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Safety of switching biologics and their interchangeability

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Safety of switching biologics and their interchangeability

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Declaration of Interests

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Responsibility

INESSS takes sole responsibility for the final form and content of this document. The conclusions do not necessarily reflect the opinions of those consulted for the purposes of this project.

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Introduction

A biosimilar is a biologic drug that has been shown to be very similar to a biologic drug already approved for sale. Health Canada approval of biosimilars is based on quality, safety and efficacy data. It should be noted, however, that a biosimilar cannot be considered identical to the reference biologic because of the nature of the production processes for biologics, even if its efficacy and adverse events are the same or similar to those of the reference biologic. The primary purpose of marketing biosimilars is to reduce economic burden and thereby facilitate access to this type of therapy. Their use remains low in Québec, even though the ministère de la Santé et des Services sociaux (MSSS) put restrictive rules in place promoting the expansion of the biosimilar market in 2017. If biosimilars are not used optimally, a significant increase in the use of biologics could create an untenable financial strain on public drug insurance plans, which could greatly compromise access to innovative therapies. The MSSS therefore asked the Institut national d'excellence en santé et en services sociaux (INESSS) to produce a state-of-knowledge report on the risks associated with switching biologics and their interchangeability. This report will be incorporated into the national action plan for which MSSS is responsible.

To respond to the MSSS's request, INESSS used an approach based on scientific data and the perspectives of Québec clinicians. The purpose of the present report is to provide scientific data on the efficacy and safety of switching biologics, the features of policies put in place in other countries and Canadian provinces, the guidance from learned societies, and the perspectives of Québec clinicians and pharmacists.

Methodology

Scientific data

To assess the safety of switching biologics, systematic literature searches were conducted in several bibliographic databases from 2006 (when the first biosimilars were marketed) to December 2019, in order to identify all primary studies and systematic reviews published on the subject.

To document the conditions of use and the positions of learned societies, a systematic literature search was conducted to identify guidance documents, clinical practice guidelines (CPGs), position statements and all other documents containing recommendations published between January 2013 and December 2019. Grey literature and government websites were consulted to complete the search for the features of policies put in place in other countries and Canadian provinces.

Documents were selected according to predefined exclusion and inclusion criteria, and their quality was evaluated using appropriate tools. These steps were carried out independently by two reviewers. The data were then extracted by one reviewer and verified by another. The results are presented in tables and summarized in the form of an analytical narrative synthesis.

Process for assessing the strength of the scientific evidence

The main results reported by the retained studies are presented as summary statements of scientific evidence. An overall strength of scientific evidence was assigned to each statement according to a four-level scale (high, moderate, low, insufficient).

Perspectives of Québec clinicians

INESSS formed a committee of experts in order to obtain the perspectives of Québec clinicians on switching biologic drugs. This committee brought together 19 healthcare professionals representing the main professional associations concerned by the use of biologics. Discussions with the committee enabled INESSS to gather clinician perspectives on the following general features: clinical aspects and social and organizational considerations.

Results

Safety of switching

The immunogenicity of a biologic can vary according to the patient's characteristics, the molecule used, and the disease being treated. However, the loss of a biologic's efficacy over time is not solely due to immunogenicity. It can also be caused by natural disease progression or by more rapid drug elimination. The systematic literature reviews carried out for this report to assess the safety of switching between biologics did not reveal a statistically significant difference, in terms of loss of therapeutic efficacy, immunogenicity, retention rate, and adverse events, between patients whose treatment was switched and those who remained on the reference biologic. The levels of evidence associated with these findings were considered moderate overall for inflammatory arthritis, diabetes, anemia, and plaque psoriasis. However, the levels of evidence were considered low for loss of therapeutic efficacy in inflammatory bowel disease, and insufficient in oncology and with respect to multiple switches.

