up-to-date overview of possible criteria to consider when selecting (a) best-value biological(s). Furthermore, we provide the necessary context that may assist hospital pharmacists and clinicians when choosing criteria appropriate to the product and their decision-making context.

TABLE 22. EARLIER PUBLICATIONS THAT ADVANCED CRITERIA TO GUIDE SELECTION

Study	Year*	Info on criteria	Methodology
Crommelin, D et al. (404)	2005	Development of checklist to evaluate biosimilars	Preparation by an international working group, involving scientists, hospital pharmacists, representatives from a manufacturing company (based on an Advisory Board Meeting)
Kramer, I et al. (405)	2008	Development of checklist to guide originator and biosimilar evaluation	Further development of 2005 checklist by authors
Boone, N et al. (406)	2013	Development of shortlist of criteria to guide biosimilar selection	Identification of criteria by involved researchers, evaluation of criteria with SOJA and InforMatrix tools
Griffith, N et al. (410)	2014	Development of formulary selection criteria for biosimimars (US focus)	No information on methodology
Barbier, L et al. (56)	2021	Overview of possible criteria to consider and steer away from when selecting a best-value biological	Overview of criteria informed by quantitative (by means of a web-survey across EU countries) and qualitative insights (by means of semi-structured interviews with EU experts) from suppliers and purchasers

3.2 ASSIGNMENT OF WEIGHTS AND SCORING SYSTEM

In the second step of the decision-making model, relative weights are to be assigned to each of the criteria. Information is provided on what to consider when deciding on the weight allocation and the scoring system.

3.3 DECISION-MAKING

Evaluating the candidates is product and context dependent. Hence, the provided guidance should be translated and tailored to each specific situation.

4. CRITERIA TO SELECT A BEST-VALUE BIOLOGICAL

Criteria for selection should allow an objective comparative assessment of the multiple candidates. The criteria need to be transparently formulated, factually measurable, and differentiating without being discriminatory.

An overview of possible criteria that can be considered for best-value biological selection is given in Table 23. The criteria are classified into three main categories: product-driven, service-driven and patient-driven criteria. Each of these categories consists of two to three subcategories.

TABLE 23. OVERVIEW OF POSSIBLE CRITERIA TO CONSIDER, BESIDES PRICE

I. Product-driven criteria	
Technical product features	<ul style="list-style-type: none"> ▪ Available strengths ▪ Product administration form: available administration routes, efficient product use ... ▪ Storage conditions: stability, shelf life ... ▪ Reconstitution: handling needs, time ... ▪ Packaging: lookalike, box volume, ease of handling ...
Indications	<ul style="list-style-type: none"> ▪ Authorized indications ▪ Reimbursement of indications
Real-world product experience	<ul style="list-style-type: none"> ▪ Data to substantiate claims regarding patient experience, injection pain etc
II. Service-driven criteria	
Supply conditions	<ul style="list-style-type: none"> ▪ Location of manufacturing, packaging and storage sites ▪ Logistics arrangements ▪ Modalities for urgent deliveries ▪ Customer support ▪ Policy on returns/expired products ▪ Policy on strategic stocks
Value-added services	<ul style="list-style-type: none"> ▪ Therapeutic drug monitoring support ▪ Training and educational support for healthcare professionals
Environment & sustainability	<ul style="list-style-type: none"> ▪ Sustainability/environmental company policy (production, transport) ▪ Sustainability/environmental policy of subcontractors ▪ Packaging material
III. Patient-driven criteria	
Product user-friendliness	<ul style="list-style-type: none"> ▪ Ease of use of device ▪ Injection comfort
Patient support programs	<ul style="list-style-type: none"> ▪ Online disease education, device training, adherence program, patient informational material, nurse service at home ...

4.1 PRODUCT-DRIVEN CRITERIA

4.1.1 TECHNICAL PRODUCT FEATURES

Differentiation on product-related elements such as presentation (including available strengths and administration routes), reconstitution, storage conditions and packaging may provide products with a competitive advantage over their alternatives.

4.1.1.1 AVAILABLE STRENGTHS

The availability of multiple, and especially more, strengths compared to other candidates can have both economic and operational advantages. For example, several biosimilars of trastuzumab (Herzuma®, Kanjinti®, Trazimera®) offer the benefit of being available in both single-dose 150 mg and multi-dose 420 mg vials, where the reference product (intravenous) is only available in 150 mg vials (116),(411). The multi-dose vial may allow to better tailor to the dosage needs of the individual patient, resulting in a more efficient use of resources (less spillage) (412). The higher the number of strengths available, the higher the product could be scored on this criterion.

4.1.1.2 PRODUCT ADMINISTRATION

Product availability in multiple formulations can provide products with a competitive advantage as it offers multiple treatment options (for the patient and the healthcare provider) to choose between. For instance, trastuzumab and rituximab, both originally approved as intravenous (IV) formulations, have also been developed for subcutaneous (SC) administration. Launching such an alternative administration form around the time of protection expiry of the original formulation is a well-known originator defence strategy to retain market share and defend against biosimilar competition (11). Where exclusivity rights on the IV formulations expired, opening up the market to biosimilar competition, the SC route of administration is still under patent protection. The SC formulation is currently thus only available for the trastuzumab and rituximab reference products (Herceptin® and Mabthera® respectively) (413),(414) The SC route of administration may offer advantages compared to IV infusion, by reducing in-hospital treatment time and resources. Especially hospitals with less day care capacity may benefit from the more time efficient SC formulation. However, some licensed indications might differ between SC and IV products, such as rheumatoid arthritis that is not a licensed indication of SC rituximab (415),(416). In addition, the SC route of administration may be preferred by patients due to increased convenience. This leads to the question if these advantages outweigh the reduced price of the IV administration form for which biosimilar competition is available (413),(414). In order to adequately answer this question, product price and other cost elements (e.g. IV vial sharing, healthcare professional time, business model of the hospital) should be included in the trade-off (417).

Not only originator developers invest in the development of alternative administration routes. The 2019 EU-approved SC formulation of infliximab was developed for CT-P13 (Remsima®), an infliximab biosimilar that was first developed as IV administered product (418). Remsima® is currently the only infliximab product that is available in both the SC and IV formulation. The

reference product (Remicade®) and other biosimilar competitors (Inflectra®, Flixabi®, Zessly®) are present-day only available in IV formulation (418).

In conclusion, availability of multiple formulations may increase patient choice and allows tailoring of formulation choice to the set-up of the hospital (e.g. organized to cater to IV and/or SC administration).

Differences in infusion time (*i.e.* demonstration of the safety of a shorter infusion time compared to other candidates), if these would be present, could be considered when evaluating IV administered products. Self-injectable products that offer a temperature sensitive indicator on the injection device, showing if the product has been stored at the appropriate temperature, may guide patients with correct medication storage. Products that require a less frequent administration compared to their competitors may also receive a higher score.

For subcutaneously administered biologicals, the user friendliness of the injection device and the product's injection comfort should also be considered. These elements are discussed under Patient-driven Criteria.

4.1.1.3 RECONSTITUTION

For IV products, the product's reconstitution needs should also be considered. For instance, the availability of a ready-to-use formulation could reduce the medicine handling time for the healthcare provider compared to a product that requires in-hospital pharmacy preparation. The dissolution rate – relevant under everyday use conditions – could also be a point of consideration.

4.1.1.4 STORAGE CONDITIONS

Differences in storage conditions (*i.e.* in the freezer, fridge or at room temperature) could be scored on convenience. Cooled storage space is costly; therefore large volume packaging of biologicals needs to be avoided. Also, the product's shelf life could be a possible differentiator. Data on extended in-use stability could be advantageous, as it may permit safe in-advance preparation, allowing to optimize pharmacy and nurse workload management (419). In addition, data on stability under different storage conditions (e.g. storage in fridge *versus* at room temperature), could be informative in case temperature deviations would occur during product transport or storage (419). Additional research and documentation regarding product stability can thus be included as criterion.

4.1.1.5 PACKAGING

The product packaging and labelling should be clear and easy to read. In addition, the packaging should allow to sufficiently differentiate with products from other suppliers and between products from the same supplier (410). Barcoding on the product per-dose packaging will also aid to limit medication errors. The availability of products in per-dose packaging takes away the need for hospitals to repackage blisters to individual unit-doses, and may as such have a positive impact on associated pharmacy workload.

Product pack size (determining how frequently prescriptions need to be filled) should also be considered, as it may affect patient co-payment in reimbursement systems that are sensitive for this.

To fight medicine falsifications and ensure safe and controlled trade, documentation regarding adherence to the Falsified Medicines Directive, should be present. The presence of a unique identifier and anti-tampering device on the outer packaging of medicines is obligatory for all medicines, and is thus not expected to be a differentiating element between products (420).

4.1.2 THERAPEUTIC INDICATIONS: AUTHORIZATION AND REIMBURSEMENT STATUS

Biosimilars are generally approved for the same indications as the reference product. In some instances, a biosimilar may however have fewer licensed indications than the reference product, as companies may choose not to apply for all therapeutic indications of the reference product (6). Not all indications of the reference product may be eligible for the biosimilar to include in its label at the time of initial marketing authorization due to patent or regulatory exclusivity coverage. In addition, some licensed indications might differ between SC and IV products, such as rheumatoid arthritis that is not a licensed indication of SC rituximab.

Although this is not yet the case for the biosimilars that are currently available in Europe, biosimilars can also obtain additional licensed indications compared to the reference product. From a regulatory point of view, it is possible for a company to apply for an additional, new therapeutic indication beyond the indications included in the label of the reference product, for their biosimilar product upon initial marketing authorization. Seeking additional indications during the product's life cycle is thus a differentiating strategy that theoretically can be applied for both originators and biosimilars.

Also, the reimbursement status of the product and its reimbursed indications are important factors. In some countries there can be differences in reimbursed indications between biological products, while the licensed indications are the same. For example, if certain indications of the original product fall under a managed entry agreement (MEA) at the time of market access of the biosimilar, the biosimilar company might opt out for reimbursement for this particular indication. For example in Belgium, due to an ongoing MEA for adalimumab for the indication hidradenitis suppurativa, biosimilars were initially not reimbursed for this indication. Beyond the product acquisition cost, differences between products in out-of-pocket co-payment or coinsurance costs for the patient should be reviewed (410).

4.1.3 REAL-WORLD PRODUCT EXPERIENCE

As biosimilar development aims to demonstrate biosimilarity to the reference product and not independently establish the efficacy and safety of the proposed product, as this is already well known for the reference product, the requirements for clinical development are different from those for the reference product. The tailored clinical development package for a biosimilar generally consists of a phase I study, and depending on the complexity of the product, a confirmatory efficacy and safety trial in patients in one therapeutic indication of the reference product. In addition to

being a tailored package, the clinical study(ies) generally differ from those conducted for the reference product in terms of design. As the goal is to confirm comparable clinical outcomes between the biosimilar and reference product, the study must be designed (e.g. choice of patient population and endpoint) to be as sensitive as possible to identify any possible differences in clinical outcomes (413),(16). Pharmacists need to be well informed about the biosimilarity concept and how the clinical development is tailored to this. Some companies may endeavour to differentiate their product by investing in a more extensive clinical program (413). The clinical development package (its extensiveness, the patient setting study etc.) should however not be reassessed during best-value biological selection, as it is part of the product's regulatory evaluation (56).

As for any new approved medicine, utilisation and clinical experience data may be informative. However, the real-world utilisation of the reference product will logically outweigh that of recently approved biosimilar entrants. Biosimilars must demonstrate, based on an extensive head-to-head comparability with the reference product, that there are no clinically meaningful differences between the two. As such, biosimilar and reference products can be considered to have a similar offering, although the utilisation and experience may differ at the time of biosimilar market launch. In relation to switching, the relevant guidance from regulators must be considered. Several national medicines agencies in Europe have provided clear guidance regarding switching patients from the reference medicine to a biosimilar, indicating that no effect on efficacy or safety is to be expected (97),(99),(421). Similarly, the European Medicines Agency included in its guidance on biosimilar medicines to healthcare professionals that "*there is no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines*" (6).

4.2 SERVICE-DRIVEN CRITERIA

4.2.1 SUPPLY CONDITIONS

Supply criteria are related to the manufacturer of the pharmaceutical product. These requirements are related to manufacturing capacity, storage locations, modalities for urgent deliveries, customer support, policy for expired or products or returns, and policy about strategic stocks. The production (including manufacturing, packaging, and storage) capacity of the company must be sufficient to guarantee supply continuity (405),(406). Also, a history of possible stock-outs or back orders of the supplier may be informative regarding supply reliability. Strategic stocks are useful in order to guarantee continuous delivery in case of supply-chain issues or batch failures.

In the context of tender or procurement procedures, suppliers are often selected in advance on whether they meet to a certain set of requirements, including these related to supply. Indeed, as continuous and reliable supply are of utmost importance, criteria related to supply may be a prerequisite as minimum requirements that a supplier must meet, prior to applying product-specific criteria (406).

4.2.2 VALUE-ADDED SERVICES

Value-added services (VAS) have the intention to add value to the biological product, in terms of improving patient and health outcomes (55),(422). VAS are often directed at improving patient care and adherence in the hospital environment, or in support of the delivery of the medicine at home. They may exist in several forms or modalities, such as nurse services at home, therapeutic drug monitoring support, and training or education of health care professionals. In many European countries, such services that improve quality of care are not readily available and thus could be seen as an added value in the selection of the best-value biological product (55). Although, an important requirement is that these services actually contribute to the value of the product. In other words, they must achieve the goals for which they were developed.

However, the value for particular services will strongly depend on the needs and expertise within the hospital. Considering additional services is one way to include other elements beside price in product decisions, particularly in contexts where such services are not part of routine care. As a result, these proposed criteria cannot be applied to every context, but must leave room for local interpretation. It is the responsibility of hospital pharmacists involved in these decisions to assess whether such VAS have real added value within their environment. In addition, the generated savings resulting from tenders can be used to finance some of these services as well (385). This is another reason why in some contexts such services might be of less importance.

4.2.3 ENVIRONMENTAL AND SUSTAINABILITY FACTORS

When selecting a best-value biological medicine, part of that value lies also in the way the supplier has taken care of environmental aspects. The company's policy on environmental factors such as production and transport could therefore be considered, as they might have a considerable environmental impact. Green Public Procurement (GPP) therefore refers to environmental criteria in addition to traditional selection criteria such as price, quality, and technical modalities of a product (373). This part of purchasing decisions has gained attention during past years, in particular by national and international legislations promoting sustainable patterns of purchasing.

On a product level, differences may especially relate to the packaging material. Pharmaceutical packaging refers to the technology of protecting pharmaceutical products for distribution, storage, and usage (423),(424). Ecologically friendly packaging includes packaging material emerging from natural sources (i.e. proteins, starch), which do not cause harm to the environment. Green packaging materials will often include a specific eco-label (424),(425). These labels can be used to evaluate whether a product contains eco-friendly packaging material. In other words, whether the packaging material is either recyclable or biodegradable.

4.3 PATIENT-DRIVEN CRITERIA

4.3.1 PRODUCT USER-FRIENDLINESS

Favorable patient-related features of the product add value to the medicine and should especially be considered for SC administered biologicals. For such products, the patient is often responsible for injecting and a more user-friendly injection device may lead to favorable clinical outcomes in terms of adherence (426). A patient-intuitive device may thus score higher compared to a standard prefilled syringe. Biological medicines for SC administration are generally available in three main types of device: pre-filled syringe (PFS), pre-filled pens (PFP) and electronic devices, which range from less to more automation and technical features (426),(427). Product availability in different devices for administration may address the needs of patients with self-injection.

For instance, insulin products are usually available in pen injection systems. Yet, individual vials can be made available that fit flexibly into different pen systems. This increases the number of injection systems the patient can choose from, which may have an impact on the patient-friendliness of the device (427). For injection systems of SC administered anti-rheumatic medicines, patients may prefer ergonomically adapted self-injection systems that help patients overcoming issues with dexterity (426).

In addition to the characteristics of the injection systems, the patient's experience with the formulation can be a differentiating factor. Certain formulations of the same biological have proven to be less painful when injecting or administering than others (428),(429). Several factors may influence injection site pain such as excipients, needle size, and injection volume. Both a more user-friendly and a less painful injection can improve quality of care, and contribute to a better medication adherence (428),(429),(430),(431).

An essential condition is that the added value in terms of user-friendliness is proven in a clinical setting (432). For example, certain formulations of adalimumab products claim less painful injections (429),(433),(431). However, evidence about possible beneficial effects of citrate-free formulations is weak. This was only tested among patients that experienced at least moderate injection-site pain with the original formulation, and differences were only seen for 15 minutes after administration. Moreover, real-world data show that for most patients the difference is not enough to justify a change towards citrate-free formulations. The UK National Health Service (NHS) therefore concluded that these results should not be extrapolated to a wider patient population (431).

4.3.2 PATIENT SUPPORT PROGRAMS

Patient support programs (PSP) are a subtype of value-added services, with specific attention for patient support. Such services are designed to support with chronic treatments in particular, where poor medication adherence is more problematic (434),(435). Therefore, several pharmaceutical companies offer additional services to their products with the purpose to improve patient care. PSP have the objective to help patients manage their medication regimens and improve therapy adherence.

Examples of PSPs include injection device training, educational material for patients, or adherence programs. The value of such programs lies in their potential to improve adherence and clinical outcomes (436). However, some hospitals will be able to organize such support programs on their own, using their own resources. Therefore, as with all added-services, their value will depend strongly on the needs of the setting where the biological medicine is dispensed.

5. ASSIGNMENT OF RELATIVE WEIGHTS AND SCORING

Once the relevant criteria are identified, their relative weight, i.e. the impact they have on the decision, needs to be determined. The weights given to the criteria should be proportional to their respective relative importance. The relative weight that is assigned to each criterion is subject of discussion and can vary between setting and countries (407). Although the determination of weights is context dependent, sufficient weights need to be attributed to non-price related elements for them to have an impact on the decision-making (56).

The inclusion and assignment of weights depends on the context of the product (class). For example, the consideration of the product's user friendliness will only be relevant for subcutaneously administered products. The relevance of certain criteria and their weighting may also depend on the dispensing context. For instance, the assigned importance to VAS may vary across hospitals. Hospital pharmacies with limited capacity and biosimilar expertise to organise these themselves may deem this important, others may wish to organise this in-house and allocate no or no significant weight to it in the decision. Third, the healthcare system decision-making context may play a role in attributing more weight to some factors than others.

As such, the assignment of individual weights to the criteria requires a dynamic approach. Product selection makers need to decide on relative weights for the selection criteria based on the context of the product and their hospital, making a tailored but nonetheless transparent and evidence-based product selection.

Criteria must be formulated as objectively measurable questions, to ensure objective and transparent assessment. In Table 24, the criteria are provided in question format. Answers need to be supported with data and/or other documents (e.g. scientific publications, the European Public Assessment Report (EPAR), production planning, history of recalls) to allow for an objective and evidence-based assessment (405),(404). In addition to formulating criteria and determining their relative weights, it needs to be prospectively defined how the answers will be scored (e.g. 100% of score awarded if answers falls under answer category A, 90% of score awarded if answer falls under answer category B, etc).

TABLE 24. OVERVIEW OF POSSIBLE QUESTIONS RELEVANT TO THE SELECTION OF A BEST-VALUE BIOLOGICAL

I. Product-driven criteria
1. Technical product features
<ul style="list-style-type: none"> - Q1. Are there any differences in the number of strengths available compared to the other candidate(s)? - Q2. Are there any differences in product administration compared to the other candidate(s)? (e.g. administration route, infusion speed, vial protectors, temperature sensitive indicator, less frequent administrations) - Q3. Are there any differences in formulation (excipients, stabilizers, etc) compared to the other candidate(s)? - Q4. Are there any differences in the product's reconstitution compared to the other candidate(s)? (e.g. ready-to-use formulation, dissolution rate) - Q5. Are there any differences in storage conditions (including shelf life) compared to the other candidate(s)? - Q6. Are there any differences in packaging or labelling of the product compared to the other candidate(s)? (i.e. easiness to read, barcoding per dose, products per dose packaging (optimal package size with regard to co-payment), volume of packaging, documentation regarding adherence to FMD, ...)
2. Indications: authorization and reimbursement status
<ul style="list-style-type: none"> - Q1. Are there any differences in registered indications compared to the other candidate(s)? - Q2. Are all registered indications reimbursed?
3. Real-world product experience
<ul style="list-style-type: none"> - Q1. Are there real-world data to substantiate claims regarding patient experience, injection pain, etc?
II. Service-driven criteria
4. Supply conditions
<ul style="list-style-type: none"> - Q1. How does the supplier ensure supply? - Q2. How does the supplier ensure and document that the product integrity is maintained from the production site to the administration to the patient (e.g. storage and handling)? - Q3. Does the supplier maintain adequate levels of reserve product in stock? Metric: stock volume versus batch frequency
5. Value-added services
<ul style="list-style-type: none"> - Q1. Does the company offer services that improve patient care and adherence in the hospital environment or in support of the delivery of the medicine at home? (e.g. training of healthcare professionals, nurse services at home, ...) - Q2. Does the company support the performance of antibody testing in patients?
6. Environmental and sustainability factors
<ul style="list-style-type: none"> - Q1. Does the supplier make use of ecological friendly policies for production and transport? - Q2. Does the company make use of ecological friendly packaging material for its product (i.e. biodegradable or recyclable material)
III. Patient-driven criteria
7. Product user-friendliness
<ul style="list-style-type: none"> - Q1. Are there differences in device user friendliness compared to the other candidate(s)? (e.g. flexible vials, patient-intuitive device, ...) - Q2. Are there several injection devices available to choose between (i.e. pre-filled syringe (PFS), pre-filled pens (PFP) and electronic devices)?

-
- Q3. Are there proven differences regarding injection site pain compared to the other candidate(s)?
-

8. Patient support programs

- Q1. Does the company offer patient-oriented services such as injection device training, educational material for patients, or patient adherence programs?
-

The relevance and corresponding weight of the abovementioned criteria or questions needs to be tailored to the product specific and local context.

6. DISCUSSION

Although biosimilars and reference biologicals offer the same clinical outcomes, other criteria beyond price can be relevant in the product decision-making. Clinicians need to make informed decisions when selecting a best-value biological medicine(s), and they need transparent and rational selection criteria to guide them during this process. This article provides an up-to-date overview on criteria that may be useful to consider which may aid hospital pharmacists and clinicians with the decision-making in practice. Since the context differs between products and the needs within regions or hospitals may vary, the provided guidance should be translated and tailored to each specific situation (412),(437),(438).

The evaluation of best-value biologicals based on the advanced model may facilitate a transparent consideration of both price and qualitative criteria in the decision-making. The proposed selection criteria in this article are categorized in product-driven, service-driven, and patient-driven criteria. Criteria in each of these categories add value to the biological product and/or may impact practical product implementation. However, the extent to which some criteria are more or less important will strongly depend on the local needs where the biological product will be delivered or administered. It is the task of the hospital pharmacist to assess and decide on the extent of their importance for a particular biological product.

The term of best-value biologicals has been advanced to emphasize the focus on improving patient outcomes as well as healthcare processes while maintaining an affordable medicines bill, rather than focusing on either originator or biosimilar uptake, as both contribute to a sustainable off-patent biologicals marketplace (439).

National authorities have already been actively involved in guiding purchasers to select the best-value biological. In Ireland, the Health Service Executive (HSE) has established the best-value biologicals program in 2019 for off-patent TNF-alpha inhibitors etanercept and adalimumab (440). All patients who are treated with either etanercept or adalimumab should be prescribed a best-value biological. In this context, an exhaustive list of 13 criteria were formulated to select the best-value biological. These criteria include acquisition costs, as well as qualitative criteria such as therapeutic indications, formulation considerations and patient factors. This example underlines the importance of a more inclusive approach when selecting a best-value biological, as its value goes beyond price considerations alone, and may be informative for hospital pharmacists and other stakeholders in

their decision-making. Differentiation based on these criteria may also have a tangible clinical and practical impact, both on purchasers and patients (i.e. more user-friendly injection devices).

Selecting the best-value biological requires adequate understanding by clinicians of the science behind the development and evaluation of biosimilars, and how regulatory frameworks are tailored to the biosimilarity principle (14). Besides this, pharmacists should, as pharmaceutical product specialists, be well informed regarding the qualitative aspects that bring product value and may have an important impact on its practical implementation in clinical care. While purchasing biologicals solely based on price may generate important short-term savings, this approach may overlook important product characteristics and lead to less sustainable practices on the longer term (56),(379). Achieving the lowest price possible for biological medicines may lead to market impoverishment. Instead, competition on value-adding criteria should be stimulated. In this way, companies are stimulated to innovate on product features such as dosage, package sizes, administration route, formulation and patient-friendly injection devices (126),(441). Importantly, EPARs or other scientific documents should serve as a reliable reference to substantiate the value of additional differentiating criteria.

It should be noted that the selection process can and may lead to several best-value biologicals, instead of only one. In settings where the market volume allows to have multiple winners, the selection of multiple winners should be strived for, as by stimulating market plurality, it benefits both the sustainability of the market and the availability of the biological medicine for the patient (53),(56).

7. CONCLUSION

With a growing number of biosimilar products coming available on the European market, hospital pharmacists have a wide range of off-patent biological products to choose from. This article advances a model to select best-value biologicals, taking additional qualitative criteria besides price into account. While the model may facilitate informed and transparent decision-making, the overview of criteria and the allocated weights need to be adapted to the local and product-specific context.

1. ABSTRACT

Background: Biosimilar medicines are equally safe and effective treatment options compared to their originator biological medicine, and their market entry may provide significant benefits to healthcare systems and patients. In Belgium, the uptake of biosimilars is limited compared to other European markets. Whereas certain European countries have initiated a structured biosimilar introduction or switching plan, no such framework or guiding principles to support biosimilar use have been introduced in Belgium.

Objective: This study aims to develop consensus-based recommendations and inform policy action in Belgium on the use of biosimilars, especially in the context of switch decision-making, and this by building on the perspectives of healthcare professionals involved with in procuring, prescribing, switching and dispensing biological including biosimilar medicines.

Methods: This study made use of the Nominal Group Technique (NGT), consisting of a three-step research process involving an expert group of Belgian medical specialists and hospital pharmacists (n=13). The three-step NGT process combined (1) an individual grading of pre-identified topics, (2) three structured group discussions and (3) a final individual grading of the derived study recommendations. The collected quantitative data were analysed descriptively, and the qualitative data were analysed according to the thematic framework method.

Results: Six key areas for policy development to support healthcare professionals with biosimilar use and switch decision-making are put forward: (i) addressing stakeholder reservations regarding (multiple) switching, (ii) providing meaningful stakeholder incentives, (iii) guiding healthcare professionals with product decision-making, (iv), aligning practical product modalities (to the extent possible), (v) involving healthcare professionals in biosimilar policy making, and (vi) providing healthcare professionals with practical switch support and patient information material, particularly in the ambulatory setting. For each area, specific consensus-based recommendations were derived, but in general, policy measures should be tailored to the dispensing and product specific context, take the broader product landscape into account, and should form an integrated and pro-active policy framework. In addition, guiding principles on how to manage a switch and inform the patient were formulated, including amongst others, generating buy-in from involved stakeholders prior to switching and communicating with a one-voice message.

Conclusion: Healthcare professionals face challenges with the use of biosimilars and switching in practice, and incentives appear to be lacking. Without cohesive actions to reduce hurdles and without tangible benefits or steering mechanisms, changes in biosimilar use may be limited, particularly in the ambulatory care context where drivers for biosimilar use are largely absent. An integrated policy framework that includes guidance and incentives for healthcare professionals with biosimilar use and switch management is needed in Belgium. Considerations should extend beyond stimulating biosimilar use, and focus on the broader aim of stimulating healthy competition for a sustainable off-patent biologicals market.

2. INTRODUCTION

The market entry of biosimilars – biological medicines that are highly similar to an already approved biological medicine (14) – has shown to lead to lower treatment costs and in some cases increased patient access to biological therapies (11),(442),(39), delivering benefits to both healthcare systems and patients. With biological therapies already accounting for 40% of total pharmaceutical spending in Europe and still expanding, biologicals represent a growing budgetary challenge for many EU health systems (9). Biosimilar medicines are an important lever to manage this growing biopharmaceutical expenditure by fostering competition. However, in order to reap the benefits of biosimilars, healthcare systems must be well organized to allow for effective biosimilar competition and stimulate their long term presence (9),(10).

Compared to other European countries, biosimilar market shares are considerably lower in Belgium. In 2020, Belgian biosimilar market shares, with the exception of filgrastim, infliximab and follitropin alfa, continued to be below 20% (443). Of the 67 biosimilars (of 16 distinct original biological medicines) that have a valid marketing authorization for the European Union, 34 (of 13 original biological medicines) are available at present (June 2021) in Belgium (444),(445). At policy level, awareness exists that changes are required to ensure a more attractive climate for continued biosimilar market presence in Belgium (446). In 2016, a convention was agreed between the Ministry of Social Affairs and Health with industry and professional associations with the aim of fostering biosimilar uptake (138). Despite this, and a series of *ad hoc* measures over the past years, biosimilar adoption in Belgium remains fairly low (443),(447),(412),(154). Notwithstanding the short-term savings that have been realized due to biosimilar market entry (443), which can be mainly attributed to the mandatory price reductions that original biologicals undergo at the time of biosimilar entry and further confidential discounting in tendering, it can be argued that the way the healthcare system is organized in Belgium may impede the establishment of a sustainable, off-patent biological and biosimilar market environment with continued competition over the longer term (412),(448). Table 25 provides an overview of relevant Belgian biosimilar policy parameters.

Earlier research already pointed out that comprehensive policies to ensure a sustainable off-patent biologicals climate, with sustainable competition from biosimilars, are missing in Belgium (412),(154). In particular, more attention was considered needed to develop healthcare professional oriented policy measures (154). Indeed, physicians and pharmacists are key stakeholders as they are the ones in charge of purchasing, prescribing or dispensing off-patent biologicals and biosimilars. Furthermore, specific attention is required to investigate healthcare professional needs and considerations regarding switching and its management as biologics for which biosimilars are available are often used in a chronic treatment setting.

This study aims to inform policy action for biosimilar use and switch management in Belgium from the perspective of Belgian healthcare professionals, by examining and prioritizing their needs and views in a structured manner.

TABLE 25. THE BELGIAN BIOSIMILAR POLICY ENVIRONMENT

Uptake	While market shares vary across product types, market shares in 2020 were for most biosimilars below 20% (443),(154).*
Pricing	List price is negotiated on a case-by-case basis, and cannot exceed the reference product's list price (449). Original biologicals undergo mandatory price reductions at the 12-year reimbursement mark - if no longer protected by patent or other exclusivities at that time - which can be up to 47,18% depending on yearly product turnover. If biosimilar market entry proceeds the 12-year reimbursement mark of the originator, the mandatory price reduction is expedited (450). On list price level, generally only limited differences exist between the reference product and its biosimilar(s) (154),(445).
Dispensing context	In public pharmacies, medicines are dispensed at the publicly available list price. For biologicals dispensed in the hospital, which are subject to tenders, confidential discounts are offered. The difference between the net tendered price and list price is largely retained by the hospitals (reimbursement limit for biologicals for which a biosimilar is authorized has been reduced by NIHDI to 85%) (442).
P & R procedure	Takes 90 days (448),(451). Evaluation for reimbursement is conducted by the CRM, and the final decision is taken by the Minister of Social Affairs and Health. The Minister of Economic Affairs is in charge of setting the maximum price (451).
Inter-changeability	The national medicines agency, FAMHP, has no publicly available statement on interchangeability of biosimilars with their reference product (452).
Switching	Switching can be done under the responsibility of the prescribing physician. FAMHP advises that a switch must be accompanied with the necessary follow-up and accurate recording of the modification. Excluding INN prescribing for biologicals is recommended, to avoid switching without prescriber follow-up (452).
Substitution	Substitution by the pharmacist without consultation with the prescriber is not authorised in Belgium for biological medicines (452).
Physician incentives	In the ambulatory care setting: a temporary pilot project in 2019 introduced a personal financial incentive for physicians who prescribed a certain quota of prescribing adalimumab and etanercept biosimilars. Depending on the percentage of biosimilar prescribing (5, 10 or 20%), physicians could receive €750- €1500 (453). In the hospitals: benefit-sharing agreements, in which savings from tenders partly flow back to the hospital department, are generally not installed.
Education & info	End of 2018, FAMHP and NIHDI launched a national information campaign with dedicated website, radio commercials, brochures and posters (145).
<i>CRM: the Commission for Reimbursement of Medicinal Products, FAMHP: Federal Agency of Medicines and Health Products, NIHDI: National Institute for Health and Disability Insurance, P&R: Pricing & Reimbursement</i>	
<i>*Exceptions include infliximab, filgrastim and follitropin alfa for which biosimilars attained respectively approximately 39%, 34%, 46% market share in 2020 (443).</i>	

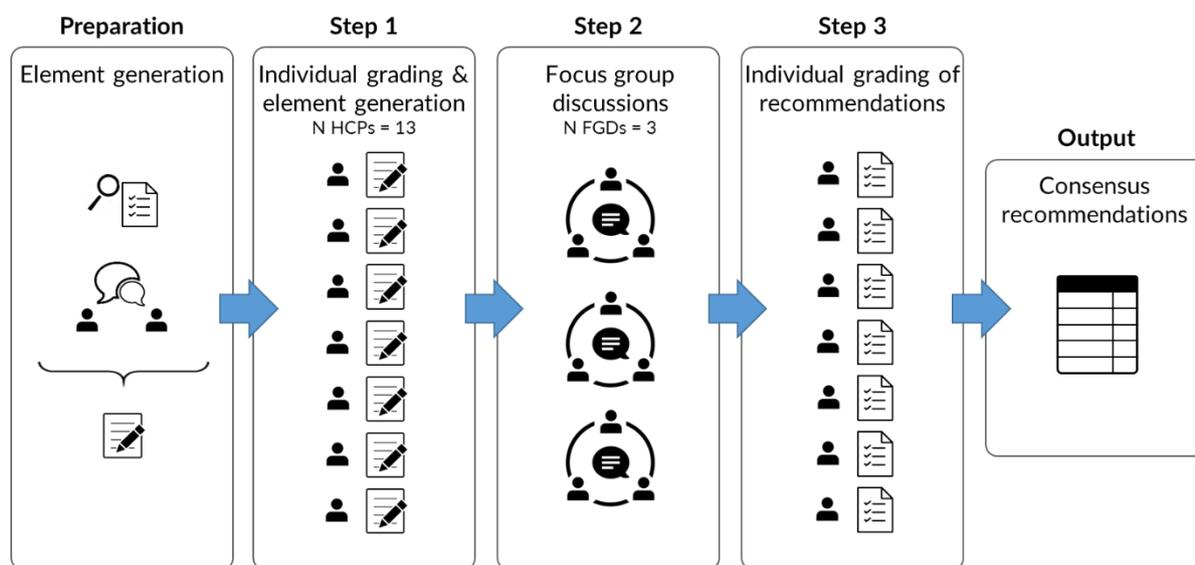
3. METHODS

3.1 GENERAL STUDY DESIGN

The methodology of the Nominal Group Technique (NGT), a type of structured focus group discussion method, was chosen because it is effective in identifying stakeholder priorities and allows to generate recommendations with consensus (454). The NGT combines in-depth discussions of a standard focus group methodology with a structured grading process in which participants are asked to rank and reach consensus on certain elements, in this case considerations regarding biosimilar

use and switch management in the Belgian context (455),(454). The applied NGT methodology consisted of the following steps: (1) initial individual grading and idea generation, (2) structured group discussions and (3) a second round of individual grading of derived recommendations. Such stepwise NGT method enables participants to express their views both individually and collectively (456),(455). An overview of the different methodological steps is shown in Figure 24.

FIGURE 24. OVERVIEW OF THE APPLIED STEP-WISE NOMINAL GROUP TECHNIQUE



3.2 RECRUITMENT AND STUDY POPULATION

Both Belgian physician specialists and hospital pharmacists involved in purchasing, prescribing, switching and dispensing of biologicals, including biosimilars, were purposively selected and invited to participate. Physician specialists across the different disease disciplines in which biosimilars are currently available were invited (dermatology, rheumatology, gastroenterology, oncology, and endocrinology). Participants were invited from both university and regional hospitals across different geographical areas in Belgium. Recruitment was done via e-mail invitation, which included an information sheet with detailed information about the aims and set-up of the study. Upon expression of interest to participate, an informed consent form was shared with the participant. The study involved 13 expert physician specialists and hospital pharmacists. The informed consent form was signed by all participants before participation.

3.3 THREE-STEP STUDY DESIGN

3.3.1 INITIAL INDIVIDUAL GRADING STEP

First, participants were asked to grade and comment on a number of statements, capturing their individual perspective on topics related to biosimilar use, switch decision-making and management. For this, each participant received a written answer sheet.

The answer sheet consisted of two parts. First, questions were posed about the participant's characteristics. In the second part, participants were asked to indicate their level of agreement (LoA) with various statements on a 5-point Likert scale (from 1 = strongly disagree to 5 = strongly agree). Statements were categorized in three main themes: (1) possible participant needs regarding biosimilar use and switching, (2) possible elements to consider in biosimilar use and switch decision-making and (3) possible elements to consider when managing a switch in practice. Participants were given the option to provide written comments on any of the statements. Further, an open answer field was included where participants were asked to include additional ideas or points of interest. Topics and statements included in the answer sheet were informed by earlier biosimilar stakeholder oriented research (119),(115), and participants were asked to add their insights to this.

3.3.2 GROUP DISCUSSIONS

Second, three structured group discussions were organized. As described by McMillan *et al.* NGTs generally include between 2 and 14 participants, but a maximum of seven is recommended to allow for an efficient structured discussion with room for contribution from every participant in a given timespan (454),(456),(457). As such, three separate group discussion were conducted, with each involving three to six participants ($n = 13$). Each group discussion consisted of both physician specialists and hospital pharmacists to capture and stimulate discussion between both stakeholder groups. In qualitative research, saturation, *i.e.* "the point when no new information or themes are observed in the data" is often used to determine when data collection can stop (458),(459). Upon analysis of qualitative data collection of the three group discussions, no new themes or information appeared to emerge from the third round. Hence, it was concluded that data saturation was reached.

The group discussions were organized in person at the KU Leuven university campus Gasthuisberg between December 2019 and February 2020. The option to participate online was provided when a participant could not be physically present. The discussions lasted approximately two and a half hours. Three researchers were involved in the group discussions: a moderator who guided the discussion and raised dialogue elements, and two observers who were in charge of taking notes, drafting summary slides and practical arrangements such as time keeping.

A structured discussion guide was used to inform each group discussion. The guide included an introduction about the role of the moderator and the observers and an explanation about the study. In addition, the guide contained detailed instructions for the researchers to follow throughout the discussion. Each group discussion consisted of several phases. First, the participants were welcomed and an introduction was given. Also the study set-up and aims were explained. In the subsequent discussions, participants were asked to share their needs and perspectives regarding biosimilar use and decision-making and management of switching in clinical practice. Participants were offered the opportunity to accentuate the importance given to certain elements, share nuances and discuss their underlying reasoning. The discussion was initiated by inviting each participant to speak. Next, open discussions, structured by the moderator, were held. At the end of the discussion, draft summaries were presented to the participants, on which they were asked to comment and indicate

their agreement. A PowerPoint presentation was used to visually guide the session and present discussion elements to the participants.

3.3.3 SECOND INDIVIDUAL GRADING STEP

Third, a second written, individual grading round was prepared. Again, participants were asked to indicate their LoA on a 5-point Likert scale, this time on a concrete set of proposals derived from quantitative analysis of the first individual grading and qualitative analysis of the group discussion transcripts.

3.4 DATA ANALYSIS

Both quantitative and qualitative data were gathered. A combined quantitative, descriptive analysis of participants' first grading and qualitative, thematic analysis of the discussion transcripts was performed to identify (1) the overarching themes that emerged from the study for policy action, and (2) a set of guiding principles for switch management. For each overarching theme, a concrete set of proposals was derived. This led to the development of the second written answer sheet, in which participants were asked to indicate their level of agreement. Grading data of this third study step were analysed descriptively to determine the level of consensus achieved.

3.4.1 QUANTITATIVE ANALYSIS

Participants' characteristics and grades from the written answers sheets were analysed descriptively in Microsoft Excel. Each participant was given an identifier code with which the research data were coded (pseudonymization) and subsequently tabulated. The participants' grades from both grading rounds were analysed descriptively, by calculating mean values for each statement. For the second and final grading, we considered strong consensus to be achieved for a recommendation when at least 80% of participants agreed with the statement (yes/no) and the overall participant mean LoA was ≥ 4 on the Likert-scale (256),(460). Recommendations with a mean LoA ≥ 3.5 were regarded as recommendations with moderate consensus. If the overall mean LoA was < 3.5 , no consensus was considered to be reached.

The participants' average grading per statement (ranked according to level of importance/agreement) on the first answer sheet are given in [Tables S1-3](#) in Online Supplementary Material.

3.4.2 QUALITATIVE ANALYSIS

The structured group discussions were audio-recorded and the audio tapes were transcribed *verbatim*. The transcripts were pseudonymized and qualitatively analysed according to the thematic framework method of Lacey and Luff, which involved an iterative process of data familiarization, identification of a thematic framework, coding of transcripts with NVivo data analysis software, charting the data by code and mapping and interpretation steps (59). Summaries prepared during the group discussions and the written comments from the open answer fields in the answer sheets were tabulated in Microsoft Excel and included for qualitative analysis.

4. RESULTS

4.1 PARTICIPANT CHARACTERISTICS

In total, 13 Belgian specialists in rheumatology, oncology, gastroenterology, endocrinology and hospital pharmacy participated across three structured group discussions. In terms of geographical spread, participants worked in either Flanders or Brussels. No healthcare professionals from Wallonia (French speaking Belgian region) participated. Both academic and regional hospitals were represented, with the majority of participants working in an academic setting. A complete overview of the participant characteristics is shown in Table 26.

TABLE 26. PARTICIPANTS' CHARACTERISTICS

Characteristics	Participants (n total = 13)	
	n	%
Sex		
Female	3	23
Male	10	77
Age		
<30 years	1	8
> 30 years – 45 years	3	23
> 45 years – 60 years	6	46
> 60 years	3	23
Years of work experience		
< 5 years	2	15
≥ 5 years – < 10 years	0	0
≥ 10 years – < 20 years	2	15
≥ 20 years – < 30 years	6	46
≥ 30 years	3	23
Discipline		
Physician specialist	6	46
Hospital pharmacist	7	54
Work environment		
Flemish-Brabant	8	62
Brussels	1	8
Antwerp	1	8
West-Flanders	1	8
East-Flanders	1	8
Limburg	1	8
Work environment		
Academic hospital	9	69
Regional hospital	4	31

N: number, percentages are rounded to the nearest integer

4.2 OVERARCHING AREAS FOR POLICY ACTION WITH A SET OF CONSENSUS RECOMMENDATIONS

From the analysis, six main areas for policy development regarding biosimilar use and switch decision-making in Belgium emerged:

- i. Addressing stakeholder reservations regarding (multiple) switching
- ii. Providing meaningful stakeholder incentives
- iii. Guiding healthcare professionals with product decision-making
- iv. Aligning practical product modalities (to the extent possible)
- v. Involving healthcare professionals in biosimilar policy making
- vi. Providing healthcare professionals with practical switch support and patient information material, particularly in the ambulatory setting.

For each of the six main areas for policy development, the context is provided below. The set of concrete recommendations for each area, as derived from participant proposals, together with the level of consensus is shown in Table 27.

4.2.1 ADDRESSING STAKEHOLDER RESERVATIONS REGARDING (MULTIPLE) SWITCHING

Participants underlined the reassuring impact that both the availability of supportive data from clinical switch studies and own positive switch experiences have had. Despite the fact that the availability of clinical data regarding switching was considered to be paramount in generating trust in switching, some participants cautioned to continue to request more clinical switch data, which are in essence beyond EU biosimilar regulatory requirements (“*when will it ever be enough?*”).

While participants largely expressed to be sufficiently assured regarding the safety of a switch from reference product to a biosimilar, they indicated that this was not always the case for their peers. Also concerns were raised by physicians regarding liability in case a switch would lead to an undesirable effect, illustrating that doubts regarding the practice of switching persisted among some of the participants. Especially, questions and hesitations were voiced around switching multiple times between biosimilar and reference product. A few participants mentioned that for this particular reason the tender contract which introduced the first switch to a biosimilar in their hospital was maintained for the maximum duration of four years, postponing a second switch as long as possible. Some argued that industry outreach has instilled reservations in the switch debate, accentuating the need for communication from independent bodies.

While a supportive statement regarding switching from reference products to biosimilars, *vice versa* or between biosimilars of the same reference product is available from the Belgian medicines agency, the Federal Agency for Medicines and Health Products (FAMHP) (461), some participants requested a more explicit and detailed guiding statement which includes information about multiple switching and guidance on which measures to consider when conducting such a switch. FAMHP mentions that a switch “*must be done with the necessary follow-up*”. Participants mentioned that for them it is not fully clear what is meant with this (routine monitoring as done for the reference

product, or a need for additional monitoring). In addition, the suggestion was made for the medicines agency to communicate on available data from clinical switch studies on an aggregated level.

In general, participants pointed out the need for (1) more explicit guidance from regulators and professional stakeholder associations and (2) the collection of multiple switch and/or long-term follow-up switch clinical data, together with a more active leveraging of the available clinical switch data to adequately inform switch decision-making in clinical practice. The recommendations to address stakeholder reservations regarding (multiple) switching, as proposed by participants, are shown in Table 27.

4.2.2 GUIDING HEALTHCARE PROFESSIONAL PRODUCT DECISION-MAKING

Participants discussed the need for guidance on product decision-making. Besides this being relevant in the context of choosing between biological reference product and biosimilars, participants pointed towards the availability of second-generation and newer therapeutic alternatives, for which the therapeutic benefit is considered equal to the off-patent biologic therapeutic option (reference product and biosimilars). Depending on the context in which product selection takes place, different needs and proposals were formulated by the participants.

In the hospital setting, the tender process can be considered as main driver of product decision-making. Tenders for hospital medicines in Belgium are generally organized by individual hospitals or hospital groups and typically induce competition on the active substance level (*i.e.* competition on international non-proprietary (INN) level) or possibly second-generation products (e.g. long-acting granulocyte colony stimulating factors (G-CSFs), pegfilgrastim and lipegfilgrastim are generally grouped in the same lot) (32). A first challenge mentioned in the context of hospital tendering pertains to the appropriate use of tender award criteria. As explained by participants, a certain dissonance seems to exist between criteria deemed valid according to healthcare professionals (such as rewarding longer market presence of the product or need for additional switch data) and their competitive nature in terms of the impact they might have on the level playing field. In 2019, the Belgian medicines agency, FAMHP, circulated a letter to Belgian hospitals with information regarding the nature of award criteria, clarifying that these criteria need to be related to the subject matter of the tender itself (462). Regardless, healthcare professionals argued there is still ambiguity regarding the appropriateness of award criteria. As a second challenge, hospital pharmacist participants pointed towards the need for timely information on biosimilar market entry to allow for a timely organization of tenders. As a third point of consideration in the hospital setting, participants underlined the need for a revision of the hospital financing system, as the current set-up incentivizes hospitals to opt for products with high list prices. The price difference between the tendered price and list price is largely retained by the hospital, and accounts for an important portion (approximately 20% on average) of revenue of Belgian hospitals (463). Products with a high list price allow for greatest margin between list price and tendered price and as such oh higher economic value for the hospital (43). Finally, also the availability of second-generation biologicals such as subcutaneous formulations for trastuzumab and rituximab were mentioned as reasons why the

market opportunity for biosimilars is in some cases limited in hospitals (as currently only the intravenous formulation are available as biosimilar).

For products dispensed by the community pharmacy (i.e. ambulatory setting), product selection was argued to largely remain at the discretion of the individual prescriber. Participants were of the opinion that factors driving product choice may vary between physicians and believed that price is not routinely taken into account. Other factors such as brand loyalty and direct “informal” incentives offered to physicians by pharmaceutical companies were mentioned as potential drivers in decision-making. Moreover, it was emphasized that argumentation to choose for a biosimilar from the perspective of the physician in the ambulatory setting is limited. This point is further discussed under 3.2.3. Further, participants argued that physicians may also shift to newer, higher priced products, although the added clinical benefit compared to the off-patent biological for which a biosimilar is available may not always be clearly established. For example, in the treatment of diabetes mellitus with long-acting insulin, product shifts to the higher concentrated insulin glargine formulation Toujeo® (300 U/ml compared to the traditional formulation of 100 U/ml (reference product Lantus® and biosimilar Abasaglar®)) or insulin degludec (Tresiba®) were mentioned. In rheumatology, physicians mentioned the increasing use of higher priced Janus kinase (JAK) inhibitors, although the clinical benefit of JAKs compared to the off-patent tumour necrosis factor-alfa (TNF) inhibitors (of which several have lost their exclusivity and have biosimilar alternatives on the market: infliximab, etanercept, adalimumab) is questioned. Physician participants pointed out the following elements to potentially explain these shifts to higher priced innovator products: strong pharmaceutical company outreach activities, inclination to possible product innovations (although clear clinical superiority may not always be established) and brand loyalty.