Features of policies

Most jurisdictions favour switching patients being treated with a reference biologic drug to a biosimilar, without imposing this for all patients. Only a few European countries and two Canadian provinces have instituted policies leading to mandatory non-medical switching for most patients (through a national tendering process or reimbursement only for the biosimilar).

Positions and perspectives of Québec clinicians

Clinicians generally accept the preferential use of biosimilars in naïve patients, as well as switching to a biosimilar under medical supervision in patients already receiving treatment with a reference biologic. Non-medical switching in patients being treated with a reference biologic is generally not accepted by learned societies and the consulted clinicians. The latter have concerns about the destabilization of patients who are complex cases and for whom few treatment options are available, among other issues. They also have concerns about the absence of mechanisms for preventing such patients from being excluded from a non-medical switch, the fact that it is not possible to switch back in the event of a loss of efficacy or significant adverse events following the switch, and the risks associated with multiple switching. To improve medication monitoring, the consulted clinicians indicate that greater use could be made of anti-drug antibody, neutralizing anti-drug antibody and biologic drug assays. If a non-medical switch policy were to be implemented in Québec, they stress that the transition should be gradual and be aimed primarily at stable patients presenting with no particular condition. They add that good communication between the MSSS, clinicians and patients will be very important for facilitating the transition. Lastly, they underline that the savings generated should be used to improve patient services and could thus offset the loss of manufacturer-supported assistance programs.

Conclusions

This work has allowed for the identification of specific populations or biologics for which very little or no data are available regarding the safety of switching the biologic, and the significant concerns that clinicians have about non-medical switching. Most of the available scientific data have methodological limitations and raise significant uncertainty. Therefore, conducting adequate clinical studies with a larger number of individuals from these populations and with greater homogeneity in the participants' baseline characteristics would be useful to better determine the impact of switching between biologics.

ACRONYMS AND ABBREVIATIONS

AACODS	Authority, accuracy, coverage, objectivity, date and significance
ABCD	Association of British Clinical Diabetologists
ACD	Association canadienne de dermatologie
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
AGES	Austria Medicines and Medical Devices Agency
AGREE-GRS	Appraisal of Guidelines for Research and Evaluation*;* Global Rating Scale
aHR	Adjusted hazard ratio
AIDS	Acquired immunodeficiency syndrome
APFH	Portuguese Association of Hospital Pharmacists
AS	Ankylosing spondylitis
ASCO	American Society of Clinical Oncology
BC Cancer	British Columbia Cancer
BIRD	Belgium Inflammatory Bowel Disease Research and Development Group
BOPA	British Oncology Pharmacy Association
BS	Biosimilar drug
BSG	British Society of Gastroenterology
BSR	Brazilian Society of Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CAG	Canadian Gastroenterology Association
CASP	Critical Appraisal Skills Programme
CCC	Crohn’s Colitis Canada
CD	Crohn’s disease
CI	Confidence interval
CPG	Clinical practice guideline
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
EAHP	European Association of Hospital Pharmacists
ECCO	European Crohn’s and Colitis Organisation
EMA	European Medicines Agency
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
EU	European Union

EULAR	European League Against Rheumatism - People with Arthritis and Rheumatism
FBG	Brazilian Federation of Gastroenterology
FDA	Food & Drug Administration (United States)
GEDIIB	Brazilian Study Group on Inflammatory Bowel Disease
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAS	*Haute Autorité de Santé* [French National Authority for Health]
HbA1c	Glycated hemoglobin
HBI	Harvey-Bradshaw index
HIS	Healthcare Improvement Scotland
HKSR	Hong Kong Society of Rheumatology
HLA	Human leukocyte antigen
IDF	International Diabetes Federation Europe
IG-IBD	Italian Group for Inflammatory Bowel Disease
INESSS	*Institut national d'excellence en santé et en services sociaux*
ISOPP	International Society of Oncology Pharmacy Practitioners
IBD	Inflammatory bowel disease
MHC	Major histocompatibility complex
MSSS	*Ministère de la Santé et des Services Sociaux* [Ministry of Health and Social Services, Quebec]
MTX	Methotrexate
NAb	Neutralizing antibody
NICE	National Institute for Health and Care Excellence (United Kingdom)
NRAS	National Rheumatoid Arthritis Society (United Kingdom)
NRCT	Non-randomized clinical trial
OR	Odds ratio
PASI	Psoriasis Area Severity Index
PCD/PSDV	Portuguese College of Dermatology & Portuguese Society of Dermatology and Venereology
PGA	Patient global assessment
PGS	Patient global scale
PHAC	Public Health Agency of Canada
PNCG	Polish National Consultant in Gastroenterology
PsA	Psoriatic arthritis
Ps	Plaque psoriasis
RA	Rheumatoid arthritis
RAMQ	*Régie de l'assurance maladie du Québec* [Québec Health Insurance Plan]