Participants underlined that the availability of newer, competing products should be considered in the context of off-patent biologicals selection making. It was mentioned that shifts to higher priced innovator products should only be made in case clinical superiority is clearly established. Participants argued the need for a reassessment of the value of second-generation products and by extension the entire product class at the time of biosimilar market entry. Although consensus existed among study participants on the importance of cost-effective prescribing, it was argued that the responsibility to consider cost should not be placed on the shoulders of the individual physician. In other words, guidelines and mechanisms were considered needed to assist physicians and steer them to prescribe in a rational way.

In terms of stimulating biosimilar use in the ambulatory care setting, the use of biosimilar market share quota was put forward by some participants during the group discussions. However, no consensus among participants was achieved in the final step of grading for this recommendation. An overview of the proposals on how to support healthcare professionals with product selection making in both the hospital as well as ambulatory care context and steer cost-effective choices are shown in Table 27.

TABLE 27. BIOSIMILAR USE AND SWITCH DECISION-MAKING IN BELGIUM: POLICY ACTION PROPOSALS

	Level of Agreement* Mean value on a scale from 1-5, with 5 being the highest value	Level of consensus**	Authors' assessment of priority***
1. Addressing stakeholder hesitations regarding the safety of (multiple) switching			
<i>Providing clear and transparent position statements</i>			
A. The <u>Belgian medicines agencies</u> (FAMHP) should provide a <u>more explicit position</u> on interchangeability, switching and multiple switching between biological reference products and biosimilars. Guidance on the measures that should be taken by healthcare providers should be more clear. This could help address medico-legal concerns of healthcare providers when switching.	4.0	Strong consensus	High
B. <u>Scientific professional associations</u> should provide <u>position statements</u> and keep these updated about biosimilar use and elements such as switching and interchangeability.	4.4	Strong consensus	High
<i>Pro-actively sharing switch experiences and clinical switch data</i>			
C. <u>Sharing switch experiences</u> between hospitals can help to generate peer-to-peer guidance and overcome hesitations with biosimilar use.	4.1	Strong consensus	High
D. The gathered clinical data regarding switching between biological reference products and biosimilars (sourced from either RCTs, RWE, registries etc.) should be <u>actively communicated</u> (not study per study, but on an aggregated/overview level) to HCPs, instead of made passively available. This will help to ensure that the existing data and information reaches the target audience and can support them with biosimilar use in clinical practice.	3.7	Moderate consensus	Intermediate
E. Gathering clinical data about the <u>long-term safety</u> of switching between biological reference products and biosimilars could help to instil further trust about switching among stakeholders. Gathering RWE while switching in clinical practice, for example by collecting patient outcomes in a registry or observational study, could be explored to generate long-term safety data.	3.6	Moderate consensus	Intermediate
F. Clinical data about <u>multiple switching</u> should be generated, as only limited data are available so far. Gathering RWE while switching in clinical practice, by for example organizing an observational study when managing a multiple switch in clinical practice or collecting patient outcomes in a registry, could be a way to generate such multiple switch data.	3.9	Moderate consensus	Intermediate

2. Guiding HCP product decision-making: steering cost-effective prescribing and biosimilar use

General

Increasing awareness about prescribing behaviours and increasing transparency

A. <u>Awareness among healthcare providers about cost-effective prescribing</u> should be stimulated.	4.4	Strong consensus	High
B. Making prescribing information available on a <u>peer-to-peer level</u> (such as done with the TARDIS platform for rheumatologists) could allow prescribers to compare own prescribing patterns to these of colleagues on a group level (peer-to-peer benchmarking), and increase awareness about cost-effective prescribing.	4.0	Strong consensus	High
C. There should be <u>transparency</u> about financial ties between HCPs and pharma industry (for example by making the beTransparent initiative (https://www.betransparent.be/en/) more well-known or other initiatives that increase transparency).	3.9	Moderate consensus	Intermediate

Revision of pricing and reimbursement modalities

D. <u>Price and reimbursement conditions</u> of same INN products with a different route of administration (e.g. SC rituximab and trastuzumab) should be reassessed upon biosimilar market entry.	4.2	Strong consensus	Intermediate
E. <u>Price and reimbursement conditions</u> of innovator/second-generation products should be reassessed upon biosimilar market entry.	3.9	Moderate consensus	Intermediate

Hospital context

Supporting hospitals with tender organization

F. The government should support hospital pharmacies by performing <u>horizon scanning</u> to identify the upcoming loss of exclusivity of reference products and anticipated biosimilar market entry dates.	4.2	Strong consensus	High
G. <u>Guidance</u> by responsible bodies should be provided to hospital pharmacists (and procurement colleagues) about the design and application of appropriate <u>tender criteria</u> for off-patent biologics and biosimilars (e.g. via a tender template).	3.95	Moderate consensus	High
H. <u>Guidance</u> about the design and application of appropriate tender criteria for off-patent biologics and biosimilars should be provided on an <u>overarching level</u> and allow room for tailoring.	3.85	Moderate consensus	High

Reforming hospital financing

I. The <u>reform of the hospital financing system</u> will be important to make hospitals less financially dependent on the revenue generated from discounts in pharmaceutical product procurement.	4.7	Strong consensus	Intermediate (high impact, low feasibility)
Ambulatory care context			
J. Cost-effective prescribing should be stimulated via <u>prescription guidelines/treatment decision trees/steering software</u> . This may help to avoid a shift to prescribing higher priced innovator/second-generation products, which in some cases may have a limited/questionable added clinical benefit compared to the reference product/biosimilar alternatives.	3.6	Moderate consensus	High
K. Cost-effective prescribing and biosimilar use should be stimulated via (temporary) <u>prescription quota</u> . The installation of (temporary) prescription quota could be accompanied with a stakeholder incentive.	2.6	No consensus	Intermediate
3. Providing meaningful incentives for involved stakeholders			
General			
A. There should be a <u>transparent reporting about the savings</u> derived from biosimilar use and the <u>allocation</u> .	4.4	Strong consensus	Intermediate
Hospital context			
B. <u>A gainsharing program</u> , where a part of the tender savings flow back to the clinical unit and HCPs that were involved in the switch (such as for example by financing specialist nurses), should be applied to reward involved HCPs for the time and effort associated with a switch.	3.6	Moderate consensus	Intermediate
Ambulatory care context			
C. <u>A gainsharing program</u> , where a part of the savings are used for the financing of care processes (budget for a nurse or increased physician consultation honorarium) should be applied to incentivize prescribers in the ambulatory care setting, and reward them for the time and effort associated with a switch.	3.8	Moderate consensus	Intermediate
D. <u>An incentive at the level of the patient</u> , by for example lowering patient co-payment for the biosimilar versions, could be a way to stimulate biosimilar use in the ambulatory setting.	3.6	Moderate consensus	Intermediate
4. Aligning practical product differences, to the extent possible			
A. <u>Product labels</u> (in terms of registered indications) should be <u>aligned between the reference product and its biosimilars</u>	4.8	Strong consensus	Low

B. Reimbursement conditions should be actively and timely aligned <u>between second-generation products, reference product and its biosimilars</u>	4.4	Strong consensus	High
C. Benefits provided in the context of <u>Medical Need Programs</u> , which involved the offering of free goods, should be aligned between reference products and biosimilar medicines	4.5	Strong consensus	Low
5. Involving HCP stakeholders in policy making			
A. <u>Biosimilar policy making</u> would benefit from actively involving <u>HCP stakeholders</u> . Involving HCPs in incentive design could for example help to establish incentives that can lead to meaningful improvements in patient care.	3.7	Moderate consensus	Intermediate
6. Providing practical switch support and patient information material, especially in the ambulatory setting/for subcutaneous products			
A. <u>Practical support</u> (switch management information and resources) should be provided about switching, especially to support stakeholders with SC product switching/switching in the ambulatory setting	3.9	Moderate consensus	High
B. <u>Independent and objective patient information materials</u> should be <u>prepared</u> to support physicians with switch management	4.0	Strong consensus	High
C. <u>Education and information</u> for HCPs should be <u>extended to community pharmacists and general practitioners</u> , as more and more biosimilars (e.g. for insulin, adalimumab, etanercept) are becoming available in the community pharmacy	4.2	Strong consensus	High

* Participants expressed their level of agreement (LoA) on a five-point Likert scale, with 1 = strongly disagree to 5 = strongly agree. The column shows the calculated mean LoA.

**Strong consensus: when at least 80% of participants agreed with the statement (yes/no) and the mean overall LoA was ≥ 4 on the Likert scale

Moderate consensus: a mean overall LoA of ≥ 3.5 on the Likert-scale

No consensus: a mean overall LoA of < 3.5 on the Likert scale

***Authors' assessment of priority is made by considering the following two elements (1) implementation feasibility of the proposal and (2) estimated impact: high, intermediate or low

HCPs: healthcare professionals, FAMHP: the Federal Agency of Medicines and Health Products, RCT: randomized controlled trials, RWE: real-world evidence, TARDIS: Tool for Administrative Reimbursement Drug Information Sharing

4.2.3 PROVIDING MEANINGFUL STAKEHOLDER INCENTIVES

Participants raised the need for incentives to stimulate biosimilar use and support healthcare professionals with switching in clinical practice. Besides general elements, specific considerations and proposals were given for both the hospital and ambulatory context.

In the ambulatory care setting, participants felt little motivated to prescribe a biosimilar or burden themselves to switch to one due to a perceived lack of benefits for all parties involved. To the contrary, participants identified hurdles to opt for a biosimilar, especially when it involves switching a patient who is being treated with the reference product, were identified. Besides the lack of incentives for the physician, they argued also that for the patient there is no direct benefit from receiving a biosimilar as it provides similar clinical outcomes compared to the reference product for which (*largely*) the same reimbursement conditions apply (*Of note, for some molecules there is in fact a (small) difference in patient co-payment between the originator and biosimilar in Belgium (445)*). Furthermore, participants argued that also for the healthcare budget there is no immediate cost advantage in terms of savings as list prices for biosimilars and reference products are largely the same. The general tenor of the participant perspective could be summarized as “*why the hassle of prescribing a biosimilar or switch a patient if there is no benefit for anyone involved?*” Moreover, participating physicians contended that it would require additional consultation time to introduce a biosimilar to the patient, especially if a possibly different injection device would be involved. Moreover, physicians mentioned that unlike in the hospital setting, there is a lack of a framework to support a switch (e.g. staff capacity, information material). This element is further discussed under 4.2.6.

The argument that biosimilar suppliers, without the prospect of reaching a meaningful market share, might lose interest in the Belgian market, which in turn might lead to impoverished market dynamics, was perceived as too intangible to consider in daily practice. It was clear from the discussion that structural change needs to be installed in the form of a concrete incentive, benefit or steering mechanism to stimulate biosimilar uptake, if policymakers deem it important to support market plurality and longer-term competition in the ambulatory setting.

The 2019 anti-TNF pilot project, which offered a direct financial incentive to physicians for the prescription of a certain percentage of adalimumab and etanercept biosimilars (453), was challenged by participants. First, a financial gain on an individual level was perceived as questionable from an ethical point of view. Second, the compensation which was offered was considered insufficient to offset the time investment in terms of patient consultation. Third, the additional administrative practicalities that were associated with the financial incentive pilot were considered to not outweigh the compensation. Participants voiced their support for an incentive which would lead to improvements in patient care. A type of benefit share agreement which would provide funding for additional nurses or pharmacy technicians to assist with the switch process and change in injection device was considered valuable.

In the hospital setting, the lowering of invoicing to 85% for biological medicines for which a biosimilar is available by hospitals to the Belgian national health insurer (National Institute for Health and Disability Insurance, NIHDI) which allows to recoup a part of the savings that are realized in hospital tenders at the national level was recognized as a potent driver for hospitals to organize competitive tenders (442). As tenders are the main driver of in-hospital product decision making, the need for stakeholder incentives was less pronounced than in the ambulatory setting. Participants argued that tenders do not *per se* result in biosimilar uptake, since also the reference product can win – depending on who offers the most competitive bid. It was mentioned that a level playing field must be ensured in tenders to secure fair competition between the reference product and biosimilar competitors.

In the hospital setting, incentives on the basis of a benefit share model, where savings are partly reinvested to improve care processes in the department(s) that helped to generate the savings, were considered valuable. Physicians especially stressed the value of a specialist nurse to guide patients with their biological therapy, and the essential role they have in switch management and as such to ensure quality of care. In the tender context, it was debated from which savings bucket such benefit share could come. As the savings are mainly made at the hospital level, a benefit share agreement for tendered products is likely to be negotiated between clinical departments and a hospital's general management. Alternatively, a benefit share agreement could be made on the basis of the savings generated by the health insurer from the reduced hospital billing (85% billing of the list price for every biological for which a biosimilar alternative is available). However, participants considered the possibility that NIHDI would foresee a benefit share agreement based on the 15% margin to be unlikely, since healthcare budgets are already pressured.

In general, participants mentioned to be not informed about the level of savings that are realized from biosimilar market entry (on the level of the health insurer and hospital) and how these are utilized, expressing a need for more transparency. More transparency was argued to be beneficial to raise awareness among healthcare professionals on the role biosimilars have in creating a more competitive market.

Benchmarking systems, which would enable to mirror own purchasing and prescribing decisions to those of peers, were among the proposed suggestions. An overview of proposals is shown in Table 27.

4.2.4 ALIGNING PRACTICAL PRODUCT MODALITIES, TO THE EXTENT POSSIBLE

Participants mentioned that in some cases differences between reference biologicals and biosimilars are present in terms of the approved indications, reimbursement conditions and medical need programs. It was mentioned that these 'practical' differences may complicate the implementation of biosimilars (also in tenders) and steer choices to the originator product. Arguments were made to align and eliminate these differences where possible, to ensure a level playing field between reference and biosimilar product.

Although the label of biosimilars in terms of registered indications is generally the same as that of their reference product, certain indications might be omitted if these are still patent protected. This may lead to off-label use of the biosimilar in a certain indication and create differences in terms of reimbursement (i.e. no reimbursement for that particular indication).

While generally the reimbursed prices are aligned between the reference product and biosimilar, differences in reimbursement conditions may exist compared to second-generation products. Reference was made to the fact that the higher reimbursed price for lipegfilgrastim, compared to pegfilgrastim (both long-acting G-CSFs) provided lipegfilgrastim with a competitive advantage in tenders over the pegfilgrastim reference product as well as pegfilgrastim biosimilars. Changes were made to align the reimbursement of pegfilgrastim and lipegfilgrastim in 2020, after which the price of pegfilgrastim products was subsequently lowered again because of a mandatory price reduction, leading again to a competitive advantage for lipegfilgrastim (412).

Also Medical Need Programs (MNP), which involve the offering of free goods by a pharmaceutical company for a certain disease indication which is still investigated in clinical trials or under evaluation for authorization when there is a medical need for patients, were quoted as a reason to prefer the originator product over the biosimilar in some cases.

While participants considered that these elements may impact the practical implementation of biosimilars, in practice it is likely not feasible to align elements of registered indications and MNP as they are linked to lifecycle management in terms of seeking approval for new indications that are covered by additional patent protection and may involve additional benefits such as the offering of free goods under a MNP. The concluded overarching area for policy making is thus aligning practical product differences, to the extent this is possible. In terms of aligning reimbursement conditions between reference products, biosimilars and second-generation products, NIHDI should foresee a timely and synchronized revision to eliminate temporary reimbursement differences which negatively impact the level playing field.

4.2.5 INVOLVING STAKEHOLDERS IN POLICY MAKING

Arguments were made by participants that policy development would benefit from early stakeholder consultation. The anti-TNF financial pilot was given as an example of a policy measure that missed its goal, due to the fact that it was insufficiently aligned with the perspective of the physicians. Involving healthcare professionals in stakeholder-oriented policy measures could help to create a broader support base for these measures, and result in the development of measures that are considered valuable in terms of improving care. Some physicians also felt that opportunities were missed in terms of organizing stakeholder consultations already prior to biosimilar market introduction.

4.2.6 PROVIDING PRACTICAL SWITCH SUPPORT AND PATIENT INFORMATION MATERIAL

Participants mentioned a lack of practical, non-industry sponsored information and guiding principles in relation to switch management. Both materials that can assist with switch management

and patient communication were considered needed. In terms of patient communication, reference was made to the 2018 information campaign of the national medicines agency, which offered information brochures and posters. It was pointed out that no specific information on switching was included in these materials (147),(145). Especially in the ambulatory care setting, where there is no structural framework to support healthcare professionals like in the hospital, practical support materials for structured switch management and patient communication are most needed. Where most education initiatives have traditionally focused on specialist physicians and hospital pharmacists, efforts should be expanded to also reach general practitioners and community pharmacists.

4.3 SET OF GUIDING CONSENSUS PRINCIPLES FOR SWITCH MANAGEMENT

In a second part of the study, stakeholders were asked what elements they consider important to take into account when planning a switch. Broad consensus was obtained on a set of guiding principles for switch management, which are outlined in Table 28. Applying a structured switch plan and informing patients was believed to be key, which in turn requires training of staff. In terms of involving patients in the product-decision making, participants argued this to be likely more important for self-administered than IV administered biologicals. Finally, Independent information for both healthcare professionals as patients was considered essential to avoid misconceptions.

TABLE 28. GUIDING PRINCIPLES ON HOW TO EFFICIENTLY MANAGE A SWITCH AND INFORM THE PATIENT

	Level of Agreement* Mean value on a scale from 1-5, with 5 being the highest value	Level of consensus* *
When implementing a switch it is important to...		
General elements		
A. Communicate with a <u>one voice principle</u> (coherence in communication and terminology used among physicians, pharmacists, nurses)	4.7	Strong
B. Search for <u>consensus</u> and <u>support</u> from involved stakeholders <u>prior to the switch</u>	4.5	Strong
C. <u>Inform/educate/train involved physicians, pharmacists, nurses</u> about the switch and/or general concepts of biosimilars	4.3	Strong
D. Follow a <u>planned</u> and <u>stepwise</u> approach	3.9	Moderate
Elements related to the patient		
A. In the hospital setting: <u>inform</u> patients <u>in advance</u> about the switch	3.7	Moderate
B. For subcutaneous (self-administered) products: <u>inform</u> patients about the switch <u>and involve</u> them in the decision-making	4.5	Strong
C. Provide an <u>opportunity to discuss</u> the switch with the physician/nurse prior to the switch, provide patients with the opportunity to <u>ask questions</u>	4.5	Strong
D. For subcutaneous products (self-administered): <u>provide training</u> to the patient on the new <u>injection device</u>	4.6	Strong
E. <u>Keep it simple</u> . Providing patients with excessive information may invoke uncertainty about the change/biosimilar	4.5	Strong
F. Assess the <u>information need</u> on the <u>individual patient</u> level	4.3	Strong
G. <u>Frame</u> the switch <u>positively</u> , and focus on equality of the treatments	4.7	Strong
H. Allow <u>room for deviation</u> in case a patient objects to switch	3.7	Moderate
* Participants expressed their level of agreement (LoA) on a five-point Likert scale, with 1 = strongly disagree to 5 = strongly agree. This column shows the calculated mean LoA.		
**Strong consensus: when at least 80% of participants agreed with the statement (yes/no) and the mean overall LoA was ≥ 4 on the Likert scale		
Moderate consensus: a mean overall LoA of ≥ 3.5 on the Likert-scale		
No consensus: a mean overall LoA of < 3.5 on the Likert scale		
HCPs: healthcare professionals		

5. DISCUSSION

Fifteen years after the first biosimilar approval in Europe, Belgium continues to lag behind in terms of biosimilar market competition compared to other European countries. While achieving high biosimilar uptake is not a goal in itself, stimulating biosimilar use is essential to unlock the full potential of biosimilar competition now and over the longer term. Instead of focussing on installing *ad hoc* and short-term cost containment measures, an integrated policy framework to foster a long-term healthy competitive climate is required (464).

Healthcare professionals are key stakeholders in any policy framework, since they are in charge of procuring, prescribing, switching and dispensing off-patent biologicals and biosimilars. The structured examination in this study of healthcare professionals' views on off-patent biological medicines' decision-making, use and switch management resulted in the generation of a concrete set of stakeholder-identified recommendations. The study findings may add to the recommendations proposed by two recent reports (154),(465) from the perspective of the healthcare professional as main stakeholder in the Belgian off-patent biologicals market with specific learnings regarding switch management.

First, study findings highlighted the need for *tailoring of policy measures* to the specific dispensing context and product category. For example, switching a subcutaneous administered biological requires more time from the involved healthcare professionals compared to intravenous administered products, due to possible differences in injection devices. Consequently, this should be reflected in an appropriate incentive scheme and support program. Also the dispensing context requires specific consideration as the incentive and decision-making structure for in-hospital and community pharmacy dispensed biologicals are distinct.

Second, a broad set of recommendations was formulated, indicating that healthcare professionals require policy actions on multiple dimensions. As mentioned barriers are multifactorial and often highly interlinked, with standalone measures unlikely to yield sufficient results (no "cherry-picking"). Therefore, an *integrated approach* has to be formulated. Although we underline the importance of a holistic policy framework, a prioritization can be helpful when implementing policy measures in practice. Based on the estimated feasibility of the recommendations and their estimated impact, we assigned recommendations a high, intermediate or low priority (Table 27).

Third, it became clear that *biosimilar use and switching is especially challenging in the ambulatory setting*. Because of the mandatory price reduction off-patent biologicals undergo after 12 years of reimbursement, or earlier if a biosimilar alternative enters the market before that time (450), differences in list price between reference biologicals and biosimilars tend to be small. While the system of mandatory price decreases in Belgium locks in substantial savings for the national health insurer, it may actually limit biosimilar market competition in the ambulatory setting. Whereas in the hospital context, tenders drive product decision-making and competition beyond list price, no such driver is available for products dispensed via the community pharmacy. Here, decision-making is

largely up to the individual physician. As a consequence of the small price differences between reference product and biosimilar, physicians are little motivated to prescribe a biosimilar or invest time in switching a patient under treatment to a biosimilar. Without clear and transparent savings for the healthcare system or a direct benefit for the prescriber or its patients, physicians are, as argued in this study, unlikely to increase biosimilar prescription. While indeed differences in list price between reference products and biosimilars indeed tend to be small, a 50% adoption of the biosimilars adalimumab and etanercept would still lead to yearly savings for the national health care budget of approximately €1,5 million and €4 million respectively (465). To optimize short term budgetary spending, whilst simultaneously ensuring sustainable competition long-term through the creating of a more attractive ambulatory market environment for biosimilars, clear push and pull mechanisms should be foreseen. Since the in 2019 financial incentive pilot, which aimed to increase the prescription of biosimilars etanercept and adalimumab in the ambulatory setting by means of offering a financial bonus at the level of the individual prescriber (453), no other incentives have been tested. Participants in this and other studies advocated for incentives that improve care rather than a personal financial compensation (115),(154),(255),(465). Benefit share models, in which savings are generally shared between the national health insurer or hospital and the healthcare professionals involved in biosimilar use, have been implemented in several European countries (32). Typically, such a benefit share model provides remuneration for additional staff who can assist with switch management (105),(466). Although immediate savings from increased biosimilar use are generally small in the ambulatory setting, increased biosimilar use should be strived for to reach a more dynamic market with multiple competitors over the longer term. To *change the status quo in ambulatory care*, physicians should be appropriately incentivized, which may require combining such a benefit share incentive with a prescription target or even introducing a temporary biosimilar market share quota. However, no consensus was reached for such a measure in this study, highlighting a certain degree of resistance among healthcare professionals potentially explained by the fact that it touches upon the physician's prescribing autonomy. Currently, biosimilars are part of the quota for prescribing of "cheap" medicines. However in its current form, since both reference and biosimilar medicines fall in the category "cheap" medicines because of the mandatory price decrease system, this measure is not really effective in driving biosimilar use (467). Pharmaceutical companies can also incentivize stakeholders to consider their product by for example creating benefits at the level of the patient, such as lowered patient co-payment or improvement to the product's administration device.