RADS	Danish Council for the Use of Expensive Hospital Medicines
RBD	Reference biologic drug
RCT	Randomized controlled trial
RR	Relative risk
SR	Systematic review
SAA	Spondylitis Association of America
SAE	Serious adverse event
SAMAC	South Australia Medicines Advisory Committee
SBOC	Brazilian Health Surveillance Agency
SEFH	*Sociedad Espanola de Farmacia Hospitalaria* [Spanish Society of Hospital Pharmacy]
SFDA	Saudi Food and Drug Authority
SPR	Portuguese Society of Rheumatology
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFUBTRD	Task Force on the Use of Biosimilars to Treat Rheumatological Diseases
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TNF	Tumour necrosis factor
UC	Ulcerative colitis

INTRODUCTION

Issues

Biologic drugs are substances derived from living organisms (cells or tissues), often through biotechnology due to their greater complexity. Biologic drugs include insulins, erythropoiesis-stimulating agents, growth factors and monoclonal antibodies. They are generally much more expensive than other drugs and their use is increasing.

A biosimilar drug (BS) is a biologic drug that has been shown to be very similar to a biologic drug already approved for sale. Biosimilars enter the market when reference biologic drug (RBD) patents expire. Health Canada approval of a biosimilar is based on quality, safety and efficacy data. It should be noted, however, that a biosimilar cannot be considered identical to the reference biologic because of the nature of the production processes for biologics. Even with an identical amino acid sequence, glycosylation profile variations or other post-translational modifications may occur in the resultant protein. A biosimilar is therefore not a generic, even if its efficacy and adverse events (AEs) are equivalent or similar to those of the reference biologic drug. The primary purpose of marketing biosimilars is to reduce economic burden and thereby facilitate access to this type of therapy.

The usage rate of biosimilars is highest in Europe. Incentives targeting prescribing physicians, pricing, interchangeability, switching, and information policies on biosimilars have contributed to the increased use of these products. However, their usage rate is very low in Canada. In Québec, despite the fact that the Ministry of Health and Social Services (MSSS) put restrictive rules in place in 2017 promoting the expansion of the biosimilar market, their use remains low. The approach aimed at treating all treatment-naive patients registered with the Québec Health Insurance Plan (RAMQ) with a biosimilar and covering the costs of the reference biologic drug for only certain patients. There are some initiatives being undertaken elsewhere in Canada to promote the use of biosimilars. From May to November 2019, British Columbia implemented the first phase of its strategy entitled the Biosimilars Initiative, by which patients treated with the reference biologic drugs Enbrel®, Remicade® and Lantus® for certain indications (e.g. ankylosing spondylitis (AS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis (Ps) and diabetes) were switched to a biosimilar. The second phase of this initiative, which began in September 2019 and also spans a six-month period, has the same objective and is intended for people treated with Remicade® for Crohn's disease (CD) or ulcerative colitis (UC). Alberta also announced the implementation of a policy similar to that of British Columbia's starting on July 1, 2020. Ontario is following suit, via Cancer Care Ontario, and implementing an information program for healthcare professionals and patients to promote the use of biosimilars in people with particular cancers and who are treated with one of the following generics: bevacizumab, trastuzumab, and rituximab (treatment-naive or already treated patients).

Context for initiating the project

The efficacy of biosimilars appears to be widely accepted by clinicians, and there seems to be little objection to initiating such therapy in a treatment-naive patient. However, certain concerns are frequently raised about the safety of switching or substituting (interchanging) biologics, including: (1) non-medical switching of a biologic when the symptoms of a chronic disease are stable; (2) transparency for prescribing physicians regarding drug choices for switching or interchangeability; and (3) the obligation to switch the treatment of a patient who wishes to remain on the reference biologic product.

If biosimilars are not used optimally, a significant increase in the use of biologic drugs could create untenable financial strain on public drug insurance plans, which could greatly compromise access to innovative therapies. The biosimilars industry in Québec has not yet managed to establish itself firmly enough to stimulate the market, and investments by some manufacturers do not generate enough profit, which does not encourage market development. Consequently, the MSSS asked the Institut national d'excellence en santé et en services sociaux (INESSS) to produce a state-of-knowledge report on the risks associated with switching biologics and their interchangeability.

Excluded aspects

For this project, the scientific literature related to the issues evaluated by Health Canada (safety and efficacy of biologic drugs) was not analyzed, nor that related to pharmacoeconomic, ethical, social or legal issues. Scientific literature on the perspectives of patients or clinicians was not included. However, the latter aspect was documented through consultations with stakeholders or review of documents presenting contextual information.

1. METHODOLOGY

1.1. Research questions

Research questions 1 to 4 were developed, in general, using items from the PICO model – population under study (P), intervention (I), comparators (C), outcomes (O) – and are presented below.

Question 1 (pathophysiology):

How does immunogenicity develop in response to a biologic and what are the risk or mitigating factors (e.g. type of molecule, type of underlying pathology/condition, comorbidity, acute vs. chronic treatment, special populations, etc.)?

Question 2 (safety)

Does switching one biologic drug with another (reference or biosimilar) increase the risk of immunogenicity, loss of efficacy, decreased retention rate, or occurrence of AEs? What about multiple switching?

Question 3 (features of implemented policies)

In Canadian provinces or countries that have implemented strategies based on the switching or interchangeability of biologics, do these strategies apply to all biologics regardless of the nature of the drug, indication, population or healthcare setting?

Question 4 (position statements of learned societies)

What is the position of learned societies specializing in oncology, rheumatology, gastroenterology, metabolic diseases, haematology or immunology on the clinical interchangeability and switching of biologics or that of other organizations that have expressed an opinion on the subject?

Question 5 (clinician perspective)

What is the clinician perspective on immunogenicity and on the switching and interchangeability of biologics?

1.2. Methods of synthesizing scientific data

1.2.1. Type of literature review

For research questions 1 and 3, a narrative literature review was conducted. For research questions 2 and 4, a systematic literature review was conducted.

1.2.2. Literature search strategies

Question 1

A single author searched the MEDLINE and Embase databases using combinations of the following keywords: "immunogenicity", "biologics products", "biosimilars". The following selection criteria were used: the article must have been published in a peer-reviewed journal specializing in the subject in question with an impact factor greater than 2.5 based on the rating determined by the Scientific Journal Rankings organization. Only articles written in English or French published between January 1, 2000 and December 1, 2019 were retained. A single author then read each complete document to confirm its relevance. Only articles presenting theories based on human studies were selected.

Questions 2 to 4

The data search strategy was developed in collaboration with a scientific information specialist (librarian). To reduce bias, the information search was carried out in more than one database: MEDLINE (Ovid), Embase (Ovid), and Evidence-Based Medicine Reviews (EBM Reviews; Ovid). The literature search period was from January 2006 (the year the first biosimilar was marketed) to December 1, 2019. Only works published between January 2012 and December 2019 were retained for CPGs and position statements. In addition, only publications in French or English were selected. A specific search was also performed using the Google search engine to identify documents that were not published in the periodicals indexed in the databases.