While in the hospital setting, tenders are a natural driver of product-decision making, benefit share agreements may still help to foster broader support among healthcare professionals. An example of this in the Belgian context is the managed switch program of inflammatory bowel disease patients in the regional hospital AZ Delta Roeselare. Here, part of the savings generated by the switch to an infliximab biosimilar went to increase nurse staffing to support patients with their treatment (105). While physicians underlined the importance of having specialist nurses to improve care for patients under treatment with biologicals on a continuous basis, it is important to note that benefit share

agreements in the context of stimulating biosimilar use will usually be *temporary in nature* to support a specific switching period.

Importantly and as outlined by multiple medical society position papers over recent years, physicians have *the responsibility* to consider the societal cost associated with their prescribing choices (460),(468),(469). When medicines with a similar efficacy and safety profile are available, the medicine that is less costly must be preferred (469). However, other steering/guiding mechanisms (see also below) may be needed to support healthcare professionals in making cost-effective prescribing choices. Generally, awareness should be raised about cost-effective prescribing and the role biosimilars have in creating a competitive market.

Fourth, physicians – while generally little motivated to consider a biosimilar or a switch in a non-tender driven setting – appear to be open to *shift towards newer versions of existing products, second-generation products and new therapeutic alternatives*. This finding is confirmed by a recent analysis of Belgian market data which demonstrated these type of shifts after loss of exclusivities of originator biologicals, and noted that at present these largely offset the savings generated after biosimilar market entry (412). In some cases the therapeutic added value of these newer and often more expensive alternatives may not be clearly established compared to the off-patent originator biological and biosimilar, especially relative to its higher price (460),(468),(469). Although the factors physicians consider when prescribing are not yet elucidated in a systematic manner, physicians' brand loyalty, low price sensitivity and the promise attached to innovation may possibly explain this behaviour. Notwithstanding that physicians have the *societal responsibility* to consider the best-value biological or most cost-effective option, physicians argued that there is a *need for structural guidance* and revisions to guide them with cost-effective prescribing. To this end, *considerations should extend beyond off-patent biologicals and associated biosimilar use and take the broader competing product availability into account*. Mandatory price decreases and biosimilar market entries alter the cost-effectiveness of a biological therapy. This should trigger a revision of reimbursement modalities within the broader therapeutic class and possibly even other competing product classes (which e.g. may result in alignment of reimbursement modalities or changes in treatment line) (470),(471), and be reflected in prescribing guidelines or prescribing software in order to offer prescribers a framework for rational prescription of medicines (154).

Fifth, while the increasing use of biosimilars in clinical practice and growing body of clinical data regarding switching was argued to have led to increased stakeholder confidence in biosimilars, uncertainties appear to remain, particularly in the context of multiple switching. *Hurdles associated with switching* in terms of both stakeholder uncertainty and practical feasibility should be addressed for all healthcare professionals involved. To mitigate for this, actions are recommended to focus on the following three pillars:

(i) Developing managed biosimilar introduction and switching protocols with patient communication strategies can help to provide a clear and structured framework to appropriately inform and assist healthcare professionals with biosimilar use and switch management. Specific

consideration should be given to the dispensing context. Besides building trust and practically supporting healthcare professionals, a managed switch program may be a successful strategy to counter the nocebo effect which is understood to lead to higher than anticipated discontinuation rates among patients (466),(472),(51),(473). Consensus was reached in this study on a set of guiding switch principles, which may shape such a managed switch protocol. In addition, switch management protocols and guidance materials have already been developed by professional associations in several other EU countries (104),(105),(383),(474) which can be leveraged in Belgium. For example in Ireland, in the context of their best-value biological Medicines Management Programme for TNF- α inhibitors, the Irish Health Service Executive (HSE) agency developed healthcare professional and patient support materials. More specifically, initiation and switching support documents, healthcare professional Q&A documents, switching letter templates, a patient information leaflet and detailed reports and information sheets on a product-specific level, including information regarding the injection device, are offered (474).

(ii) Clinical outcomes of switching between reference products and biosimilars, and increasingly of multiple switching, have been reported for several presently available products in a large number of scientific publications (51),(112). Data from both randomized controlled trials as well as from observational studies did not corroborate the voiced safety concerns with switching (51),(112). However, a number of real-world studies did demonstrate the need for nocebo effect mitigation when switching, underlining the importance of a managed switch approach with appropriate patient communication strategies (51),(475),(476),(477),(333). The available clinical data from switch studies should be, together with sharing of peer-to-peer experiences, leveraged in an aggregated and active way to inform healthcare professionals.

(iii) A more explicit position of the national medicines agency regarding biosimilar interchangeability and (multiple) switching should be made available. Regulators should act swiftly to provide a central uniform scientific position on biosimilar interchangeability to inform national policy making and clinical practice (280),(269). Similarly, clear and up-to-date position statements from medical associations regarding biosimilar use and switching are paramount in building trust among healthcare professionals.

Sixth, in the context of ensuring good stakeholder outreach, a *clear information dissemination strategy* should be devised. A central dedicated online platform for biosimilars could be developed, where all relevant information and stakeholder materials are integrated and made readily available for healthcare professionals and patients to consult. Such a central repository could be modelled to the example of the Australian 'biosimilar hub' website which is funded by the Australian government (478). Also here, the positions from the national medicines agency and professionals associations should be linked. This initiative could jointly be led by the national medicines agency and NIHDI, similar to the information campaign on biologicals including biosimilars which was launched in 2018 in Belgium (145),(147).

Seventh and ultimately, combining above mentioned discussion elements, Belgium should strive to set out a cohesive policy framework which includes a *clear and pro-active best-value biological implementation roadmap* per therapeutic area which can be applied to timely prepare for new biosimilar market entries. A framework for such a Biosimilar/Best-Value Biological Adoption Roadmap is offered in Figure 25. Biosimilar/Best-Value Biological Adoption Roadmap, relevant for the Belgian context. Timely preparation and stakeholder engagement is essential to support stakeholders, anticipate and respond to challenges and stimulate on-set competition. Best-practice examples are available in other European countries, such as Ireland, the UK and Denmark who developed pro-active biosimilar/best-value biological implementation frameworks, with clear steps, early stakeholder dialogue and assigned responsibilities to the different stakeholders involved (383),(396),(399),(474),(479),(480),(481). The term best-value biological is used to emphasize that rather than high biosimilar uptake, the goal is to achieve healthy competition and sustainable market dynamics that ensures affordable access for patients to biological therapies.

As put forward by study participants, consulting healthcare professional stakeholders in the policy preparation stage allows to gather insights from the field, which may lead to policy measures that are more in-tune and adjusted to realities in clinical practice. However and importantly, stakeholder consultation should be done early on and not restrain or delay policy decision-making (448).

In terms of study strengths and limitations, the following elements are relevant to take into account. The NGT is a recognized consensus method to identify priorities of stakeholders and develop recommendations for integration in healthcare policy making (454),(455). Compared to individual stakeholder interviews, the NGT allows participants to exchange views on a group level, which consequently allows to deepen the discussion with input from different viewpoints. Compared to standard focus group discussions, which also stimulate the exchange of views, the NGT allows for a more balanced contribution from and consideration of views of all study participants because of the individual grading steps (two rounds of written feedback) and structured discussion approach by calling pro-actively upon each person to provide feedback (456),(482).

A purposive sample of stakeholders with relevant expertise was invited to generate a range of ideas and solutions regarding the study topic (454),(482). A heterogeneous participant sample was assembled, with the purpose of reflecting the considerations of the broader spectrum of healthcare professionals who are exposed to biosimilars. The interaction between healthcare professionals representing different medical specialities, dispensing contexts and regional and academic hospitals allowed to formulate nuanced recommendations and underlined the importance of tailored approaches to the product and dispensing context. Consequently, it became clear that policy measures should strive beyond a one-size fits all policy approach and tailor to these specific needs which the study design allowed to differentiate for. Although participants with a diversity in therapeutic and dispensing context were invited, it is worth mentioning that no HCPs from the French-speaking region of Southern Belgium, Wallonia, partook. Where general challenges are

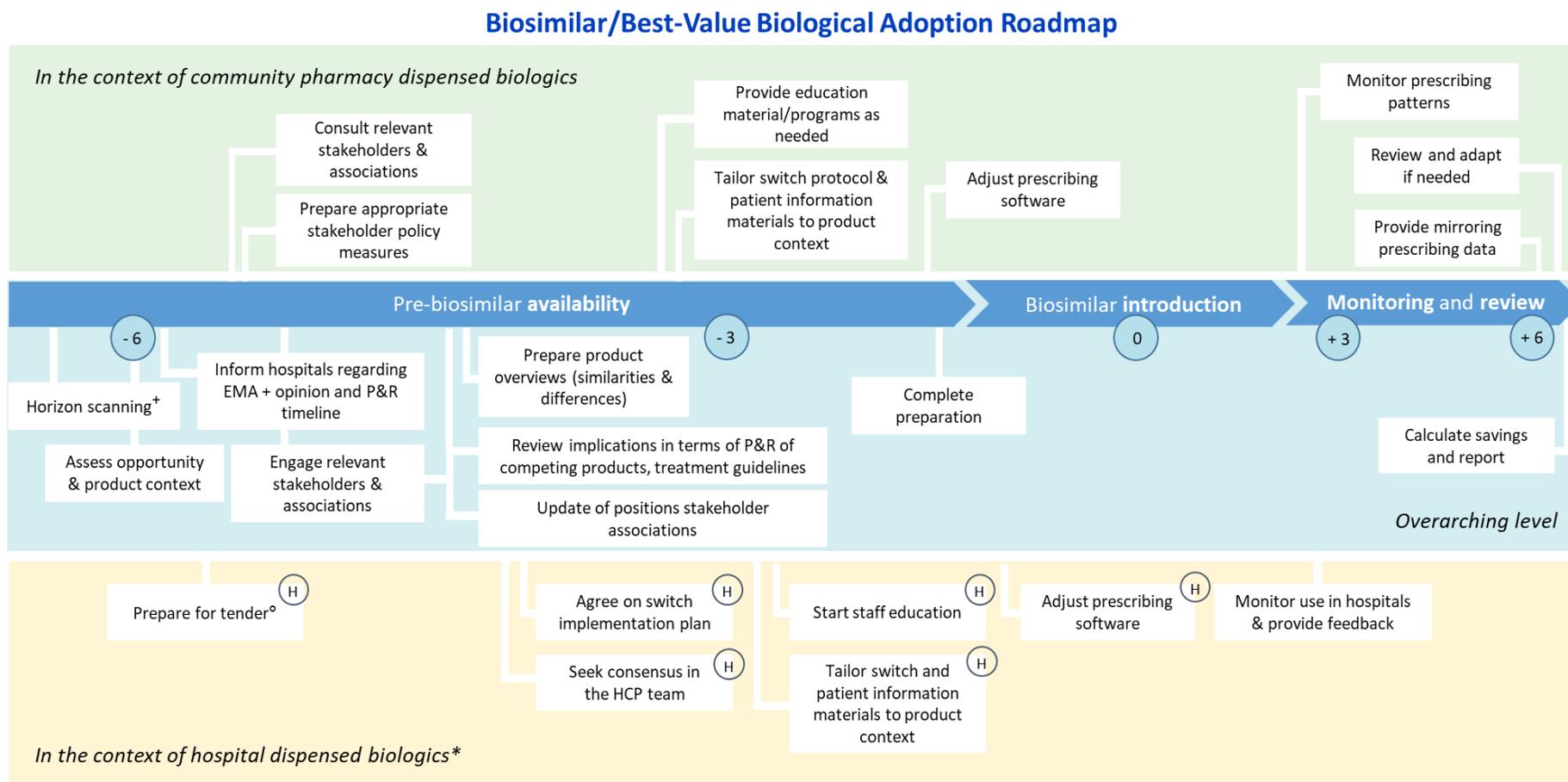
expected to be similar across Belgium, regional differences in attitudes may exist. As with qualitative studies in general, study results are bound to the participant sample and study context.

6. CONCLUSION

In conclusion, healthcare professionals experience challenges with biosimilar use and switch management in Belgium. There is a lack of structural guidance and tangible benefits or steering mechanisms for healthcare professionals, particularly so for products dispensed in the ambulatory care. An integrated policy framework, with a clear, best-value biological roadmap and implementation plan that supports Belgian healthcare professionals with biosimilar use and switch management is needed in order to support a more competitive and long-term sustainable off-patent biological medicines climate.

FIGURE 25. BIOSIMILAR/BEST-VALUE BIOLOGICAL ADOPTION ROADMAP, RELEVANT FOR THE BELGIAN CONTEXT

Figure developed based on the Cancer Vanguard NHS Biosimilar Adoption Process Timeline (479), applied and tailored to the Belgian context



-6 months: around time of EMA positive opinion, -3 months: around time of EC granting marketing authorization, start of national P&R dossier (3 month procedure, could be advanced to start at time of EMA positive opinion), 0: biosimilar available on market (P&R concluded/start tender contract), * Subject to tenders, ⁺Continuous process, ^oto stimulate on-set competition upon patent expiration of the originator, the opening of a tender should be made possible prior to patent expiration of the originator ("Bolar" exemption to start tender preparation prior to expiration, for the purpose of start of enabling timely contract start/product delivery upon patent expiration), (H) : hospital-led

PART 5

CONCLUDING DISCUSSION

1. GENERAL DISCUSSION: HOW WERE THE THESIS OBJECTIVES ACHIEVED

Biosimilars and the competition they introduce into the off-patent biological medicines market hold the promise of relieving pressured healthcare budgets and increasing patient access to biological therapies. However, at present, biosimilar adoption faces several challenges, limiting their competition potential and therefore also the associated benefits for healthcare systems and patients. Consequently, questions have risen on how to unlock the full potential of biosimilars and build a more sustainable off-patent biological medicines market environment with continued competition now and in the future.

This thesis offers insights into the barriers and drivers of biosimilar adoption. It does this through a multifaceted lens, integrating multi-stakeholder informed learnings from a clinical, regulatory, and policy angle. Proposals on how to address the identified barriers are put forward and best practices to leverage biosimilar competition in a more sustainable way are shared. This with the ultimate goal to help biosimilar competition reach its full potential and contribute to a more sustainable off-patent biological medicines market.

This dissertation adds to the state of the art on the introduction and use of biosimilars in Europe. The insights and recommendations put forward intend to foster the multi-stakeholder debate on biosimilar medicines, help healthcare decision-makers with the development of coherent biosimilar policy making, and simultaneously support healthcare professionals and patients with biosimilar use in clinical practice.

Here, a concluding discussion on the PhD project and how the thesis objectives were achieved is provided.

1.1 INSIGHTS ON STAKEHOLDER KNOWLEDGE AND PERCEPTIONS OF BIOSIMILARS

The first objective was to investigate stakeholders' knowledge and attitudes on biosimilar medicines and their use in clinical practice, and explore multi-stakeholder informed solutions to overcome barriers identified in this context.

First, the structured literature review in Chapter 3 showed that the knowledge healthcare professionals and patients have on biosimilars is generally low to moderate, and that they have considerable uncertainties and misconceptions regarding biosimilar approval and their use. This observation appears to persist across different stakeholder groups, therapeutic areas, care settings, and geographical regions. While improvements over time were observed, healthcare professionals' and patients' knowledge and confidence in biosimilars remained largely unsatisfactory over time. While arguably only those patients that come in contact with biosimilars need to be informed, it is paramount that healthcare professionals have a good understanding so they can make informed treatment decisions and adequately counsel patients regarding their biological therapy. Furthermore, review results highlighted that, whilst there is an overall high research interest in the topic of biosimilar stakeholder knowledge and perceptions, research was lacking on the knowledge

and attitudes of nurses, despite them playing a substantial role in biosimilar introduction in clinical practice. A similar shortfall was observed for healthcare professionals in the ambulatory care setting (i.e. general practitioners and community pharmacists), notwithstanding the growing availability of biosimilars outside of the hospital. The survey conducted in Chapter 5, zooming in on the preparedness of Belgian healthcare professionals in the ambulatory care setting to prescribe and dispense biosimilars, highlighted a considerable need for not only targeted educational measures to increase understanding of biosimilars, but of biological medicines more in general. The statistical analysis demonstrated that younger healthcare professionals are not necessarily better trained to prescribe and dispense biosimilar medicines compared to their older peers. As such, the results argue for an examination of the existing educational outreach and curricula on biological including biosimilar medicines, both for current as well as the future generation of healthcare professionals (i.e. medical and pharmacy students).

Second, based on qualitative, semi-structured interviews with various stakeholders (physicians, pharmacists, nurses, patients and regulators), a series of drivers was identified that may explain the low level of knowledge and uncertainties on biosimilars (see Chapter 3). In summary, these drivers include (i) a lack of understanding about the regulatory and scientific concepts underpinning biosimilar approval and their safe use including the reduced role of clinical testing, (ii) a lack of understanding of biologicals in general, (iii) different terminology and regulatory concepts between jurisdictions leading to misconceptions, (iv) (industry-driven) misinformation, (v) a lack of effective communication strategies, (vi) a lack of consistency in the available information, and (vii) a lack of clear guidance and practical information about biosimilars and their use.

Third and final, based on the drivers identified, actionable recommendations were proposed to build stakeholder trust in biosimilars (see Chapter 3 and below recommendations in section 2). In general, concerted action on a European and national level was argued needed, requiring close collaboration and coordination between the different actors involved.

1.2 INSIGHTS ON THE ADOPTION OF BIOSIMILARS IN CLINICAL PRACTICE

In this section, we discuss how the first and also the clinical component of the second objective (“to assess clinical challenges that may impact biosimilar adoption”) were addressed.

Besides a general lack of knowledge of and hesitation towards biosimilars (see section 1.1), three main barriers for biosimilar use in clinical practice were identified: (i) uncertainties about the safety of switching (“can a patient under stable treatment with the reference product safely switch to the biosimilar?”), (ii) a lack of practical support on how to initiate/switch to a biosimilar (“how to initiate/switch and communicate with the patient?”), and (iii) a lack of motivation to use biosimilars (“why would I initiate a biosimilar/switch my patient? What is in it for me/us?”) (See Chapters 3, 4 and 11).

The systematic literature review of clinical switch studies in Chapter 8 investigated the uncertainty around the safety of switching between reference products and biosimilars, with the aim of aiding

informed decision-making in clinical practice. From a heterogeneous but vast body of evidence (over 170 switch studies consisting of RCTs, open-label extension studies, observational studies, and registries), no relevant differences in terms of clinical outcomes pre- and post-switching or between switched and non-switched patient groups were found. Although most studies were not designed to identify differences in rare adverse events, the combined body of studies support that there are no indications that switching between a reference product and its biosimilar would be associated with any particular safety, efficacy or immunogenicity issues. At the same time, the placebo effect emerged as an important aspect to mitigate for when switching. In a number of open-label, observational studies (studies in which patients are aware of being switched), a higher discontinuation rate was reported after switching. Negative patient perceptions may lay at the root of this, as drop-out was mainly attributed to worsened patient reported outcomes that could not be substantiated by objective clinical or laboratory parameters. Consequently, while there is no evidence to substantiate an inherent risk with switching between original biologicals and biosimilars, attention should be paid to mitigate possible placebo effects when switching in clinical practice.

In Chapter 4, drivers and possible solutions to address healthcare professional and patient concerns regarding switching were elucidated through multi-stakeholder expert interviews. In summary, recommendations included: (i) disseminate clinical switch data and share positive switch experiences, (ii) avoid top-down organized switching, (iii) allow motivated exceptions on an individual patient level, and (v) ensure adequate switch management and patient communication.

Whereas the large body of clinical evidence on switching from reference product to biosimilar, together with increasing practical experience, translated in a growing trust in a single switch (see Chapters 4 and 11), the evolving and increasingly complex biosimilar landscape raised new questions on multiple switching and switching between biosimilars of the same reference product (see Chapters 4, 6 and 11). Especially in tender-driven contexts and among patients who are under chronic treatment with a biological, multiple exchanges may be likely. Data on multiple switching (including RCT data) and on switching between biosimilars of the same reference product (few real-world data) are progressively becoming available, and no unexpected findings or concerns have been observed. To support physicians in treatment decision-making, it is important that regulators but also medical societies elaborate on multiple switch scenarios beyond that of a single switch in their positions and recommendations (Chapters 4, 7, 11).

While switch management and patient communication were found important to guide patients with a switch and mitigate for possible placebo effects (see Chapters 4, 8), a lack of *guidance on how to switch and communicate with the patient* was reported (see Chapters 3, 4 and 11). Patients reported to rely heavily on the physician and her/his decision to initiate or switch to a biosimilar (see Chapters 3, 4), and as such, building patient trust should start at the level of the healthcare professional. Physicians – and the broader care team – need to be well-trained and confident in the safe use of biosimilars, so they can in turn transmit this trust to the individual patient. The need for practical switch guidance and patient communication strategies was addressed in Chapters 4 and 11. In

Chapter 4, practical considerations and concrete strategies on how to manage a switch and communicate biosimilar initiation or switching to a patient were formulated. In Chapter 11, consensus on the main principles for switch and patient communication strategies was reached among a group of healthcare professionals (see also below recommendations in section 2).

In Chapters 4, 5 and 11, we explored the *willingness and motivations of stakeholders to use biosimilars*. In Chapter 4, we did this on a European level by consulting stakeholders from across European Member States and where possible those with pan-European insights. In Chapters 5 and 11, we zoomed in on the insights of Belgian healthcare professionals to derive context-specific insights. Initiating a biosimilar requires an active behavioural change from prescribers, as it is more convenient to customarily continue using the originator biological they are familiar with. This familiarity and convenience argument, together with possibly a perceived uncertainty regarding the efficacy and safety of biosimilar use (also termed as “familiarity-”, “status quo-”, and “risk avoidance” biases in behavioural economics (483),(484)) might result in physician inertia to change and as such impede biosimilar prescribing. Furthermore, the value offering of biosimilars may not be clear to all. This effect of low willingness to opt for a biosimilar may be larger in contexts where biosimilar use requires considerable effort of the prescriber and/or the broader healthcare professional team, i.e. when biosimilar use involves switching a patient from reference to biosimilar, *vice versa*, or between biosimilars (See Chapters 4, 11). Furthermore, this effect may be more pertinent to take into account in decision-making structures that are solely or predominately physician steered (see Chapter 11). Whereas in the in-hospital setting, tenders and formularies generally act as a natural driver of product decision-making, such a mechanism may be absent for biological medicines dispensed in the ambulatory care setting (generally not subject to procurement mechanisms, but steered by physician choice). While prescribers have a societal responsibility to consider the societal cost associated with their prescribing choices, these factors, amongst others, may play a role in their willingness to prescribe biosimilars.

From the qualitative expert insights in Chapter 4, several ways to improve the willingness of stakeholders to use biosimilars were identified. These can largely be categorized under non-tangible/in-direct and tangible/direct incentives. Examples of non-tangible/in-direct incentives include amongst others creating awareness on the benefits from biosimilar introduction, transparent reporting on savings and how these are reinvested in the healthcare system, and increasing familiarity with biosimilar use through peer-to-peer experience sharing. Besides offering in-direct incentives, stakeholders advocated to combine this with a tangible (direct) incentive to compensate for the additional time and workload induced by a switch. Such a tangible benefit may take the form of a benefit share agreement. Rather than offering a personal monetary compensation, a benefit share with the goal of improving care was generally considered more appropriate (e.g. budget for additional staff) (see Chapters 4, 11 and also below recommendations).

Besides the qualitative insights in Chapter 4, several studies identified in the literature review in Chapter 3 described that physicians showed increased willingness to use biosimilars if this would

result in increased patient access, highlighting that information on the benefits derived from biosimilars use can be a motivational factor for adoption. As such, it proves important to communicate clearly about the value proposition of biosimilars and that beyond (direct) cost savings, biosimilar competition can bring various downstream benefits. As discussed in Chapter 4, and further elucidated throughout Chapters 9 and 10, these include: (i) increased patient access to biological therapies (earlier initiation of biological in treatment pathway or access for a greater number of patients), (ii) increased patient access to innovative therapies (within the same therapeutic area or outside, e.g. by increased cost-effectiveness combination therapy (485)), (iii) offering of additional services and incremental product innovation that can improve product administration and patient satisfaction (e.g. improvements in delivery device, administration route, available concentrations), (iv) broader product innovation (e.g. development of second-generation products or innovative alternatives within or outside the therapeutic area).

In addition to offering new incentives, reviewing existing incentive streams, and readjusting those that are not aligned with using the economically most advantageous product, might perhaps be equally or even more important. Throughout the project several mentions were made of misaligned incentives that favour a higher priced product rather than the most cost-effective one, either on the level of the individual prescriber, the clinical department or the procurement unit (Chapters 9, 11).

1.3 REGULATORY INSIGHTS

To address the regulatory component of the second objective (“*to assess regulatory challenges that may impact biosimilar adoption*”), we conducted two main studies (see Chapters 6 and 7).