The literature was also researched manually by consulting the websites of health technology assessment agencies and bodies, as well as those of government agencies, associations or professional bodies linked to the area of study. A list of the main organizations consulted is presented in Appendix A.

Documents from North American regulatory agencies, including the Food & Drug Administration (FDA) and Health Canada, were consulted.

Websites containing theses were consulted as well as those containing information on scientific studies in progress (Appendix A). This was also the case for documents published by the various departments of INESSS, including drug evaluation notices for listing purposes. The lists of drugs published by the RAMQ for institutions and the public drug insurance plan were also consulted during the project.

Lastly, the bibliographies of the retained publications were consulted in order to identify other relevant documents.

1.3. Literature selection process and criteria

Documents identified through the scientific information search were selected independently by two reviewers based on the criteria shown in Table 2. Differences in opinion were resolved by considering the opinion of a third reviewer. Where multiple publications were identified, only the most recent version was retained for analysis.

Table 1 Summary of information sources by research question

RESEARCH QUESTIONS	INFORMATION SOURCES			Synthesis method
	Scientific literature	Grey literature	Stakeholders	
Q1. Immunogenicity development	NR, SR, CPG		EC	NR
Q2. Safety	SR, RCT, OS			SR
Q3. Features of implemented policies		GR, ER, GW, EAR		NR
Q4. Positions statement of learned societies	CPG, PS	PS, EAR		SR
Q5. Clinician perspective (no literature review)			EC, KI	NR

Abbreviations: RCT: Randomized controlled trial; OS: Observational study; PS: Position statement; EC: Expert committees; KI: Key informant; EAR: Evaluation agency report; ER: Economic report; GR: Government report; NR: Narrative review; SR: Systematic review; GW: Government website

Table 2 Inclusion and exclusion criteria of scientific studies for questions 2 and 4

INCLUSION CRITERIA	
POPULATION	People treated with a biologic drug
INTERVENTION	Switch from a reference biologic drug to a biosimilar (or vice versa) or between two biosimilars
COMPARATORS	No switch (treatment maintenance)
OUTCOMES	Q2: Safety (e.g.: immunogenicity) Q4: Position statements of learned societies
STUDY TYPE (DESIGN)/ DOCUMENT TYPE	Q2: Systematic reviews with or without meta-analysis Randomized (RCT) or non-randomized controlled trial (NRCT) Comparative quasi-experimental before/after studies Observational studies (cohort study) Q4: Clinical practice guidelines Position statements
PUBLICATION YEARS	Q2: January 1, 2006 to December 1, 2019 Q4: January 1, 2012 to December 1, 2019
EXCLUSION CRITERIA	
POPULATION	Q1 to Q4: Non-human subjects
LANGUAGE	Other than French or English

1.3.1. Reference management

References were managed with EndNote bibliographic software. The studies were categorized by groups identified according to the research questions or outcomes. The EndNote file was saved in a project-specific electronic directory and managed by members of the project team.

1.4. Assessment of the quality of information from the literature

The documents were independently evaluated by two scientific professionals. In the event of a significant difference in the assessment, consensus was sought. In the absence of consensus, the opinion of a third evaluator was sollicited.

The tools and checklists used to evaluate methodological quality were:

- AGREE GRS *(*Appraisal of Guidelines for Research and Evaluation; Global Rating Scale) to assess the quality of documents containing guidelines [Brouwers *et al.,* 2012; Brouwers *et al.,* 2010].
- The critical appraisal tool for analytical studies by the Public Health Agency of Canada (PHAC) for randomized controlled trials (RCT) and observational (cohort) studies [Moralejo, 2017].
- AACODS checklist (*Authority, Accuracy, Coverage, Objectivity, Date and Significance*) for position statements [Tyndall, 2008].