As discussed earlier, Chapter 3 identified a lack of understanding in the clinical community of the biosimilar development pathway. Compared to the development of a new biological, there is less emphasis on clinical studies for a biosimilar, which is understood by some stakeholders as a development shortcut. With a view to elucidate this for healthcare professionals, Chapter 6 laid out the biosimilar development pathway and in particular shed light on the biosimilar clinical development guidelines for (mAb) biosimilars. More specifically, in view of the emerging arrival of the first mAb biosimilars in oncology, we decided to review the available clinical data of the different trastuzumab biosimilar candidates (that were in clinical development at the time of the study), and compare the parameters of their clinical development programs with the EMA biosimilar (clinical) development guidelines. This study elucidated how clinical studies for biosimilar candidates, while following a different design than in traditional drug development, are designed to confirm biosimilarity between the candidate and the reference product, and not to independently establish clinical efficacy and safety. Furthermore, the study showed differences in clinical trial design, patient population and primary endpoint between the clinical development programs of the different candidates. This underlined that biosimilar evaluation involves a case-by-case assessment based on the totality of evidence for biosimilarity, of which the comparative clinical efficacy trial is one and a confirmatory piece of the puzzle. With clinical data requirements in biosimilar development expected to continue to reduce (allowed for by the accumulated experience with biosimilar

evaluation together with analytical advancements ((19),(486),(487)), clarifying the biosimilar development and regulatory approval pathway to stakeholders will continue to be paramount to build trust in the robust evaluation of biosimilars.

As reported in Chapters 3 and 4, access to reliable information on biosimilars and the scientific principles underlying their development, approval, and appropriate use are essential to enable biosimilar adoption and use in clinical practice. This includes the availability of guidance on interchangeability and the related practices of switching and substitution. The study in Chapter 7 revealed that, despite strong EU-level regulatory biosimilar information, information and guidance on biosimilars and their use differs considerably across national regulatory agencies in Europe in terms of availability, extent, and content. These differences may be explained by the fact that providing guidance on interchangeability, switching, and substitution falls outside the otherwise centrally organized evaluation and approval of biosimilars, and is managed at Member State level. Study results indicated that strong involvement in EU-level biosimilar regulatory activities (i.e. as national rapporteur/co-rapporteur for biosimilar MAA or BMWP member) seemingly correlates with the availability of more elaborate information and guidance on the national level. According to the findings reported in Chapters 4 and 11 and from the qualitative part of the study in Chapter 7, heterogeneity between positions of national regulatory agencies, together with the absence of a clear EU-wide position on interchangeability, may instil uncertainty among stakeholders about the safety of an exchange between a reference product and biosimilar. While prescriber practices across Member States are expected to show a certain degree of heterogeneity as these practices are shaped in the context of their respective healthcare systems and medical culture (i.e. frameworks to allow for physician-led switching and/or pharmacy-led substitution), a clear and common position on interchangeability from a scientific viewpoint is warranted across Member States. Furthermore, the study in Chapter 7 showed a large opportunity to expand information on biosimilars and the science underpinning their evaluation and safe use at the Member State level.

In addition, Chapter 7 illustrated that whilst most Member States do not allow or implement substitution for biologicals on a large scale, this may change in the near future as legislative changes are foreseen in a few countries in this regard. In fact, in Germany, substitution for biologicals is expected to become reality in 2022. Also in Finland, the Finnish Medicines Agency, Fimea, has been making careful preparations for pharmacist-led substitution (488). As reported in Chapters 4 and 5, healthcare professionals responded to be open towards substitution for biologicals, on the condition that the prescriber would be informed about the change (i.e. non automatic or with feedback loop to prescriber), and that the prescriber would be able to make motivated exceptions on a patient individual level. On the other hand, stakeholders argued that introducing substitution might be too premature since the level of trust in biosimilars is considered still fragile. Besides psychological considerations, organizational and policy barriers are important to consider (e.g. efficient pharmacist-physician communication infrastructure is needed to support roll-out). Another important prerequisite is the need for education and training of community pharmacists to ensure proper patient counselling and switch management (see Chapter 5). Hence, it is clear that the

discussion on interchangeability, switching and substitution is not only scientific in nature but also requires important psychological, educational, organizational, and policy considerations (see Chapters 4, 7, 11).

1.4 TENDER AND POLICY INSIGHTS

The third objective of this PhD research program was to study biosimilar procurement and market entry policies and explore proposals for more sustainable practices.

Chapter 9 revealed that tenders are a key driver in biosimilar adoption and offer the opportunity to generate significant savings while actively stimulating competition between the originator and biosimilar(s). While tendering is widely applied across Europe in the context of off-patent biologicals procurement especially for those used in the in-hospital setting, their organization was found to vary considerably on multiple variables including the level on which they are organized (central *versus* regional *versus* hospital group *versus* individual hospital level tendering), the number of awarded winners (single winner *versus* multiple winner tender), and the award criteria on which the bids are evaluated (price only *versus* price plus additional product-related criteria). The tender level and design may impact biosimilar uptake, the competitive pressure level, as well as the obtained discount level. For example, countries with a national tender system generally report a high and rapid biosimilar uptake, together with significant discounts, as suppliers are eager to win the total market volume, creating strong competitive pressure in the tender. While central tender organization holds various benefits, including consolidated tender expertise, consolidated workload and coordination opportunity, national tenders - especially when these award only one single winner - may decrease supplier plurality in the market, and as such result in reduced market competition, especially over the longer term. In other words, centralization and coordination should be stimulated but without consolidation of market volume to a single winner, i.e. central organization should go hand in hand with dividing the market among multiple suppliers (multi-winner tender for national tenders, or coordinated, multiple single winner tenders on a regional level). A focus on single winner, price-only tendering, together with the existence of originator favouring tender practices (e.g. blocking contracts with the originator, steering of the tender outcome) were identified as elements that may limit competition from and the market opportunity for biosimilars. Furthermore, increasing competitive product differentiation on elements beyond price comes with a specific set of challenges (i.e. not routinely included in tenders, questions on how to formulate and include them in tenders, steering of tender outcome via non-price criteria, and identification of truly differentiating criteria). These challenges underscore the need to develop guidance on the (appropriate) inclusion of award criteria beyond price to support stakeholders and foster their inclusion in tender procedures. Overall, Chapter 9 highlighted the complex balance between optimizing short-term savings and creating a sustainable competitive market environment over the long run. Five main avenues for more sustainable off-patent biological and biosimilar tender practices were proposed. For each of these avenues, detailed recommendations were derived. While there is no one-size-fits-all approach for sustainable tender practices, pro-active planning,

early stakeholder engagement and consolidation of tender expertise are among the identified best-practices.

Building further on the identified need for guidance with product selection making, we reviewed in Chapter 10 possible award criteria with the aim of providing a practical framework to support transparent product selection making. Three main categories of criteria besides price were identified (product-driven, service-driven and patient-driven criteria), and discussed.

In Chapter 11, we zoomed in on the off-patent biological and biosimilar landscape in Belgium with the aim of developing consensus-based recommendations for policy making. The findings of this study argue for the development of an integrated policy framework that guides and incentivizes stakeholders with biosimilar use and switch management. Furthermore, study findings exemplified the need to extend policy making beyond just stimulating biosimilar uptake, tailor policy measures to the dispensing and product-specific context, and mitigate for shifts to higher priced, therapeutically equivalent product alternatives. In addition, the study indicated that the implementation of cost-containment measures that focus on mandatory price discounts of the originator at the time of biosimilar market entry may, while generating immediate savings, in fact restrict competition and limit the incentive for biosimilar uptake.

Finally, as identified in Chapters 3 and 9, market competition strategies from originator manufacturers may hinder the entry of biosimilar competitors, for example through a negative framing of biosimilar concepts, or by impacting the level playing field in tenders via blocking contracts or steering. This (anti-)competitive behaviour may warrant the scrutiny of competition authorities (as observed in Belgium and the Netherlands), and active mitigation by other stakeholder groups.

2. RECOMMENDATIONS

In this section, we provide recommendations to overcome main challenges for biosimilar adoption, and by extension support a long-term sustainable off-patent biological medicines market with continued biosimilar competition. Our recommendations are built on the integrated knowledge and insights from the individual studies of this project (Objective 4) and target four key pillars:

- i. Build stakeholder understanding of and confidence in biosimilars
- ii. Support stakeholders with biosimilar use and switching in clinical practice
- iii. Strengthen one-voice regulatory guidance on biosimilar use
- iv. Develop sustainable biosimilar policy and procurement practices

For each of these pillars, a specific set of recommendations is put forward. The recommendations in this Chapter are formulated in such a way that they can be read on a standalone basis. An overview is provided in Table 29.

TABLE 29. AN INTEGRATED PATH FOR IMPROVED BIOSIMILAR ADOPTION & SUSTAINABLE COMPETITION

4 MAIN PILLARS	RECOMMENDATIONS
<p>I. Build stakeholder understanding of and confidence in biosimilars</p>	<ol style="list-style-type: none"> 1. Ensure that correct and consistent (one-voice) information is available for stakeholders <ol style="list-style-type: none"> A. Foster cooperation between the EMA & national medicines agencies B. Make correct & trustworthy information more easily retrievable C. Invest in information & education on biologicals more general 2. Build trust in the information available <ol style="list-style-type: none"> A. Foster partnerships between regulators & stakeholder associations B. Leverage better peer-to-peer experiences & position statements 3. Ensure information is effectively disseminated to reach the target stakeholder groups <ol style="list-style-type: none"> A. Develop effective information dissemination strategies B. Extend information & education to the broader HCP community C. Review & strengthen curricula of future HCPs 4. Train HCPs to ensure clear and consistent patient communication
<p>II. Support stakeholders with biosimilar use and switching in clinical practice</p>	<ol style="list-style-type: none"> 1. Leverage evidence base from existing clinical switch studies actively to build trust and inform use 2. Support HCPs with structured switch management 3. Provide HCPs with product selection making and rational prescribing guidance 4. Create demand-side stakeholder incentives
<p>III. Strengthen one-voice regulatory guidance on biosimilar use</p>	<ol style="list-style-type: none"> 1. Create a common European scientific position on biosimilar interchangeability 2. Improve clarity and consistency of regulatory guidance on biosimilar use & switching at national level
<p>IV. Develop sustainable biosimilar policy and procurement practices</p>	<ol style="list-style-type: none"> 1. Create a holistic, multi-stakeholder policy framework for sustainable biosimilar competition <ol style="list-style-type: none"> A. Implement policy measures in an integrated way B. Involve all stakeholders closely throughout biosimilars policy making & implementation 2. Foster competition for long-term sustainable markets <ol style="list-style-type: none"> A. Implement policy measures that stimulate long-term competition B. Focus on level of competition, evolution in treatment costs, and patient access rather than uptake C. Take the broader competitive landscape & value offering into account 3. Construct sustainable tender practices that ensure a level playing field & stimulate competition 4. Develop a pro-active biosimilar implementation plan 5. Tailor policies to market and product specific context

2.1 RECOMMENDATIONS TO BUILD STAKEHOLDER UNDERSTANDING & CONFIDENCE

One of the foundations to support biosimilar use is to ensure that all involved stakeholders, including healthcare professionals and patients, are well-informed about biosimilar medicines. To this end, there is a need to invest in effective information strategies and appropriate resources to support this. Below, we detail multiple possible actions.

2.1.1 ENSURE THAT CORRECT AND CONSISTENT (ONE-VOICE) INFORMATION IS AVAILABLE FOR STAKEHOLDERS

2.1.1.1 FOSTER COOPERATION BETWEEN THE EMA & NATIONAL MEDICINES AGENCIES

As shown in Chapter 7, there are important gaps and differences in the availability and extent of information on biosimilars offered by national medicines across Member States. A closer collaborative framework between the EMA (BMWP, EMA Biosimilar Matrix) and the national medicines agencies could strengthen information dissemination from the central to the national level, and allow for better leverage of the healthcare professional and patient information materials developed by EMA/EC locally. In addition, closer cooperation between the different national medicines agencies may help to further ensure there is clear, one-voice regulatory information on biosimilars across Europe. In addition, closer collaboration between regulators may stimulate the exchange of biosimilar best practices among Member States, and result in coordinated action to respond to biosimilar misinformation and queries that emerge at the national level (Chapter 3). As a final advantage, it may facilitate the leverage and transfer of EU level biosimilar expertise across the European regulatory network.

In terms of concrete initiatives to foster this collaboration, the recent establishment of the Heads of Medicine (HMA) Biosimilar group, which is composed of representatives nominated by interested national medicines agencies and an EMA representative, is an important step forward (276),(277).

2.1.1.2 MAKE CORRECT & TRUSTWORTHY INFORMATION MORE EASILY RETRIEVABLE

Biosimilar misinformation is widespread, and the breadth and heterogeneity of the information available on biosimilars makes it challenging for stakeholders to access correct and reliable information (Chapters 3, 7). Therefore, developing and providing easy access to independent, evidence-based information is crucial to counter this and enable building trust in biosimilars and their use.

Regulators and other stakeholder groups have already invested in developing clear and reliable information materials about biosimilar medicines and the scientific concepts underpinning their approval. Yet, this information may not be easy to retrieve for everyone and may as such insufficiently reach the target stakeholder groups (Chapters 3, 7). A centralised, European-led (EC, EMA) repository for healthcare professionals and patients on biosimilar medicines could serve as central go-to information hub, with one-voice, factual, and industry-independent information on biosimilars that is in line with the latest scientific evidence and best-practices. Such central

information hub is already in operation for several years in Australia [19], and may serve as a blueprint. Since guidance and practices regarding biosimilar use may differ between Member States, the website should link to the websites of the national regulatory agencies and websites of other relevant national stakeholders. Creating such a central hub will enable stakeholders to efficiently retrieve information needed to support their local information and education initiatives.

Secondly, the European Public Assessment Report, which contains information on product-individual level on how and on which data the product was evaluated by the EMA, may be leveraged more actively by creating awareness on its existence, and especially the dedicated discussion section on biosimilarity in the assessment report itself (e.g. by providing this as a more user-friendly excerpt in addition to the full report) (Chapter 7).

2.1.1.3 INVEST IN INFORMATION & EDUCATION ON BIOLOGICALS MORE GENERAL

Since misconceptions about biosimilars are often grounded in a general lack of knowledge of biological medicines (Chapters 3 and 5), education initiatives on biosimilars should go hand in hand with covering biological medicines more broadly. Informing stakeholders, and in particular healthcare professionals, on the key features of biologicals and their manufacturing process (e.g. inherent variability, occurrence of manufacturing changes over the product lifecycle, the comparability exercise) may contribute to a better understanding of biosimilar medicines and the biosimilarity concept.

2.1.2 BUILD TRUST IN THE BIOSIMILAR PATHWAY

2.1.2.1 FOSTER PARTNERSHIPS BETWEEN REGULATORS & STAKEHOLDER ASSOCIATIONS

The biosimilar pathway is generally difficult to understand for healthcare professionals. Especially the reduced clinical testing compared to that of a reference product challenges healthcare professionals' trust in biosimilars (Chapters 3, 6, 7). To build confidence in biosimilars, the biosimilar approval pathway, and how the clinical development of a biosimilar is tailored to meet the licensing requirements should be clarified to healthcare professionals (Chapter 6). Instead of developing new materials, there are several high-quality information sources with clear information on biosimilars and the science behind the regulatory evaluation readily available that can be used or repurposed. To leverage the available information to the different target stakeholder groups, regulatory authorities should partner with scientific stakeholder organizations. In addition, such partnership may result in the development of stakeholder position statements that reflect trust in the approval process of biosimilars and their use in clinical practice. Whereas EMA is best suited to continue to engage with stakeholders on the supranational level (e.g. with European medical and patient associations), national medicines agencies should similarly seek to actively engage with healthcare professional and patients associations on the local level.

2.1.2.2 LEVERAGE BETTER PEER-TO-PEER EXPERIENCES & POSITION STATEMENTS

Professional stakeholder organizations have a prominent role in building trust in biosimilars and their use (Chapters 3, 5 and 7). Both physician and pharmacist stakeholders prefer information on biosimilars to come from within their own stakeholder group (Chapter 5). As such, up-to-date biosimilar position statements from scientific stakeholder associations, endorsing regulatory concepts and the use of biosimilars, are key. Furthermore, the integration of biosimilars in clinical guidelines (on pan-EU and national level) is an important tool to enable greater biosimilar endorsement. Importantly, attention should be paid to keep these guidelines up to date and reflect changes to clinical practice resulting from biosimilar introduction (e.g. earlier use of biological in treatment pathway). Also on a more local level, key opinion leaders have an essential role in sharing peer-to-peer experiences with biosimilar use given they are a trusted source of information for their colleagues (Chapters 3, 8).

2.1.3 ENSURE INFORMATION IS EFFECTIVELY DISSEMINATED TO REACH THE TARGET STAKEHOLDERS

2.1.3.1 DEVELOP EFFECTIVE INFORMATION DISSEMINATION STRATEGIES

Efforts made by regulators and stakeholder associations to develop clear educational materials on biosimilars can only be impactful if these reach the healthcare professionals and patient on the front-end. In this context, close cooperation is needed between stakeholder groups (Chapters 3, 7). This may materialize under the form of partnerships between stakeholder associations (cfr. earlier), tailored education strategies that target those that (will) come in contact with biosimilars, and active support of educational programs by governmental bodies.

2.1.3.2 EXTEND INFORMATION & EDUCATION TO THE BROADER HCP COMMUNITY

Whereas information and education strategies have historically focussed on healthcare professionals active in the hospital context (in particular physician specialists and hospital pharmacists), it is important that going forward this is broadened to include general practitioners, community pharmacists, pharmacy technicians and nurses. General practitioners, community pharmacists and pharmacy technicians have an increasingly important role in counselling patients with biosimilar use, as more biosimilars (e.g. biosimilars for insulin or subcutaneous administered anti-TNFs) are becoming available in the ambulatory care setting (Chapters 5, 11). Whilst broadening information and training to stakeholders in ambulatory care is essential in general, it may be even more so in Member States that are considering pharmacy-led substitution of biological medicines (Chapters 5, 7). Similarly for nurses, who evidently have an essential role in switch management and patient communication, information and education strategies should be readily available (Chapter 4). The ESNO switch management guide, published in 2018 and translated in multiple European languages in 2019, is a useful resource in that respect (489).

2.1.3.3 REVIEW & STRENGTHEN CURRICULA OF FUTURE HCPS

Whilst it is vital to continuously upskill current healthcare professionals on emerging therapies including biosimilars, education should start early on. Future healthcare professionals, i.e. medical, pharmacy and nurse students, should be trained on biological including biosimilar medicines as part of their core curricula. University curricula should be reviewed and where needed revised to ensure future healthcare professionals are appropriately educated on biological including biosimilar medicines (Chapter 5). In addition, these curricula should cover the broader context of medicine prices and rational prescribing.

2.1.4 TRAIN HCPS TO ENSURE CLEAR AND CONSISTENT PATIENT COMMUNICATION

Clear and consistent communication with patients is considered key to build trust, improve patient acceptance, and mitigate for the nocebo effect (Chapters 3, 4, 8, 11). Real-world, clinical switch studies have demonstrated that patient communication can have an important impact on treatment persistence and patient-reported outcomes. Clear and consistent patient communication requires first and foremost that all healthcare professionals along the care pathway are well-informed about biosimilars and are trained on how to communicate with and transmit their confidence in biosimilar use to the patient (Chapter 4). As derived from Chapters 4 and 11, best-practices to inform patients are: (i) providing information in an understandable way, (ii) communicating with a one-voice principle (i.e. consistent message), (iii) leveraging the physician-patient/nurse-patient relationship, (iv) using positive language (focusing on the similarities rather than the minor differences), (v) tailoring the communication to the patient's individual needs (start simple and provide more details according to patient's needs/questions), (vi) providing information that is of practical relevance to the patient, (vii) offering supporting materials and written information that the patient can (re-)read, and (viii) providing the opportunity to discuss and ask questions.

2.2 RECOMMENDATIONS TO SUPPORT STAKEHOLDERS WITH BIOSIMILAR USE IN CLINICAL PRACTICE

In this second section, we formulate recommendations to support biosimilar use in clinical practice. These can be divided into three main categories: (i) address uncertainties regarding switching patients between reference product and biosimilar, (ii) provide practical support on how to switch, and (iii) create appropriate incentives.

2.2.1 LEVERAGE EVIDENCE BASE OF EXISTING CLINICAL SWITCH DATA ACTIVELY TO BUILD TRUST AND INFORM USE IN PRACTICE

Over the past years, data from switch clinical trials, real-world observational switch studies, and registries has been instrumental to inform switching in clinical practice (Chapters 4, 8, 11). The vast body of studies that report clinical outcomes of a switch between reference products and biosimilars largely allowed to settle the discussion on the safety of switching from reference product to biosimilar and has built confidence among stakeholders (Chapter 8, 11). Based on the currently available data, there are no reasons to believe that switching for biosimilars approved in highly

regulated jurisdictions poses an inherent risk of increased immunogenicity. Post-marketing surveillance is in place to monitor any switch-related adverse events, and to identify rare immune reactions that can only be detected after long follow-up periods in large patient numbers. Consequently, systematic switch trials are arguably not needed, and could be considered questionable from a scientific and ethical point of view (350). Instead, attention should go to leveraging the existing evidence base more actively to stakeholders. Also, awareness should be promoted on the importance of batch number recording to improve product traceability (353),(490),(109). Real-world data will continue to emerge given the increasing reality of multiple switching and biosimilar to biosimilar switching in clinical practice as more biosimilars become available per reference product and their maturity on the market grows. These data may add to the growing scientific evidence base and should be communicated in an aggregated and active way to prescribers and other stakeholder groups (e.g. via position statements, systematic reviews). Finally, the aggregated body of switch studies may as well inform decision-makers with shaping switch and substitution policy making, as has been observed for example in Norway (271).

2.2.2 SUPPORT HCPS WITH STRUCTURED SWITCH MANAGEMENT

While regulatory and scientific guidance on biosimilar interchangeability and switching is necessary, healthcare professionals should as well receive support on a practical level. To ensure an appropriate transition, switching should be set up as a structured process including adequate staff training to guarantee a consistent switch approach, and a well-planned implementation and follow-up procedure that is aligned with and agreed by involved stakeholders prior to the switch (Chapter 4, 11). Top-down organized switching should be avoided: stakeholder involvement, communication and alignment throughout the process are key. In Chapter 4, a model for structured switch management is presented. In summary, it proposes the following steps and actions:

- Prior to the switch: (i) design a stepwise implementation plan, (ii) search for consensus and establish early on an ongoing dialogue with all stakeholders involved, (iii) inform, educate, and train involved physicians, pharmacists, and nurses about the biosimilar and the switch, and (iv) inform the patient and provide them the opportunity to discuss the switch with the physician/nurse
- At the time of the switch: (i) apply standard of care, (ii) for subcutaneous products, provide patient training on the injection device, and (iii) allow room to deviate in case a patient objects to switch.
- After the switch: (i) routinely follow up with the patient, (ii) offer patient the opportunity to ask questions and report back over telephone or at an upcoming appointment.

To support healthcare professionals with the implementation of structured switch management, switch management toolkits including patient communication materials should be developed. Available materials (e.g. Dutch NVZA Biosimilar Toolbox, ESNO nurse biosimilar switch guide, Cancer Vanguard NHS tools and templates) may be useful to adapt to the local context (489),(104),(479). Of note, materials should also be available for primary care healthcare

professionals. As there is no hospital network to support primary care healthcare professionals with biosimilar initiation or switching, they especially may require supporting (communication) materials about biosimilars (Chapters 5 and 11). Finally, governments should take a proactive approach to support hospitals and healthcare professionals with biosimilar implementation. As an example, in the Netherlands, government supported, tailor-made training and switch management programs to guide biosimilar introduction are offered to hospitals, and since recently also to healthcare professionals in the ambulatory care (110),(491).

2.2.3 PROVIDE HCPS WITH PRODUCT SELECTION MAKING AND RATIONAL PRESCRIBING GUIDANCE

With the availability of often multiple biosimilars per reference product, healthcare professionals have a number of off-patent biologicals to choose from. Furthermore, biosimilar and originator manufacturers (increasingly) differentiate through the offering of additional benefits or product improvements. Consequently, as products may differ not just in price, multiple elements can be considered when selecting an off-patent biological medicine. A clear overview of these features should be made available to healthcare professionals to inform product selection and the subsequent product introduction in clinical practice. Besides being important on a practical level, this may also inform healthcare professionals and patients about additional benefits the newly introduced product might bring (e.g. improved injection device).