1.5. Extraction of data from the literature

Data were extracted by one reviewer using pre-established extraction forms that were pre-tested on a few documents to ensure their validity. The data were then verified by a second reviewer.

1.6. Assessment of the quality of the scientific evidence

For evaluation question 2, the assessment of scientific evidence is based on the judgement of all the scientific data retrieved according to the following four assessment criteria: methodological quality of the studies, consistency, clinical impact, and generalizability. These four assessment criteria are described in Appendix F. To support the scientific statements made, an overall level of scientific evidence was assigned according to a four-level scale (high, moderate, low, insufficient). The overall level of scientific evidence reflects the integration of the results of the four scientific evidence assessment criteria for reporting confidence in the results (Table 3). The quality of the scientific data was assessed by the evaluators who performed the systematic literature review to answer the various evaluation questions. The levels of evidence are presented in Appendix F.

Table 3 Grading of the strength of the scientific evidence

Level of evidence	Definition
High	All of the criteria were given a positive assessment. The evaluators have a high level of confidence that the estimated effect would be comparable to the intervention objectives. It is not very likely that the conclusion drawn from the scientific data would be significantly affected by the results of future studies.
Moderate	Most of the criteria were given a positive assessment. The evaluators have a moderate level of confidence that the estimated effect would be comparable to the intervention objectives. It is fairly likely that the conclusion drawn from the data would be affected by the results of future studies.
Low	All or most of the criteria were given a negative assessment. The evaluators have a low level of confidence that the estimated effect would be comparable to the intervention objectives. It is very likely that the conclusion drawn from the data would be significantly affected by the results of future studies.
Insufficient	No scientific data are available or the available data are insufficient. The evaluators have no confidence in the relationship between the estimated effect and the intervention objectives or cannot draw conclusions from the data presented.

1.7. Analysis and synthesis of data from the literature

The scientific data were extracted and synthesized in the form of tables (Appendix E). The full data set was analyzed via an analytical narrative synthesis, presented according to the outcome parameters of interest.

1.8. Consultation with Québec clinicians

INESSS formed a committee of experts in order to obtain the perspectives of Québec clinicians on the switching of biologics. This committee was made up of 19 healthcare professionals representing the main professional associations affected by the use of biologics. The experts were selected by these associations and are listed in the introductory pages of this document.

The consultation was carried out through a single face-to-face meeting held on February 18, 2020, during which members of the expert committee were invited to discuss the subject. To prepare for the discussion, a preliminary document detailing the full set of results extracted from the literature and the analysis performed by INESSS, as well as guided questions to be addressed, was sent to the committee members ahead of the meeting. The discussion made it possible to gather clinician perspectives on the following general aspects: clinical issues and social and organizational considerations. In addition, the meeting was recorded, with the participants' consent. A written document based on

the comments received during the meeting was subsequently sent by email to the committee members for their approval, before being integrated into the present report.

1.9. Respect for confidentiality and the code of ethics

The members of the project team and all stakeholders consulted were required to respect the INESSS duties of discretion, confidentiality, integrity and respect. Each member of INESSS and each collaborator who participated in the work have read and agreed to comply with the code of ethics.

1.10. Prevention, declaration and management of conflicts of interest and roles

Various methods are used to prevent, declare, and manage conflicts of interest and roles in accordance with the applicable INESSS code of ethics, to ensure the integrity of the evaluations carried out and the recommendations made, thereby preserving public confidence in INESSS, its members and its collaborators.

- The first management method implemented is the balancing of diverse perspectives represented in the committees and working groups formed, to ensure all positions are considered. Thus, members represent the various stakeholders connected to the subject of the project, including a wide range of healthcare professionals with medical expertise and fields of work relevant to the work on optimal use conducted by the medication department (*Direction du Medicament)*.
- The members of the expert committee invited to contribute to the present report have declared whether they have personal interests that place them in a situation that could lead to the development of a conflict of interest, whether commercial, financial, professional, relational or otherwise. The various professional activities or roles that could lead to the development of a conflict of role have also been declared. This declaration was made using a standardized form applicable to INESSS.
- All declarations have been assessed by INESSS. Any conflicts of interest or roles have been publicly disclosed in the introductory pages of the report for the sake of transparency for readers and users of the intellectual output.