In addition, clear recommendations on which product is the most cost-effective should be made available to prescribers to guide them with rational prescribing. This may be particularly important in non-tender product decision-contexts, i.e. situations in which prescribers have a broader prescription choice. Guiding cost-effective prescribing may drive biosimilar uptake (in case the biosimilar is the lowest cost option) but is also important to mitigate for possible shifts to higher priced, therapeutically equivalent treatment options (Chapter 11). Guiding prescribers may also take a more prescriptive form, including the introduction of monitoring of and feedback on prescribing behaviour relative to peers or with prescription targets/quota (Chapter 4, 11). Also, general awareness should be raised on the prescriber's societal responsibility to prescribe medicines in a cost-effective manner.

2.2.4 CREATE DEMAND-SIDE STAKEHOLDER INCENTIVES

While their relative impact has to be assessed, there are several incentives possible to motivate stakeholders to use biosimilars. (Chapters 4, 5, 11). Broadly, these incentives can be non-tangible/indirect or tangible/direct in nature.

Examples of such in-direct incentives include: (i) creating stakeholder awareness about treatment costs and the societal responsibility to prescribe in a cost-effective manner, (ii) creating stakeholder awareness on the broader biosimilar value offering, and (iii) transparent reporting on the concrete savings that result from biosimilar entry and how these are allocated (*versus* "disappearing in the overall system"). While efforts should aim to maximize calling upon stakeholder's societal responsibility via non-tangible incentives, a complementary, tangible benefit share incentive in

terms of additional staff may be considered to support and compensate for switch induced, additional workload.

Finally, existing incentives should be realigned where needed to ensure everyone is pulling in the same direction.

2.3 RECOMMENDATIONS TO STRENGTHEN REGULATORY GUIDANCE ON BIOSIMILAR USE

2.3.1 CREATE A COMMON EUROPEAN SCIENTIFIC POSITION ON BIOSIMILAR INTERCHANGEABILITY

Heterogeneous and incomplete position statements on biosimilar interchangeability and switching at the national regulatory level might suggest that regulators have not crystalized their position on the safety of switching. European regulators should join forces and act swiftly to create a common EU scientific position on biosimilar interchangeability, unambiguously informing healthcare professionals, policy makers and patients about biosimilar use. Of note, it should be made clear that such a unified scientific position does not aim to interfere with local policy making or prescriber practices (i.e. switch and substitution practices), as this falls under the responsibility of the individual Member States. Nonetheless, a harmonized scientific position could inform the development of policy measures on a national or local level (and is arguably needed in this context) (Chapter 3, 7). The above mentioned recently established HMA Biosimilar group is an important vehicle in this regard (276),(277).

2.3.2 IMPROVE CLARITY AND CONSISTENCY OF REGULATORY GUIDANCE ON BIOSIMILAR USE AND SWITCHING AT THE NATIONAL LEVEL

As mentioned under recommendation 2.3.1, the fragmented regulatory guidance on biosimilar interchangeability and switching may lead to clinical uncertainty and reduce the impact of available position statements. While a common European scientific position on interchangeability is the starting point, this should translate in the availability of more homogenous and unambiguous guidance on switching at the national level. National regulatory position statements, if available, currently mostly address reference product to biosimilar switching. Hence, as some national medicines agencies already have done (e.g. Norway, the Netherlands), guidance should be broadened to cover multiple switching and switching between biosimilars of the same reference product (Chapter 7, 11).

2.4 RECOMMENDATIONS FOR MORE SUSTAINABLE POLICY AND PROCUREMENT PRACTICES

Below, we offer best-practice principles and recommendations for more sustainable policy and procurement practices.

2.4.1 CREATE A HOLISTIC, MULTI-STAKEHOLDER POLICY FRAMEWORK FOR SUSTAINABLE BIOSIMILAR COMPETITION

2.4.1.1 IMPLEMENT POLICY MEASURES IN AN INTEGRATED WAY

Biosimilar adoption challenges are multifaceted, often intertwined and involve a variety of stakeholders. Addressing them requires integrated actions across the main pillars as proposed in this dissertation, including measures to improve stakeholder understanding, reduce barriers for biosimilar use in clinical use, increase stakeholder willingness, strengthen regulatory guidance, and foster sustainable competition - and this on supranational and local level. Decision makers should seek to develop a holistic policy framework that, rather than implementing actions in isolation and in an *ad-hoc* fashion, combines them in a broader and long-term strategy.

2.4.1.2 INVOLVE ALL STAKEHOLDERS CLOSELY THROUGHOUT BIOSIMILAR POLICY MAKING & IMPLEMENTATION

A common denominator across virtually all studies in this project has been the importance of multi-stakeholder involvement, alignment, and collaboration. Pro-actively involving stakeholders, both in policy making and the clinical implementation of biosimilars may reduce hesitation, create a broader support base for (policy) actions, and foster a shared understanding on the need for effective biosimilar competition to improve affordability of treatment and ultimately the sustainability of our healthcare systems. While a structural framework with clear assigned responsibilities is needed to support biosimilar adoption, improving understanding and confidence in biosimilars and ultimately enhancing their acceptance should be viewed as a responsibility of all stakeholders across the healthcare spectrum. Notwithstanding that stakeholders have a common ownership, political will (i.e. understanding and support among decision makers to drive policy action (17)) and governmental action, both at EU and Member State level, is required at the core.

The vehicle of the newly established HMA Biosimilar working group is a welcome platform to foster cooperation between regulators on biosimilars, both with the EMA and between Member States (276). Modelled to this example, a similar group could be established to step-up cooperation between national payers and policy makers with the aim of stimulating mutual learning through information and best-practice exchange across Member States (1).

2.4.2 FOSTER COMPETITION FOR LONG-TERM SUSTAINABLE MARKETS

2.4.2.1 IMPLEMENT POLICY MEASURES THAT STIMULATE LONG-TERM COMPETITION

When designing policies, policy makers should consider the impact these may have on competition and be encouraged to implement those that aim to stimulate market competition (Chapters 9, 11).

However, some mechanisms that are currently deployed in some markets, such as mandatory price cuts of the originator product at the time of biosimilar market entry, may achieve rather the opposite in the long term, as they limit the incentive to further lower prices and take away the direct financial incentive to select a biosimilar (Chapter 11). Furthermore, it may discourage some manufacturers to launch new biosimilar entrants on the market, which could result in reduced competitive pressure, also in tenders. Notwithstanding that immediate savings are essential to relieve strained national healthcare budgets and price control mechanisms are clearly effective in this regard, biosimilar market entry policies that aim to stimulate competition should be installed, rather than (solely) lean on mandatory price cuts to ensure savings on the short-term. In general, policy makers should seek to stimulate plurality of suppliers in order to safeguard the long-term benefits of continued biosimilar competition. As discussed below (recommendation 2.4.3), tender mechanisms are a key determinant of market competition (and as such sustainability). Tender mechanisms that encourage market plurality and inclusion of award criteria beyond price should be stimulated to foster (non-solely price focussed) competition. A first step towards creating policy frameworks with a longer-term market sustainability vision may involve establishing greater awareness on drivers and possible pitfalls for competition.

2.4.2.2 EVALUATE LEVEL OF MARKET COMPETITION, EVOLUTION IN TREATMENT COSTS, AND PATIENT ACCESS RATHER THAN BIOSIMILAR UPTAKE AS KEY METRIC OF POLICY SUCCESS

Originally, the emphasis was put on the uptake of biosimilars to measure the overall success of biosimilar implementation. While fostering biosimilar uptake is essential to stimulate competition, high biosimilar uptake is not necessarily a goal in itself. Rather than focussing on biosimilar uptake in a vacuum, a more holistic approach, taking the broader market functioning into account, should be taken (Chapter 9, 11). This is important given that the main objective should be to unlock long-term benefits for healthcare systems both in terms of lowered treatment costs and possibly greater access to biological treatments. Accordingly, the level of market competition and (the involution in) treatment costs and patients access are more informative measures to assess how well healthcare systems are leveraging biosimilar competition. A proposed metric to evaluate market competition, is the Herfindahl-Hirschman Index (HHI), which measures market concentration by using market share and the total number of competitors (11). Additional indicators should be developed in this regard.

Finally, the term “best-value biological” - as proposed by NHS England and HSE Ireland (474),(396) - may be used in a policy context to clearly reflect that the broader goal is on achieving effective market competition, which improves affordable patient access to biological therapies (which can be either the reference product or the biosimilar, and requires sustainable competition between both), rather than biosimilar uptake in isolation.

2.4.2.3 TAKE THE BROADER COMPETITIVE LANDSCAPE & VALUE OFFERING INTO ACCOUNT

Competition between reference product and biosimilar(s) does not occur in silo but is part of a broader competitive landscape. This may include the availability of the same product in an alternative administration route, second-generation products or new, innovative therapies for the same indication and patient population. Biosimilar market entry may induce changes to the use of these competing products (e.g. through changes in price, reimbursement or treatment line, either curbing or widening) and *vice versa*, they may influence the uptake of biosimilars (e.g. through competition strategies). Consequently, the broader competitive landscape of which biosimilars are part should be considered and reviewed in the context of biosimilar market entry.

While realizing cost-savings is likely to be a primary driver for most decision makers, the broader value offered by biosimilars should be considered, and maximized where possible along the value chain. As proposed under recommendation 2.2.4, communicating about changes resulting from biosimilar market entry (e.g. cases in which biosimilar market entry concretely impacts accessibility) may increase awareness among stakeholders on the broader value biosimilar competition can bring.

2.4.3 CONSTRUCT SUSTAINABLE TENDER PRACTICES THAT ENSURE A LEVEL PLAYING FIELD & STIMULATE COMPETITION

When designed effectively and conducted appropriately, tenders have the potential to simultaneously drive down off-patent biological medicine prices and stimulate competition between the originator and biosimilar(s). However, tender practices across European markets are heterogeneous and need to be reviewed in such a way that they offer a level playing field and are aligned with sustainable outcomes (Chapter 9).

Given the heterogeneity in tender organization, which in part stems from the general heterogeneity in healthcare systems across European markets, there is no ‘one-size-fits-all’ approach for sustainable tendering. Yet, best-practices for tender organization have been identified and include stimulating market plurality (e.g. national multi-winner tenders or multiple sub-national single-winner opportunities), awarding on criteria beyond price, safeguarding equal opportunity for suppliers (level playing field), stimulating timely opening of tenders to ensure swift competition, and coordinating and consolidating tender expertise centrally (without consolidation of market volume to a sole winner).

Detailed recommendations on how to develop and implement sustainable tender practices for off-patent biologicals and biosimilars are provided in Chapter 9. Overall, combined action of all actors (i.e. suppliers, pharmaceutical industry umbrella organizations, purchasers, payers, governments, and competition authorities) is required to safeguard a level playing field and strengthen competition between off-patent biologicals through tenders.

2.4.4 DEVELOP A PRO-ACTIVE BIOSIMILAR IMPLEMENTATION PLAN

To ensure timely competition and unlock its associated benefits, national healthcare systems should prepare in advance for upcoming biosimilar market entries (Chapters 9, 11). A systematic horizon

scanning should be performed to identify upcoming loss of exclusivities and potential biosimilar market entry dates, allowing to take well-timed measures and to align length of procurement contracts with the reference product accordingly (Chapters 4, 9, 11). Moreover, a clear implementation roadmap that assigns responsibilities and coordinates between stakeholders should be developed (e.g. assessment of the opportunity and product context, early engagement of relevant stakeholders and associations, agreement on switch implementation plan, training of healthcare professionals, etc). Best-practice examples of pro-active biosimilar/best-value biological implementation frameworks, including well laid out process steps, early stakeholder dialogue, and clearly assigned responsibilities to all stakeholders involved, are available in Ireland, the UK and Denmark (474),(396),(383),(399),(480).

2.4.5 TAILOR POLICIES TO MARKET AND PRODUCT SPECIFIC CONTEXT

Biosimilars are not a catch-all term. Rather, biosimilars cover a wide range of product types (e.g. from simple proteins such as insulin or growth hormone to more complex mAbs, from products with a quasi immediate to longer term observability of therapeutic effect) and therapeutic areas (e.g. rheumatology, gastroenterology, oncology, and endocrinology) and may differ in product treatment setting (acute *versus* chronic treatment), product administration route (intravenous *versus* subcutaneous), competitive environment (existence and availability of competing products, deployed competition strategies), dispensing context (hospital *versus* ambulatory care), and decision-making process (tender and formulary-driven *versus* prescriber decision-driven). Hence, there is no one-size fits all framework approach to biosimilar policy making and policy measures should be developed with the necessary granularity, requiring a nuanced analysis of the product-specific context (Chapters 9, 11).

In addition, since important differences exist in healthcare organization across European markets, measures require local tailoring to the idiosyncrasies of each system. For example, the scope of tenders substantially varies between Member States, ranging from central, regional, hospital group to hospital-individual systems, necessitating different tender design approaches (Chapters 4, 9, 11). In addition, the level of maturity in terms of biosimilar policy making differs, with some countries already taking a more pro-active approach in developing biosimilar-specific policies and implementation plans (e.g. UK, Denmark). It is therefore important to analyse these factors (product and market) to determine which measures to take.

3. STRENGTHS AND LIMITATIONS OF THE PROJECT

This dissertation provides a comprehensive analysis of the hurdles and drivers of biosimilar adoption in Europe, integrating learnings from a clinical, regulatory, and policy perspective. This multifaceted approach was structurally embedded in the multi-disciplinary composition of the research team, combining expertise in regulatory sciences, clinical and hospital pharmacy, health economics, and biotechnology. Furthermore, the research drew from a broad network of key stakeholders in the field of biosimilars, including regulators, policy makers, physicians, pharmacists, nurses, patients,

researchers, and the pharmaceutical industry, as well as their respective umbrella or stakeholder associations. Stakeholder engagement was actively sought throughout the project, to capture a thorough understanding of the regulatory landscape and biosimilar market dynamics, including its actors, and, *vice versa*, to actively report back the research findings and its broader implications to the relevant stakeholders on a continuous basis.

While study specific strengths and limitations are provided within the respective Chapter discussions, some overarching methodological considerations are worth further discussion.

In the project, different research methodologies were employed, including literature review, quantitative, and qualitative research techniques, and in some individual studies a combination of these. For each main “research vertical” (i.e. (i) stakeholder knowledge and perceptions, (ii) clinical components, (iii) regulatory components, and (iv) procurement and policy practices), we drew from a combination of both review/quantitative and qualitative research. This combination strengthened the robustness of the research as it allowed to gain understanding on possible causes behind the observations and explore possible solutions.

As such, this project has a strong qualitative component. Qualitative research methods, such as semi-structured interviews and focus group discussions, were frequently chosen as these are well suited to access expert knowledge and generate in-depth insights on a given research topic. This approach was particularly needed in the context of this project since only limited information was publicly available on the challenges and drivers of biosimilar adoption at the outset of the research. This qualitative component helped us to better understand the complexities of the issues at hand, obtain insights in current and evolving practices, and – as intended – to formulate actionable recommendations that take the perspectives of the different stakeholders into account.

Throughout the project, a broad range of stakeholders, including regulators, physicians from different specialities, hospital pharmacists, community pharmacists, nurses, patients, purchasing bodies, pharmaceutical industry, and their umbrella organizations, was involved. While a purposive sampling strategy was used to involve interviewees with extensive knowledge on the study sub-topics and to assure a balanced participant group, it is important to consider that qualitative findings are always bound to the participant sample. Furthermore, qualitative research may be subject to bias in different steps of the research (data collection, analysis, reporting). To maximize the validity and reliability of the insights that were generated, interviews and focus group discussions were conducted using prepared and piloted topic guides, and the resulting *ad verbatim* transcribed data were subjected to systematic multi-step qualitative analysis, using the framework analysis method described by Lacey & Luff (59).

The PhD project and its studies focussed on biosimilar introduction and implementation in the European context. Accordingly, the studies were positioned within the EU regulatory and solidarity-based healthcare context and gathered insights on experiences and practices on a pan-European and European country level. In some studies, a specific European country or group of countries was purposively selected as a case study. Findings of these studies might not be generalizable to the

broader European setting. On the other hand, despite the fact that the scope of this dissertation is European, and caution should be exerted to extrapolate learning to other jurisdictions, some of the findings, in particular those of the systematic literature review on the clinical impact of switching, may transcend the European context, making them also informative on a more global level.

The project was initiated in 2016 at the time of the market introduction of the first mAb biosimilars. Their approval and subsequent market entry marked a significant landmark moment for biosimilars and fuelled again the debate on their use as was the case with the initial biosimilar debut. This new class of biosimilars included several multi-billion-dollar products, raising the stakes both for healthcare systems seeing the substantial savings potential associated with their entry, as well as for originator and biosimilar manufacturers looking to maintain or gain market share. While the scope of the project was not limited to mAb biosimilars in particular, it is important to note that the studies were conducted against this evolving background.

We chose to take a holistic approach to study the topic of biosimilar adoption, and as such investigated a broad range of facets related to their evaluation, entry, implementation and use. Although this approach has several advantages, it may simultaneously also be considered as a main limitation of the research. This because it may have led to a less in-depth examination on the level of the individual study facets. While the project provides a comprehensive view on the topic of biosimilar adoption, multiple avenues for further investigation and additional research emerged (see section 5).

Finally, it is important to take into account that the regulatory and market access landscape of biosimilars is continuously evolving (see section 4). While qualitative studies allowed to capture insights on some of these evolutions from the perspective of the involved stakeholders, document and literature analyses might be limited in their ability to always capture the latest developments. This evolution may also be observed throughout the studies conducted and reflected in the insights presented over the course of this PhD project.

4. THE EVOLVING DEBATE & FUTURE PERSPECTIVES

April 2021 marked the 15th anniversary of the first biosimilar approval in Europe, and by extension, worldwide. The clinical experience with biosimilars has been a success and important advances have been made over the past 15 years in the biosimilar debate. Over two billion cumulative patient treatment days for EU-approved biosimilars have been reported, and over the past years, this number is estimated to have doubled every 1,5 years (492). During this time, no EU-approved biosimilar has been withdrawn or suspended from the market for efficacy or safety issues (109),(493). Also, the EU monitoring system has not identified relevant differences in the nature, severity and frequency of adverse events between biosimilars and their reference products, which is another testament of their safe use in clinical practice (6). In terms of effect on EU healthcare systems, biosimilar market entry has demonstrated its positive impact, both in terms of lowering treatment costs and expanding patient access to biological therapies (11),(117).

While biosimilar introduction was met with scepticism and strong resistance, and questions on the soundness of scientific principles underpinning biosimilar evaluation and use have been raised at every step of the way, there is considerable evidence and experience to conclude on the robustness of how biosimilars are developed and evaluated. The latter is increasingly recognized by medical and other stakeholder organizations, but effort is needed to transmit this message to the wider decision maker, healthcare professional, and patient community. While important questions in the scientific and stakeholder debate on the safe use of biosimilars have been gradually addressed and answered, further regulatory clarity on their interchangeable use in clinical practice is required. Also new questions emerged in more recent years, including on avenues for further tailoring of regulatory clinical data requirements. Furthermore, questions have been raised on how to create a sustainable market environment that can deliver on the benefits from biosimilar competition. Important challenges remain to the wider adoption of biosimilars and concerted actions are required to sustainably integrate them in healthcare systems and deliver on their promise of making biologicals more affordable and more broadly accessible.

As total healthcare expenditure is expected to continue to experience both macro-driven, structural growth as well as see a one-off increase following the COVID-19 pandemic, biosimilars and the cost saving potential they represent will be ever so vital in supporting policy makers and society in addressing affordability and sustainability issues within our healthcare systems.

With more originator biological medicines set to lose exclusivity, the number of biosimilars available on the European market is likely to continue to grow. In fact, the next decade represents a particularly large opportunity for potential new biosimilar entrants, with approximately 100 originator biological medicines losing exclusivity, cumulatively constituting by estimation over EUR 40 billion in sales in the European market in their year of expiry (11),(9). Where historically the opportunity for biosimilar competition concentrated on a rather small number of high-value products³ (e.g. adalimumab, infliximab, trastuzumab, rituximab), this new wave of biological loss of exclusivity (LOE) holds a large number of biologicals that individually are generally smaller in market value and/or target smaller patient populations, including amongst others several biological orphan medicines (i.e. medicines for the treatment of rare diseases) (11). That being said, also several multi-billion dollar biologicals, especially in oncology, such as programmed cell death protein 1 (PD-1)-targeted mAbs pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are expected to lose exclusivity before 2030 (9),(31),(34).

Whereas commercial interest to develop biosimilars of best-selling biologicals such as adalimumab and trastuzumab has shown to be high, ultimately resulting in multiple approved biosimilars for each, interest might be lower for some of the lower-value products in the incoming wave of LOE. This lower commercial interest may in turn have implications on the level of competition and magnitude of cost savings realized. Also for orphan biosimilars, specific challenges for development have been

³ Defined as molecules that have annual sales of more than EUR 1 billion at time of Loss of Exclusivity-1.

highlighted (e.g. low patient numbers for clinical trials) (494). At present, despite the fact that 14 orphan originator biologicals have already lost their market exclusivity, no orphan biosimilars have yet been approved and only few (e.g. such as for eculizumab (Soliris®)) appear to be in late stages of development (494). In general, some differences in market dynamics and challenges may be expected for the incoming wave of biosimilars compared to those currently on the market.

Looking more short-term, the next two to three years are a rather “calm period” in terms of new biological LOEs (11),(9). This does not take away that more biosimilars are likely to enter the European market over the next few years. In fact, 12 biosimilar candidates - mainly for molecules for which already one or more biosimilars have been approved - are currently under evaluation by the CHMP (33). Policy makers should be encouraged to grasp this next “calm period” to develop and/or optimize policy measures that are fit-for-purpose to foster sustainable competition from biosimilars, now and in the future. Efforts should focus on optimizing the competition potential of currently available biosimilars, as well as preparing for the next wave. Given the expected high number of new entrants over the mid- to long term, it will be important to prepare well in advance and streamline processes as much as possible, actively leveraging insights of past and present practices. Since the next wave of anticipated biosimilars also includes therapeutic areas that are new to biosimilar market entry, it is important to pro-actively liaise with the relevant stakeholder groups, e.g. such as in ophthalmology and neurology, in order to familiarize them with biosimilars and the scientific concepts underpinning their evaluation and approval. Regarding the latter, a potential positive side effect from the COVID-19 pandemic is that there may be a greater general awareness among healthcare professionals and patients of the existence of regulatory authorities and a robust, science-driven, regulatory evaluation framework for medicines intended for use on the European market.

In general, it is expected that biosimilar development may gain in efficiency due to technological advances and the experience built with biosimilar evaluation and use in practice. While a case by case approach to biosimilar development has to be considered, these advances are expected to result in reduced clinical data requirements without compromising scientific robustness (19),(495),(496),(497),(498). Although a reduced need for large, comparative efficacy and safety trials will positively result in lower biosimilar development costs, which in turn may act as a positive stimulus for biosimilar development, it will be essential to continue to communicate on the underlying science to build trust among stakeholders in the robustness of this approach. Harmonization of regulatory requirements between different jurisdictions may further maximize efficiencies and provide opportunities to lower the overall cost of biosimilar development (490).

As highlighted by the 2020 adopted *Pharmaceutical Strategy for Europe* of the European Commission and EMA’s Regulatory Science to 2025 Strategy, broad awareness exists on a pan-European level of the value and opportunity biosimilars offer in improving affordability and accessibility of treatments, as well as of the need to take action to support their adoption and foster competition in a sustainable manner in order to ensure that those benefits truly materialize for European

healthcare systems and patients (1),(499). The European Commission has laid out its commitment to consider policies that support greater biosimilar uptake and competition, and invest in the removal of barriers that may delay their timely market entry. In view of these market competition considerations, the pharmaceutical legislation will be reviewed and mention is made of interchangeability (1). Furthermore, this is set out to be accompanied by the enforcement of the EU competition rules in order to mitigate originator company strategies that have shown to hinder entry or expansion of more affordable treatment options (1). Finally, commitment is voiced to foster the exchange of best practices between Member States to stimulate the uptake of biosimilars (1).

On a national level, as discussed above, differences exist across European markets in how they have responded to the arrival of biosimilars. Whereas some countries or regions have progressively developed a pro-active policy approach and launched specific initiatives to support biosimilar market entry and competition, others are at an earlier stage of biosimilar policy development. As discussed in the Recommendations sections, a common understanding of the role of biosimilar competition and the need to optimize systems to unlock its full potential should be fostered at national, regional, and local level. While this should be prioritised in those countries with a less developed biosimilar policy framework, it should be an ongoing effort for others, as establishing policies for a more sustainable off-patent biologicals markets is not a one-off effort but requires iteration and adaptation to the changing market dynamics and emerging therapeutic areas for which biosimilars arrive. As a side - although important - note, it should be highlighted that leveraging biosimilars competition is an important strategy, yet not the only, to optimize spending on medicines and foster sustainable healthcare systems.

5. AVENUES FOR FUTURE RESEARCH

While providing a comprehensive view on the topic of biosimilar adoption, this PhD project uncovered several avenues for future research. Below, a number of proposals are put forward.

First, for a follow-on project, it would be interesting to study this project's findings, especially those related to physician prescribing behaviour and motivations, in the context of the behavioural economics field. Doing so may help to integrate the learnings into the development of targeted incentive strategies, in which size, design and delivery are all important elements to consider. Furthermore, a study that hypothetically tests the impact of (a) specific type(s) of incentive on the willingness of prescribers to opt for or switch to a biosimilar/lowest-cost biological may provide valuable insights, especially so in prescriber (non-tender) -driven contexts.

Second, one could investigate how and to what extent healthcare systems have been able to realize cost savings and downstream benefits of biosimilars (e.g. improved patient access to (biological) therapy) thus far. Studying this across European markets may yield insights on specific contexts or settings and therapeutic areas in which downstream effects have been successfully captured. In turn, this could further inform decision makers on how to capture these within their own healthcare system. Future research would also benefit from studies that consider the broader competitive

landscape which, next to the originator biological and its biosimilar competitor(s), includes shifts to newer therapeutic alternatives.

Third, while this PhD project addressed challenges and drivers of biosimilar adoption, and studies components such as procurement that may impact competition, it did not evaluate market competition or sustainability in itself. Follow-on projects are needed to develop indicators to evaluate and quantitatively measure market competition and sustainability. Such a set of indicators may serve as additional tool to support policy makers.

Fourth, it may be of interest to study the uncaptured (“historical”) potential for biosimilar competition (11). To clarify, with this we refer to originator biologicals that are open to competition but do not (yet) have competition from biosimilars. Studying such cases may elucidate hurdles and provide insights on how these could be overcome. Furthermore, in some European markets a delayed market launch of biosimilar entrants has been observed (32). Studying causes that delayed biosimilar availability may help to identify mitigating strategies. Also, researching drivers and challenges in orphan biosimilar development may contribute novel and important insights in the context of the changing landscape and incoming wave of biological LOEs. Stimulating not only competition in the segment of high market value biological products but across product categories is important to maximize the savings opportunity, since lower value biologicals together still represent a large opportunity for healthcare systems to optimize spending. Overall, it will be of interest to closely analyse how the competitive market landscape will evolve.

Finally, the foreseen changes to substitution practices in some European countries may provide interesting, real-world case studies out of which learnings can be distilled on how and under what circumstances biological substitution might be applied. Also other jurisdictions, such as Australia, may offer valuable insights in this regard.

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SUPPLEMENTARY MATERIAL

The accompanying supplementary material per Chapter is made available on a digital repository. For published Chapters, the supplementary material is also available to consult on the website of the respective scientific journal (Open Access). Links to the digital repository and publications, where applicable, are provided below:

- **Chapter 3**
<https://link.springer.com/article/10.1007/s40259-020-00452-9> |
<https://drive.google.com/drive/folders/1O2KoTk18chzMbkLx8CW95gDahFyZDc7a>
- **Chapter 4**
<https://link.springer.com/article/10.1007/s40259-020-00440-z> |
https://drive.google.com/drive/folders/1HCBNX_u5j_aHgjwrI0_Q80T-qG5mqBA-
- **Chapter 5**
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- **Chapter 6**
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- **Chapter 7**
<https://drive.google.com/drive/folders/1B9ailFx0bWxKczlITQnjGf87ztVkyHis>
- **Chapter 8**
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- **Chapter 9**
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<https://drive.google.com/drive/folders/17uKZ8kFy0VTJzRutNxCV1Wmlv1Jvui53>
- **Chapter 10**
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- **Chapter 11**
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SUMMARY

Biological medicines represent a large and fast growing share of the total expenditure on pharmaceuticals. While biological medicines have significantly improved the treatment of a variety of complex, chronic, and in some cases life-threatening diseases, their relatively high price tag increasingly puts national healthcare budgets under pressure. Following the expiry of patent protection and other exclusivity rights on original biological medicines, the market opens up for competition from biosimilars. Biosimilars are highly similar versions of an already approved originator biological product (the reference product), that can be used as therapeutic alternatives.

Biosimilars provide opportunities to improve affordability and accessibility of biological medicines. Through their entry, biosimilars introduce price competition in the market, resulting in lowered treatment costs and possibly increased patient access to biological therapies. However, at present, biosimilar adoption faces several challenges, limiting their competition potential and therefore also the associated benefits for healthcare systems and patients. As a result, questions have been raised on how to address these barriers and foster a more sustainable off-patent biological medicines market environment.

This PhD project aims to address these adoption challenges faced by biosimilars in Europe and formulate actionable recommendations that support sustainable and balanced off-patent biological medicines market dynamics with long term competition from biosimilars. To achieve this, this PhD research draws insights through a multifaceted lens, integrating multi-stakeholder informed learnings from a clinical, regulatory, and policy perspective. The PhD research is carried out from a multidisciplinary angle, and includes a combination of literature and document analysis, and quantitative as well as qualitative studies. The framework of the research is structured around the main barriers for biosimilar use and aims to elucidate 1) stakeholder knowledge and perceptions of, and insights on biosimilars and their use including educational and incentives needs, 2) regulatory and clinical components that may impact biosimilar adoption and their implementation in clinical practice, and 3) biosimilar policies, especially those related to procurement, and best practices to leverage biosimilar competition in a more sustainable way. Finally, based on the insights of the nine individual studies performed in the context of this PhD research, recommendations were derived with the aim to support decision makers with policymaking and inform stakeholders with the implementation of biosimilars in clinical practice.

Part 1 of this dissertation provides a general introduction to the topic of biosimilar adoption and explains their evaluation and market introduction in the European context. Next, the rationale and specific objectives of the PhD project are described (**Chapter 1 and 2**).

In **Part 2**, we investigate stakeholders' knowledge of and attitudes towards biosimilars and their use in clinical practice. Moreover, we explore multi-stakeholder informed solutions to overcome barriers identified in this context. The results of the structured literature review in **Chapter 3** showed that healthcare professionals and patients have low to moderate knowledge of biosimilars, and that they

have considerable uncertainties and misconceptions regarding their approval and use. This observation appeared to persist across stakeholder groups, therapeutic areas, care settings, and geographical regions. Through qualitative, multi-stakeholder interviews, seven main drivers behind this low knowledge and trust in biosimilars were identified: (i) a lack of understanding about the regulatory and scientific concepts underpinning biosimilar approval, (ii) a lack of understanding of biological medicines in general, (iii) different terminology and regulatory concepts between jurisdictions, (iv) (industry-driven) misinformation, (v) a lack of effective communication strategies, (vi) a lack of consistency in the available information, and (vii) a lack of clear guidance and practical information about their use. To overcome these, actionable recommendations were formulated, especially highlighting the need for concerted action on a European and national level, which in turn will require close collaboration and coordination between the different actors involved.

In **Chapter 4**, we investigated stakeholder views on the use of biosimilars in clinical practice, with a particular focus on switching, patient communication, and stakeholder motivation. Three main barriers for biosimilar use in clinical practice were found: (i) uncertainty about the safety of switching, (ii) a lack of guidance on how to initiate/switch to a biosimilar and communicate with the patient, and (iii) a lack of clear motivation to use them. Recommendations to address the first and second barrier include: (i) disseminate evidence from and experience with (multiple) switching, (ii) provide clear and consistent regulatory guidance about biosimilar interchangeability (iii) avoid top-down organized switching, involve stakeholders throughout the process, (iv) allow for stakeholder alignment and motivated exceptions on an individual patient level, and (v) apply a multi-stakeholder implementation and communication protocol to guide the switch. For the latter, practical considerations and concrete strategies on how to manage a switch and communicate to the patient were gathered. Regarding the third barrier, several ways to increase the willingness of stakeholders to use biosimilars were proposed. Stakeholders themselves advocated for a combination of indirect and direct incentives. Examples of the former include increasing awareness that the benefits from biosimilar entry extend beyond direct cost savings and communicate transparently on where those benefits are allocated. Examples of direct incentives include benefit share agreements, in which healthcare professionals receive a tangible benefit to compensate for the additional time and workload induced by a switch.

In **Chapter 5**, we zoomed in on the preparedness of Belgian healthcare professionals in the ambulatory care setting to prescribe and dispense biosimilars. The results of our survey highlighted a substantial need to not only increase their understanding of biosimilars but of biological medicines more broadly. The existing educational outreach and curricula on biological including biosimilar medicines should be reviewed and this both for current as well as future generations of healthcare professionals (i.e. medical and pharmacy students). Furthermore, findings showed that healthcare professionals, despite the clear need for training, are open towards substitution for biologicals as long as the prescriber is informed.

Part 3 focusses on the regulatory and clinical components that may impact biosimilar adoption and their use in clinical practice. In **Chapter 6**, we described the biosimilar development pathway and reviewed the clinical development programs of the different biosimilars of a selected monoclonal antibody (trastuzumab) relative to the EMA biosimilar (clinical development) guidelines. Findings elucidated how clinical studies for biosimilar candidates, while following a different design than in traditional drug development, are designed to confirm biosimilarity between the candidate and the reference product and not to independently establish clinical efficacy and safety. The identified differences in clinical trial design, patient population, and primary endpoint between the clinical development programs of the different trastuzumab biosimilar candidates underlined that biosimilar evaluation involves a case-by-case assessment of the totality of evidence for biosimilarity, of which the clinical studies are only one, confirmatory piece of the puzzle.

In **Chapter 7**, we studied the role of both central and Member State level European regulators to improve the knowledge of and confidence in biosimilar medicines and their use in clinical practice. To this end, the availability, content and extent of the information and guidance provided by regulatory medicines agencies was assessed. In addition to this, qualitative stakeholder views were collected. This study revealed that despite strong EU-level regulatory information on biosimilars, the availability, content and extent of information and guidance on biosimilars and their use varied considerably across national regulatory agencies in Europe. Without aiming to interfere with local policy making or prescriber practices, regulators should strive to formulate a common EU scientific position on the interchangeability of biosimilars to provide clarity to healthcare professionals, policy makers and patients. Furthermore, there is a clear opportunity at the Member State level to expand information dissemination on biosimilars and the science underpinning their evaluation and safe use.

In **Chapter 8**, we reviewed the efficacy, safety, and immunogenicity outcomes of switching in order to address the uncertainty around its safety and aid informed decision-making in clinical practice. To this end, a systematic literature review of available switching studies was performed. Based on over 170 clinical studies that report a switch from reference product to biosimilar, or *vice versa*, no relevant differences in terms of clinical outcomes were identified. Although most studies were not designed to detect differences in rare adverse events, the combined body of studies supports that there is no indication that switching between a reference product and its biosimilar is associated with any particular safety, efficacy, or immunogenicity issues. Some real-world studies did however reveal the occurrence of possible nocebo effects, making mitigating this an important aspect when switching.

Part 4 focusses on studying biosimilar procurement and market introduction policy making. In **Chapter 9**, we studied how tenders for off-patent biologicals are currently organized across Europe and drew learnings from industry and purchasing stakeholders with the aim of developing proposals for more sustainable tender practices. The results showed a great variability in the way tenders for off-patent biological medicines are currently organized. Differences include the level on which the tender is organized (central, regional, purchasing group or hospital individual), the number of

awarded winners (single *versus* multiple winner), and the criteria (price only *versus* price plus qualitative criteria) on which the bids are evaluated. Moreover, signals emerged that some of the current tender practices might negatively affect off-patent biological market dynamics, clearly underlining a need for a more long-term and market sustainable view on tendering. In addition, challenges exist to differentiate products beyond price, showing the need and opportunity to guide stakeholders with the (appropriate) inclusion of award criteria. In general, five main avenues to optimize tenders for off-patent biologicals were found, each for which detailed recommendations are proposed. While there is no 'one-size-fits-all' framework possible to foster more sustainable tenders (given the variability in existing practices and in healthcare systems in which tenders are organized), our research identified a number of common denominators. Stimulating market plurality (i), pro-active planning and early stakeholder engagement (ii), and consolidation of tender expertise (iii) were some of the best-practices that were identified.

In **Chapter 10**, we reviewed possible award criteria with the aim of providing a practical framework to support transparent, best-value product selection. Three main categories of criteria besides price were identified (product-driven, service-driven, and patient-driven criteria), and these are discussed in detail, together with relevant information on the decisionmaking.

In **Chapter 11**, we zoomed in on the off-patent biological and biosimilar landscape in Belgium with the aim of developing concrete, consensus-based recommendations for policy making. The findings of this study argued for the development of an integrated policy framework that guides and incentivizes stakeholders with biosimilar use and switch management. Furthermore, study findings exemplified the need to extend policy making beyond just stimulating biosimilar uptake, tailor policy measures to the dispensing and product specific context, and mitigate for shifts to higher priced, therapeutically equivalent product alternatives. In addition, the study indicated that the implementation of cost-containment measures that focus on mandatory price cuts of the originator at the time of biosimilar market entry, while generating immediate savings, limit the incentive for biosimilar uptake and might restrict competition long-term.

Finally, in **Part 5 (Chapter 12)**, the knowledge and insights from the individual research studies are integrated into recommendations to overcome key challenges for biosimilar adoption, and by extension support a long-term sustainable off-patent biological medicines market with continued biosimilar competition. We propose recommendations around four main pillars:

- v. Build stakeholder understanding of and confidence in biosimilars
- vi. Support stakeholders with biosimilar use and switching in clinical practice
- vii. Strengthen one-voice regulatory guidance on biosimilar use
- viii. Develop sustainable biosimilar policy and procurement practices

For each of these pillars, a specific set of recommendations is advanced. These recommendations may inform healthcare decision-makers with the development of coherent biosimilar policies and support healthcare professionals and patients with biosimilar use in clinical practice, and may as such contribute to unlocking biosimilars' full potential.

SAMENVATTING

Biologische geneesmiddelen hebben geleid tot aanzienlijke verbeteringen in de behandeling van diverse complexe, levensbedreigende en chronische aandoeningen en vertegenwoordigen een groeiend aandeel in de uitgaven aan geneesmiddelen wereldwijd. Het succes en de vaak hoge prijzen van deze biologische therapieën hebben echter een aanzienlijke druk gelegd op de gezondheidszorgbudgetten. Na het verstrijken van de beschermingstermijn van originele biologische geneesmiddelen, bieden biosimilars - gelijkwaardige versies van het origineel met dezelfde kwaliteit, werkzaamheid en veiligheid - de mogelijkheid om de betaalbaarheid van biologische therapieën te verbeteren. De prijsconcurrentie die ontstaat door de markttoetreding van biosimilars leidt tot lagere behandelingskosten, waardoor gezondheidszorgbudgetten ontlast worden. Besparingen gerealiseerd door middel van biosimilarcompetitie kunnen ook leiden tot ruimere toegang tot biologische geneesmiddelen voor patiënten en tot budgettaire ruimte voor nieuwe, innovatieve behandelingsopties. Hoewel de voordelen van biosimilar markttoegang duidelijk zijn, is de introductie en opname van biosimilars onderhevig aan verschillende uitdagingen. Hierdoor wordt het competitievermogen van biosimilars onvoldoende gerealiseerd, en blijven de voordelen voor onze gezondheidszorgsystemen en patiënten onderbenut.

Deze doctoraatsverhandeling heeft als doel om uitdagingen omtrent de markttoegang van biosimilars in de Europese context te bestuderen en voorstellen te ontwikkelen om biosimilar competitie te bevorderen. Dit met het uiteindelijke doel om aanbevelingen te formuleren die een duurzame en evenwichtige marktdynamiek voor off-patent biologische geneesmiddelen op lange termijn ondersteunen. Om dit te bereiken onderzoeken we tijdens dit promotietraject de inzichten van verschillende belanghebbenden (waaronder zorgverleners, patiënten en patiëntenorganisaties, farmaceutische industrie, regelgevers en beleidsmakers) en andere bronnen vanuit zowel een klinisch, regelgevend als ook beleidsperspectief. Het promotieonderzoek wordt uitgevoerd vanuit een multidisciplinair kader en omvat een combinatie van literatuur- en document analyse, kwantitatief, en kwalitatief onderzoek. Het onderzoek is gestructureerd rond de belangrijkste barrières voor het gebruik van biosimilars en heeft als doel om de volgende aspecten nader te onderzoeken: 1) de kennis en percepties van belanghebbenden over, en inzichten omtrent biosimilars en hun gebruik, inclusief noden op gebied van educatie en drijfveren, 2) regelgevende en klinische componenten die invloed kunnen hebben op de acceptatie en het gebruik van biosimilars in de klinische praktijk, en 3) biosimilar beleidsmaatregelen, met name deze met betrekking tot inkoop, en best-practices voor een meer duurzame marktwerking. Op basis van negen originele onderzoeksstudies worden aanbevelingen geformuleerd die de implementatie van biosimilars in de klinische praktijk kunnen helpen informeren en beleidsmakers kunnen ondersteunen bij beleidsontwikkeling.

Deel 1 van dit proefschrift geeft een algemene inleiding tot het onderwerp en geeft duiding omtrent de evaluatie en marktintroductie van biosimilars in de Europese context. Vervolgens worden de rationale en specifieke doelstellingen van het doctoraatsproject beschreven (**Hoofdstuk 1 en 2**).

In **Deel 2** onderzoeken we de kennis en de attitude van verschillende belanghebbenden over biosimilars en hun gebruik in de klinische praktijk. Daarnaast onderzoeken we multi-stakeholder geïnformeerde oplossingen om de geïdentificeerde barrières te overwinnen. De resultaten van het gestructureerde literatuuronderzoek in **Hoofdstuk 3** laten zien dat de kennis van zorgverleners en patiënten over biosimilars beperkt is, en dat ze aanzienlijke onzekerheden en misvattingen hebben over de goedkeuring en het gebruik van deze geneesmiddelen. Deze observatie lijkt geldig in alle groepen belanghebbenden, therapeutische gebieden, zorginstellingen en geografische regio's die onderzocht en gerapporteerd werden in de literatuur. Door middel van kwalitatieve interviews met verschillende belanghebbenden (artsen, ziekenhuisapothekers, patiënten en patiëntenorganisaties, en regelgevers) werden zeven oorzaken die deze lage kennis en vertrouwen in biosimilars verklaren geïdentificeerd: (i) een gebrek aan kennis over de regelgevende en wetenschappelijke concepten die aan de grondslag liggen van biosimilar goedkeuring, (ii) een gebrek aan kennis over biologische geneesmiddelen in het algemeen, (iii) inconsistente terminologie en verschillende regelgevende concepten tussen verschillende jurisdicties, (iv) (door de industrie gestuurde) misinformatie, (v) een gebrek aan hanteerbare en effectieve communicatiestrategieën, (vi) een gebrek aan consistentie in de beschikbare informatie omtrent biosimilars, en (vii) een gebrek aan duidelijke richtlijnen en praktische informatie over het gebruik ervan in de klinische praktijk. Op basis van de vergaarde kwalitatieve inzichten werden aanbevelingen om deze problemen te adresseren geformuleerd. Er is een duidelijke nood aan gezamenlijk actie op zowel Europees als nationaal niveau, wat op zijn beurt nauwe samenwerking en coördinatie tussen de verschillende betrokken partijen vereist.

In **Hoofdstuk 4** hebben we de opvattingen van belanghebbenden over het gebruik van biosimilars in de klinische praktijk onderzocht, in het bijzonder met betrekking tot overstappen tussen originele biologische geneesmiddelen en biosimilars, patiëntcommunicatie, en de motivatie van belanghebbenden om biosimilars al dan niet te gebruiken. We identificeerden drie belangrijke barrières die het gebruik van biosimilars in de klinische praktijk bemoeilijken: (i) onzekerheid bij zorgverstrekkers en patiënten over de veiligheid van overstappen, (ii) een gebrek aan begeleiding bij het starten van/overstappen naar een biosimilar en de communicatie daarover met de patiënt, en (iii) een gebrek aan een duidelijke motivatie of drijfveer om ze te gebruiken. Aanbevelingen om de eerste en tweede barrière aan te pakken zijn onder meer: (i) het bewijs omtrent en de opgebouwde ervaring met (meervoudig) overstappen onder de aandacht brengen, (ii) duidelijke en consistente richtlijnen voorzien over de uitwisselbaarheid van biosimilars (iii) het vermijden van top-down georganiseerde overstappen; i.e. betrek de verschillende betrokken belanghebbenden in het proces, (iv) ruimte laten voor gemotiveerde uitzonderingen op individueel patiëntniveau, en (v) een duidelijk implementatie- en communicatieprotocol toepassen om de overstap te begeleiden. Voor dit laatste werden praktische overwegingen en concrete strategieën verzameld om een overstap te begeleiden en hierover te communiceren met de patiënt. Met betrekking tot de derde barrière werden verschillende manieren voorgesteld om de bereidheid van belanghebbenden om biosimilars te gebruiken, te vergroten. Belanghebbenden pleiten zelf voor een combinatie van indirecte en directe incentives. Voorbeelden van het eerste zijn onder meer het vergroten van het bewustzijn

dat de voordelen van biosimilar markttoegang verder gaan dan “louter” directe kostenbesparingen. Voorbeelden van directe prikkels zijn onder andere het aanbieden van zogenaamde ‘benefit share’overeenkomsten, waarbij zorgprofessionals en andere belanghebbende een tastbaar voordeel ontvangen ter compensatie van de extra tijd en werkdruk die een overstap met zich meebrengt.

In **Hoofdstuk 5** hebben we ingezoomd op de paraatheid van Belgische apothekers en artsen die actief zijn in de ambulante zorgomgeving, om biosimilars voor te schrijven en af te leveren. De resultaten van onze enquête toonden aan dat er een grote behoefte is om niet enkel de kennis omtrent biosimilars te vergroten, maar ook die van biologische geneesmiddelen in het algemeen. De bestaande educatieve activiteiten en curricula over biologische, inclusief biosimilaire, geneesmiddelen in de zorgsector moeten worden herzien en – waar nodig - aangepast worden, om zo zowel de huidige alsook de toekomstige generaties zorgverleners adequaat op te leiden. Bovendien toonden de bevindingen aan dat de Belgische zorgverleners in de ambulante zorg, ondanks de duidelijke behoefte aan meer training, openstaan voor een eventuele substitutie van biologische geneesmiddelen, zolang de voorschrijver hiervan op de hoogte zou worden gesteld.

Deel 3 onderzoekt de regelgevende en klinische componenten die een invloed kunnen hebben op de acceptatie van biosimilars en hun gebruik in de klinische praktijk. In **Hoofdstuk 6** hebben we de ontwikkelingsroute van een biosimilar beschreven en meer specifiek de klinische ontwikkelingsprogramma's van de verschillende biosimilars van een geselecteerd monoklonaal antilichaam (trastuzumab) vergeleken met de EMA-richtlijnen voor klinische biosimilar ontwikkeling. Bevindingen verduidelijkten hoe klinische studies voor biosimilar-kandidaten een ander design volgen dan klinische studies in traditionele geneesmiddelenontwikkeling. Klinische studies in de context van biosimilar ontwikkeling hebben als doel om de biosimilariteit tussen de kandidaat biosimilar en het referentieproduct (het origineel biologisch geneesmiddel) te bevestigen en niet om *de novo* klinische werkzaamheid en veiligheid vast te stellen aangezien dit reeds gekend en bewezen is voor het referentieproduct. De geïdentificeerde verschillen in opzet van klinische onderzoeken, patiëntenpopulatie, en primair eindpunt tussen de klinische ontwikkelingsprogramma's van de verschillende biosimilar-kandidaten voor trastuzumab onderstreepten dat de evaluatie van biosimilars een case-by-case beoordeling van het geheel aan verzameld bewijs voor biosimilariteit vereist, waarbij de klinische studies slechts een bevestigende rol spelen.