2. OUTCOMES

2.1. Description of the retained studies

The search for scientific information according to the established strategy (see Appendix A) identified 1635 publications, of which 113 were retained (see Figure B1 in Appendix B). Of these 113 publications, information was extracted from 76 primary studies and is presented in this report in sections 2.3 to 2.5. The number of studies retained for each of the subjects addressed is indicated below. Depending on the different subjects, some documents could belong to more than one category.

- Gastroenterology — Inflammatory bowel disease: 7
- Rheumatology — Inflammatory arthritis: 16
- Dermatology — Plaque psoriasis: 5
- Oncology — Neutropenia, breast cancer: 2
- Haematology/Nephrology — Anemia: 4
- Endocrinology — Diabetes: 3
- Multiple substitutions: 4
- Studies without comparators — Serious adverse events: 43

Information was also extracted from four CPGs and 33 position statements and is presented in section 2.7 of this report. A flow diagram of the study selection process, the complete list of included and excluded publications and the reasons for exclusion are provided in Appendix B. The assessment of the methodological quality of the documents cited in the outcomes section is presented in Appendix C. The characteristics of the retained primary studies are presented in the tables in Appendix D.

The data extracted from the primary studies are presented in the form of tables found in Appendix E. Statements of scientific evidence are presented in summary boxes at the end of each of the corresponding subsections. The details of the grading of the scientific evidence can be found in a table in Appendix F.

2.2. Pathophysiology

2.2.1. General information

Immunogenicity is the ability of a drug to induce an immune response in an individual. In the case of biologics, it usually results in the formation of anti-drug antibodies (ADAs) or a hypersensitivity reaction when the immune system recognizes the biologic product as an allogeneic molecule. The appearance, intensity and duration of immunogenicity are determined by the molecule’s biology and the characteristics of the patient and the disease. Although ADA formation generally does not affect the individual being treated, it can, in some cases, impair the efficacy of the biologic drug or even lead to a deterioration

in the person's state of health [Sethu *et al.,* 2012]. Two types of ADA are involved in the loss of clinical efficacy: neutralizing ADAs (NAb) that interfere with the binding of the drug to its target, and non-neutralizing ADAs that alter the pharmacodynamic profile by inducing drug clearance. Non-neutralizing ADAs are generally associated with fewer clinical consequences [EMA, 2017] and have been mostly observed in treatments with proteins such as insulin, interferons, and factor XIII. Few non-neutralizing ADAs have been observed with monoclonal antibodies [Kuriakose *et al.,* 2016]. The two types of ADA differ in their persistence in the patient since non-neutralizing ADAs remain in the system for longer than NAb [Sethu *et al.,* 2012]. ADA formation may also result in the inactivation of an essential endogenous protein or cause serious autoimmune or allergic reactions, which could lead to deterioration of the patient's state of health. Immunogenicity in the form of ADA production may occur in the days following exposure or after several weeks or months, as in the case of chronic disease treatment [Marshall *et al.,* 2018]. To limit the impact of these adverse events, it is therefore essential to recognize the factors that can influence the immunogenicity of biologics.

2.2.2. Development and production process of biologics

The development of reference biologic drugs requires the identification of coding sequences of interest whose DNA segments will then be combined to construct a functional chimeric DNA sequence that will be transformed into a mature protein in a host cell [Baldo, 2015]. In the early stages of developing these drugs, bioinformatic tools are used to predict and reduce the immunogenic potential of the molecules being developed; however, the accuracy of these tools is still considered insufficient. The host cell will then be multiplied in bioreactors before the drug is purified. Since the drug production process is carried out inside the living cell, it is impossible to control it and certain variations may occur, particularly during protein maturation. Minimal changes (base material, temperature, pH, cellular model, denaturation and aggregation) or impurities retained during the production process are closely monitored since they can go unnoticed or show marked differences in the biologic's quality [Tovey and Lallemand, 2011].