In **Hoofdstuk 7** hebben we de rol van de Europese regelgevers in het verbeteren van de kennis en het vertrouwen in biosimilars en hun gebruik in de klinische praktijk, bestudeerd. En dit op zowel centraal als Europees lidstaatniveau. Hiertoe werd de beschikbaarheid, omvang en inhoud van de verstrekte informatie door geneesmiddelagentschappen beoordeeld. Daarnaast werden kwalitatieve inzichten van belanghebbenden (zorgverleners en farmaceutische industrie) verzameld over het onderwerp. Deze studie toonde aan dat ondanks dat er sterke regelgevende informatie over biosimilars beschikbaar is op centraal EU-niveau, de beschikbaarheid, omvang en inhoud van de verstrekte informatie over biosimilars en hun gebruik aanzienlijk varieerde tussen nationale geneesmiddelagentschappen in Europa onderling. Zonder te willen interfereren met lokale

beleidsvorming of voorschrijfprijktijken, zouden regelgevers naar een gemeenschappelijk EU-wetenschappelijk standpunt over de uitwisselbaarheid van biosimilars moeten streven. Een dergelijk uniform standpunt is een essentiële stap om duidelijkheid te verschaffen aan zowel zorgverleners, als beleidsmakers en patiënten. Daarnaast is er op het niveau van de individuele lidstaten een duidelijke kans om de informatie over biosimilars en de wetenschap die ten grondslag ligt aan de evaluatie en het veilige gebruik ervan uit te breiden en te versterken.

In **Hoofdstuk 8** hebben we de impact van overstappen op het gebied van werkzaamheid, veiligheid en immunogeniciteit onderzocht. Dit met als doelstelling om de onzekerheid omtrent de veiligheid van overstappen te adresseren, en geïnformeerde besluitvorming in de klinische praktijk te ondersteunen. Hiertoe voerden we een systematische literatuurstudie uit van de beschikbare wetenschappelijke literatuur over overstapstudies. Op basis van onze analyse van meer dan 170 klinische onderzoeken die een overstap van referentieproduct naar biosimilar of *vice versa* rapporteerden, werden geen relevante verschillen in klinische uitkomsten vastgesteld. Hoewel de meeste overstap onderzoeken niet waren opgezet om verschillen in zeldzame bijwerkingen op te sporen, ondersteunen de onderzoeken dat er geen aanwijzingen zijn dat het overschakelen tussen een referentieproduct en zijn biosimilar verband zou houden met bepaalde veiligheids-, werkzaamheids- of immunogeniciteitsproblemen. Sommige *real-world* studies brachten echter mogelijke nocebo-effecten (i.e. een negatief verwachtingseffect over de overstap bij de patiënt dewelke resulteert in waargenomen verminderde werkzaamheid of klachten) aan het licht. We concluderen dan ook dat er voldoende aandacht moet zijn voor het anticiperen op en mitigeren van een mogelijk nocebo effect bij overstappen in de klinische praktijk.

Deel 4 richt zich op het bestuderen van biosimilar inkoop en marktintroductiebeleid. In **Hoofdstuk 9** hebben we onderzocht hoe openbare aanbestedingen (tenders) voor off-patent biologische geneesmiddelen en biosimilars momenteel in Europa worden georganiseerd. Daarnaast hebben we inzichten verzameld bij betrokkenen uit zowel de farmaceutische industrie (de aanbieders) en de aankopers (waaronder ziekenhuisapothekers) met als doel om voorstellen te ontwikkelen voor duurzamere tenderpraktijken. De resultaten toonden een grote variabiliteit in de manier waarop de aanbestedingen voor off-patent biologische geneesmiddelen en biosimilars momenteel worden georganiseerd. Verschillen zijn onder meer waar te nemen in het niveau waarop de aanbesteding wordt georganiseerd (centraal, regionaal, groepsaankoop, individueel hospitaal), het aantal winnaars (single versus multiple winner) dat wordt aangeduid, en de evaluatie criteria (enkel prijs versus prijs plus kwalitatieve criteria) waarop de biedingen worden beoordeeld. Bovendien werden signalen gerapporteerd dat sommige van de huidige aanbestedingspraktijken een negatieve invloed zouden kunnen hebben op de off-patent biologische geneesmiddelen marktdynamiek, wat duidelijk de noodzaak voor een meer langetermijn- en marktduurzame kijk op aanbestedingen onderstreept. Bovendien bestaan er uitdagingen om producten te differentiëren op andere factoren dan prijs. Dit laatste wijst op de noodzaak en kans om belanghebbenden te begeleiden bij het correct en passend gebruik van evaluatie criteria. Samenvattend werden vijf belangrijke hoofdaanbevelingen geformuleerd om aanbestedingen voor off-patent biologische en biosimilaire geneesmiddelen te

optimaliseren. Voor ieder van deze hoofdaanbevelingen werden voorts gedetailleerde voorstellen uitgewerkt. Hoewel een 'one-size-fits-all'-aanpak niet mogelijk is voor het bewerkstelligen van meer duurzame aanbestedingen (gezien de grote variabiliteit in bestaande praktijken en gezondheidszorgsystemen waarin de aanbestedingen kaderen) identificeerden we op basis van ons onderzoek een aantal gemene delers. Het stimuleren van marktpluraliteit (i), een proactieve planning en vroegtijdige betrokkenheid van belanghebbenden in het proces (ii), en het consolideren van aanbestedingsexpertise (iii) zijn enkele van de *best-practices* die werden verzameld.

Verder bouwend op de bevindingen in **Hoofdstuk 9**, hebben we in **Hoofdstuk 10** verder onderzoek verricht naar de criteria die mogelijks een rol kunnen spelen in het maken van een aankoop of voorschrijfkeuze tussen verschillende beschikbare biologische geneesmiddelen (referentie product en biosimilar(s)). Deze studie had als doel om een praktisch kader te bieden aan de belanghebbenden in het veld en zo een transparante, 'best-value' productselectie te ondersteunen. Naast de geneesmiddelprijs werden criteria in drie categorieën geïdentificeerd (product-georiënteerde, service-gerelateerde en patiënt-gerelateerde criteria). Deze, en informatie over het beslissingsproces, worden in detail besproken in het betreffende hoofdstuk.

In **Hoofdstuk 11** hebben we ingezoomd op het off-patent biologische en biosimilar geneesmiddelen landschap in België. Dit met als doel om concrete, en op consensus gebaseerde aanbevelingen voor beleidsvorming te ontwikkelen. De bevindingen van deze studie pleitten voor de ontwikkeling van een geïntegreerd beleidskader dat belanghebbenden begeleidt en stimuleert bij het gebruik van biosimilars en het overstappen in de klinische praktijk. De onderzoeksresultaten onderstreepten bovendien de noodzaak om (i) beleidsvorming uit te breiden tot meer dan alleen het stimuleren van biosimilar opname, (ii) beleidsmaatregelen af te stemmen op de aflever- en product specifieke context, en (iii) verschuivingen naar duurdere, therapeutisch gelijkwaardige productalternatieven te beperken. Bovendien illustreerde de studie dat de kostenbeperkende maatregelen die gericht zijn op verplichte prijsverlagingen van het referentieproduct op het moment dat biosimilars de markt betreden, de prikkel voor biosimilar opname tenietdoen, en dit met name in de ambulante sector. Het ontbreekt de zorgverleners aan een voordeel voor henzelf of aan een voor hen duidelijk maatschappelijk voordeel om biosimilars voor te schrijven, laat staan over te stappen zonder ziekenhuisondersteuning. Actie is nodig om de concurrentie in de off-patent biologische en biosimilaire geneesmiddelen in markt in België te stimuleren, en daarbij de voordelen voor het gezondheidszorgbudget en patiënten te realiseren.

Ten slotte werden in **Deel 5 (Hoofdstuk 12)** de kennis en inzichten uit de negen individuele studies geïntegreerd in aanbevelingen om de belangrijkste uitdagingen op het gebied van biosimilar acceptatie en markttoegang te overwinnen, en bij uitbreiding een duurzame marktdynamiek voor off-patent biologische geneesmiddelen op lange termijn te ondersteunen met blijvende competitie van biosimilars.

We stellen aanbevelingen voor rond vier hoofdpijlers:

- i. Zet in op initiatieven om de kennis en het vertrouwen in biosimilars en hun gebruik te vergroten
- ii. Ondersteun belanghebbenden bij het gebruik van biosimilars en overstappen in de klinische praktijk
- iii. Verstrekk eenduidige regelgevende informatie en richtlijnen omtrent het gebruik van biosimilars en hun uitwisselbaarheid
- iv. Ontwikkel duurzaam biosimilarbeleid en optimaliseer inkooppraktijken om marktcompetitie optimaal te ondersteunen

Voor elk van deze pijlers wordt een specifieke reeks aanbevelingen voorgesteld. Deze aanbevelingen kunnen beleidsmakers in de gezondheidszorg informeren over het ontwikkelen van een coherent en duurzaam biosimilar beleid. Daarnaast bieden de aanbevelingen ondersteuning aan zorgverleners en patiënten met de implementatie en het goed gebruik van biosimilars in de klinische praktijk. Als dusdanig kan dit ontwikkeld kader van aanbevelingen bijdragen aan de realisatie van het volle potentieel van biosimilars, en de voordelen hieraan verbonden en noodzakelijk voor gezondheidszorgsystemen en patiënten.

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Chapter 3 & Chapter 4: Stakeholder knowledge, perceptions and insights on biosimilars

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Chapter 5: Knowledge and perceptions of HCPs in the ambulatory care

The authors would like to thank all survey participants for their participation and time. We also thank Andrea Jans for her help with survey programming and the survey's dissemination as part of her master thesis in Pharmaceutical Care under supervision of the PhD applicant. We thank Berengere Couneson for her support with translating the survey in French, and Dr. Joke Wuyts, Annebelle Thijs and Dr. Lore Billen for piloting the survey questions. We thank Dr. Annouschka Laenen for her input on the statistical analysis. A special thank you also to the following organizations for their support in disseminating the survey in their network: De Westvlaamse Apothekersvereniging, Groupement Belge de Médecins Spécialistes/Verbond Der Belgische Beroepsverenigingen van Artsen-Specialisten (GBS-VBS), Huisartsenkring Prometheus, Instituut voor permanente studie voor apothekers (IPSA), Koninklijke Apothekers Vereniging van Antwerpen (KAVA), Koninklijk Limburgs Apothekers Verbond (KLAV), Koninklijk Oost-Vlaams Apothekersgilde (KOVAG), Office des Pharmacies Coopératives de Belgique (Ophaco), Société Scientifique des Pharmaciens Francophones (SSPF), apotheken De Lindeboom, het Zwaard, Vivantia.

Chapter 7: Regulatory information and guidance on biosimilars and their use across Europe

The authors thank all interview participants for sharing their views on aspects related to regulatory information and guidance for biosimilar medicines with us. We thank prof. dr. Pekka Kurki (FIMEA, University of Helsinki, Finland) for his review of and valuable comments on the manuscript.

Chapter 8: The efficacy, safety and immunogenicity of switching

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Chapter 9: Off-patent biologicals and biosimilars tendering in Europe

The authors thank all participants of the survey and the interviews for their time and for sharing their insights on tender practices for off-patent biologicals and biosimilars. We wish to thank Dr. Thomas De Rijdt (UZ Leuven) and Ahmed Abouzid (IQVIA) for their review and valuable input on the survey. A special thank you to An Baeyens (DG GROW, European Commission), Benito Boone

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Chapter 11:

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PERSONAL CONTRIBUTION

Chapters 1 and 2: General introduction, research objectives and design

Liese Barbier wrote Chapters 1 and 2.

Chapter 3: Stakeholder knowledge and perceptions about biosimilars

Liese Barbier initiated the research, designed the study developed the research methods, performed the literature study, conducted interviews and supervised Sabur Ozcicek, Sophie Pinoy, Laura Stragier and Christophe Vanneste in conducting interviews. Liese Barbier coded the interview transcripts, analysed the literature and interview data and wrote the manuscript. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 4: Stakeholder insights on biosimilar use in clinical practice

Liese Barbier initiated the research, designed the study and developed the research methods, conducted interviews and supervised Sabur Ozcicek, Sophie Pinoy, Laura Stragier and Christophe Vanneste in conducting interviews. Liese Barbier coded the interview transcripts, analysed the interview data and wrote the manuscript. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 5: Knowledge and perceptions of HCPs in the ambulatory care

Liese Barbier initiated the research, designed the study, developed the research methods and analysed the survey data. Liese Barbier wrote the manuscript together with co-author Yannick Vandenplas. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 6: Regulatory framework & clinical data requirements for biosimilars

Liese Barbier developed the search strategy, reviewed the literature and wrote the manuscript. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 7: Regulatory information and guidance on biosimilars and their use across Europe

Liese Barbier initiated the research, designed the study and developed the research methods, collected the data, conducted interviews and supervised co-author Alary Mbuaki in collecting data and conducting interviews. Liese Barbier analysed the data and wrote the manuscript. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 8: The efficacy, safety and immunogenicity of switching

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Chapter 9: Off-patent biologicals and biosimilars tendering in Europe

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Chapter 10: How to select a best-value biological medicine?

Liese Barbier reviewed the literature and wrote the manuscript together with co-author Yannick Vandenplas. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 11: Biosimilar use and switching in Belgium: avenues for integrated policymaking

Liese Barbier initiated the research, designed the study, developed the research methods, conducted the focus group discussions with the help from Louise Van Bauwel and Charlotte Santens, analysed the data and wrote the manuscript. All co-authors provided substantial input and feedback throughout the study and/or on the manuscript.

Chapter 12: General discussion of findings & recommendations

Liese Barbier wrote Chapter 12.

CONFLICT OF INTEREST STATEMENT

PhD candidate

Liese Barbier's work as a PhD researcher at the KU Leuven was supported by the Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL). The MABEL Fund is a research collaboration between KU Leuven (Leuven, Belgium) and the Erasmus University Medical Center (Rotterdam, the Netherlands). The research of the MABEL Fund is supported by unrestricted grants from various pharmaceutical companies.

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Relevant COI statements are listed in the individual publications.

Other co-authors

COI statements of co-authors other than PhD supervisors are listed in the individual publications.

PROFESSIONAL CAREER

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2021	PhD in Pharmaceutical Sciences, KU Leuven, Belgium
2015	Master of Pharmaceutical Care, KU Leuven, Belgium, <i>Cum laude</i> - PharmD
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PROFESSIONAL EXPERIENCE

2016 - 2021	PhD Researcher KU Leuven, Clinical Pharmacology and Pharmacotherapy, Belgium
2019	Seconded National Expert European Medicines Agency, Oncology, Haematology and Diagnostic Office of the Human Medicines Evaluation Division, UK and the Netherlands
2015 - 2016	Adjunct Community Pharmacist Community Pharmacy Brussels, Belgium
2014 - 2015	Hospital and Clinical Pharmacist in training Pharmacist in training Hospital Pharmacy, UZ Leuven, Belgium Community Pharmacy, Belgium

PROFESSIONAL ENGAGEMENT

2019 - Present	Leadership, Co-Chair in Member Engagement ISPOR Biosimilar Special Interest Group
2019 - Present	Board Member Initiative Group Biosimilars the Netherlands (IBN)
2016 - Present	Researcher Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL Fund)
2017 - 2020	PhD student representative for the Faculty of Pharmaceutical Sciences in the Doctoral School Committee Biomedical Sciences, KU Leuven
2017 - 2018	PhD student representative at interim in the Faculty Board of Pharmaceutical Sciences, KU Leuven

TRAINING COURSES AND CERTIFICATES

2020	GCP – European Forum for Good Clinical Practice
2017	Interdisciplinary Program in Translational Medicine, I3h Institute & ULB

LIST OF PUBLICATIONS IN PEER-REVIEWED JOURNALS

- **Barbier L**, Vulto A.G. Interchangeability of Biosimilars: Overcoming the Final Hurdles. *Drugs*. (2021). Doi: 10.1007/s40265-021-01629-4
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- **Barbier L**, Simoens S, Declerck P, Vulto A.G, Huys I. Biosimilar use and switching in Belgium – avenues for integrated policymaking from the healthcare professional perspective. (Joint last authors). *Ready for submission*.
- **Barbier L**, Vandenplas Y, Boone N, Janknecht, R, Vulto A.G. How to select a best-value biological? (Joint first and last authors). *Ready for submission*.
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- **Barbier L**, Simoens S, Vulto A.G, Huys I *et al*. A European landscape of tenders for off-patent biologicals and biosimilars: what can we learn from current practices? (Joint last authors). *In preparation*.

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- Monograph Drug. ISPOR Book of Terms 2021. Section editors: Lopes Pereira C, **Barbier L**
- Monograph Biotechnology. ISPOR Book of Terms 2021. Section editors: **Barbier L**, Lopes Pereira C
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- **Barbier L**, Simoens S, Vulto A.G, Huys I. Improving biosimilar use in clinical practice. *GaBI*. 2021
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ORAL PRESENTATIONS AT INTERNATIONAL AND NATIONAL CONFERENCES

- Biosimilars' key next steps: what will the future bring? ISPOR SIG Webinar, January 2021, Online. *Accepted*.
- Biosimilars Tendering in Europe: Multi-stakeholder learnings towards sustainable practices. Forum presentation at ISPOR Europe 2021, 30 November 2021, Online. *Accepted*.
- Biologics including Biosimilars: Interchangeability and Switching, EUPATI Belgium, Webinar, *in preparation*.
- Biosimilars in Europe and the Netherlands. The future of biosimilar markets in the Netherlands. The Dutch Authority for Consumers and Markets (ACM), 19 April 2021, Online.
- Market Access Challenges and Opportunities and the role of key stakeholders. ISPOR Biosimilars SIG, Chat Leader, February 2021, Online.
- Tendering for off-patent biologicals and biosimilars: Considerations and Criteria. PUO Kwalitatief aankoopbeleid: how to (be) tender? Flemish Federation of Hospital Pharmacists (VZA), October 2020, Webinar.
- The Regulatory Evaluation and Use of Biosimilars in Dermatology. Local Quality Group (LOK) Meeting Dermatologists, November 2019, Hasselt, Belgium.
- EMA Regulatory Perspective on Biosimilars. European Cooperation on Healthcare Conference, Erasmus University, School of Health Policy & Management, June 2019, Rotterdam, the Netherlands.
- Affordability of Treatments. Towards more Sustainable Access to Medicines in Belgium Symposium, Session chair, April 2019, Leuven, Belgium.
- The Landscape of Biologics and Biosimilars: How can social pharmacy contribute? International Social Pharmacy Workshop (ISPW), July 2018, Leuven, Belgium.
- Switching from Biological Reference Products to Biosimilars: What do we learn from trials and registries? 3rd National Dutch Biosimilar Symposium, April 2018, Rotterdam, the Netherlands.
- Biosimilar medicines in Belgium – Perspective from Rheumatology. Symposium Biological medicines in Belgium by the Federal Agency for Medicines and Health Products (FAMHP), February 2018, Brussels, Belgium.
- Evidence: An international literature review – Insights from post-approval clinical studies, registries and clinical centers. 2nd Switch Advisory Board Meeting, December 2017, Amsterdam, the Netherlands.

- Guidance: Planning and implementing an effective HCP-patient dialogue in order to ensure adherence and positive clinical outcomes – An international review of publications, posters, abstracts. 2nd Switch Advisory Board Meeting, December 2017, Amsterdam, the Netherlands.
- “Partnering for patients” Insights: From a therapeutic area perspective: Additional insights from an international literature review in Dermatology, Gastroenterology and Rheumatology. 2nd Switch Advisory Board Meeting, December 2017, Amsterdam, the Netherlands.
- Clinical studies for biosimilar trastuzumab in the treatment of breast cancer: Similarities and differences. 22nd Congress of the European Association for Hospital Pharmacists (EAHP), March 2017, Cannes, France.
- Biologicals versus Biosimilars: A survey among patients and Rheumatologists. Panel discussion at the 21st Belgian Congress on Rheumatology (BCR) by the Royal Belgian Federation for Rheumatology (KBVR), September 2017, Bruges, Belgium.
- Clinical studies for biosimilar trastuzumab in the treatment of breast cancer: Similarities and differences. Biosimilars in (hemato-) oncology meeting by Biosimilars the Netherlands Foundation (IBN), September 2017, Utrecht, the Netherlands.
- Switching: How strong is the evidence? Systematic literature review: preliminary results. 2nd National Dutch Biosimilar Symposium, January 2017, Amersfoort, the Netherlands.
- Transitioning between innovator biological and its biosimilar – A Systematic Literature Review: Methodology. Biogen Switch Advisory Board Meeting, December 2016, Amsterdam, the Netherlands.
- Transitioning in Rheumatology: A Systematic Literature Review: Preliminary results. Biogen Switch Advisory Board Meeting, December 2016, Amsterdam, the Netherlands.
- Transitioning in Gastro-enterology: A Systematic Literature Review: Preliminary results. Biogen Switch Advisory Board Meeting, December 2016, Amsterdam, the Netherlands.
- Transitioning in Dermatology: A Systematic Literature Review: Preliminary results. Biogen Switch Advisory Board Meeting, December 2016, Amsterdam, the Netherlands.
- 2016-2021 Bi-annual research presentations for the MABEL Sponsor group.

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- **Barbier L**, Mbuaki A, Simoens S, Declerck P, Vulto AG, Huys I. Regulatory Information and Guidance on Biosimilars and their Use across Europe: a call for strengthened one voice messaging. Abstract accepted for poster presentation at DIA Europe 2022, Brussels, Belgium.
- Vandenplas Y, **Barbier L**, Simoens S, Van Wilder P, Vulto AG, Huys I. Perceptions about biosimilar medicines among Belgian ambulatory care patients. Abstract accepted for poster presentation at ISPOR Europe 2021, Online.

- Vulto, A.G, **Barbier, L.** Interchangeability of Biologicals in the EU Today. Presented at the XLII National Congress SIFO, October 2021, Rome, Italy.
- **Barbier L**, Simoens S, Vulto A.G, Huys I. Tendering of Off-Patent Biologicals and Biosimilars: A Proposal towards More Sustainable Practices. *Value in Health.* 2019 23:2 (S417). Presented at ISPOR Europe 2020, Online.
- **Barbier L**, Mbuaki A, Simoens S, Vulto A.G, Huys I. The role of regulatory guidance and information dissemination for biosimilar medicines – the perspective of healthcare professionals and industry. *Value in Health.* 2019 22:3 (S786-S787). Presented at ISPOR Europe 2019, Copenhagen, Denmark.
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- Vulto, A.G, **Barbier, L.** Overcoming the gap between clinical use of biosimilars and education of pharmacists and other healthcare providers. Presented at FIP 2018, Glasgow, Pre-Congress Satellite Symposium on Biosimilars.
- **Barbier L**, Ebbers H.C, Declerck P, Simoens S, Vulto A.G, Huys I. The safety of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Value in Health.* 2018 21:3 (S309). Presented at ISPOR Europe 2018, Barcelona, Spain.
- **Barbier L**, Simoens S, Declerck P, Vulto A.G, Huys I. The arrival of therapeutic biosimilars in oncology: The case of trastuzumab. *Value in Health.* 2017 20:9 (A460). Presented at ISPOR Europe 2017, Glasgow, Scotland.

SUPERVISION OF MASTER THESES AND MASTER STUDENT PROJECTS

Master students Pharmaceutical Care – Master Thesis

- Charlotte Santens (2018-2020) Decision-making and implementation of switching to biosimilars in practice.
- Louise Van Bauwel (2018-2020) Switch implementation in clinical practice – considerations of Belgian physicians and pharmacists.
- Caroline Soontjens (2017-2019) Procurement of biological medicines: practices and experiences in Europe
- Andrea Jans (2017-2019) Challenges in the implementation of biological medicines in ambulatory care in Belgium.
- Sophie Pinoy (2016-2018) Physician perspectives on biosimilar medicines
- Laura Stragier (2016-2018) Pharmacist perspectives on biosimilar medicines

- Christophe Vanneste (2016-2018) Regulatory perspectives on biosimilar medicines
- Sabur Ozicek (2016-2018) Patient perspectives on biosimilar medicines

Master students Biomedical Sciences – Master thesis

- Alary Mbuaki (2018-2019) Regulatory decision-making, guidance and information dissemination about biosimilar medicines: views of regulators and demand-side stakeholders
- Nadia Pacheco Blanco (2017-2018) The evaluation of European public assessment reports of biological medicines: A comparative document analysis

Master students Drug Development – Drug life cycle project

- Wim Dunford (2018-2019) Measures for affordable access to medicines in Belgium
- Salma Nachi (2018-2019) Measures for affordable access to medicines in Belgium
- Julie Van Dyck (2018-2019) Measures for affordable access to medicines in Belgium
- Bas Rommens (2017-2018) The role of market competition strategies in the biological medicines market
- Yannick Vandenplas (2017-2018) The role of market competition strategies in the biological medicines market
- Tom Verbeek (2017-2018) The role of market competition strategies in the biological medicines market
- Flore Pierloot (2017-2018) The role of market competition strategies in the biological medicines market