Despite the strong homology of biologics with human proteins, their immunogenic potential is assessed *in vitro,* in animal models and tested in humans during clinical phases. The immunogenic potential in humans is assessed according to the prototype of the reference biologic and not for each batch. There is variation in each drug production and the differences must not exceed a pre-established maximum threshold within the same batch to be brought to market. Each batch of biologic drugs (reference or biosimilar) is therefore considered similar to the prototype, but not identical because of the potential for minor changes during the production process [EMA, 2017]. Since biologics can be used in the long-term treatment of numerous chronic diseases, a patient may receive several different batches of the same drug during the course of treatment.

The approval process for biosimilars, although often considered insufficient by some, is very rigorous. For the approval of any biosimilar, Health Canada first requests that the similarity of the drug to the reference biologic is established on the basis of results of structural and functional comparative studies included in the chemistry and

manufacturing data set [Health Canada, 2016]. This forms the basis for the recognition of the molecule as a biosimilar. Subsequently, the biosimilar manufacturer must support its claims with appropriate scientific data. Health Canada's decision to authorize the indications requested by the manufacturer is "dependent on the demonstration of similarity between the biosimilar and the reference biologic drug based on data derived from comparative, structural, functional, non-clinical and clinical studies" (including pharmacokinetic and pharmacodynamic data and clinical trials on the efficacy, safety and immunogenicity of the drug) [Health Canada, 2016]. "Where similarity has been established, indications may be granted even if clinical studies are not conducted in each indication. A detailed rationale that scientifically justifies authorization of the biosimilar in each indication should be provided taking into consideration mechanism(s) of action, pathophysiological mechanism(s) of the disease(s) or conditions involved, safety profile, dosage regimen, clinical experience with the reference biologic drug, and any case-by-case considerations. Certain situations may warrant additional clinical data for a particular indication" [Health Canada, 2016].

In Canada, each biologic drug manufacturer must maintain a side effects monitoring system, periodically reassess the benefits of its products and notify Health Canada of any studies that provide new safety information. In addition, Health Canada requires its authorization to be granted before any changes are made to the manufacturing process of biologic drugs, changes that may occur quite frequently in the life cycle of these drugs [Health Canada, 2019]; for example, 50 changes to the manufacturing process for infliximab (Remicade®) were reported between 1998 and 2016 [Pivot and Goupille, 2019].

This procedure is regarded as essential ever since a case of severe clinical immunogenicity was identified in the early years of biologic drug use. EPREX®, a synthetic erythropoietin that had never shown any risk of immunogenicity in its early stages, had to undergo a formulation change to meet a new European Health Authorities regulation. This substitution resulted in the production of NAbs against endogenous erythropoietin in some patients, resulting in severe anemia [Casadevall, 2009; McKoy *et al.,* 2008]. These immunogenic events led to the implementation of a verification mechanism whenever a change is made to the manufacturing process. The case of Aranesp®, a modified form of erythropoietin, is a good example: since the manufacturing process was changed to increase production, several comparative clinical studies were requested by EMA to determine the bioequivalence of Aranesp® pre- and post-modifications [MacDougall *et al.,* 2015].

At a minimum, when changing the manufacturing process of a biologic drug, the manufacturer must demonstrate, theoretically or experimentally, that there is no foreseeable significant change in the physical characteristics of the drug from those initially demonstrated (for example: physico-chemical properties, biologic drug activity, immuno-chemical properties, purity, contaminants, quantity) [FDA, 2005]. However, if this cannot be demonstrated, the manufacturer must justify why these changes should not have a foreseeable effect on the drug's safety or efficacy profile, based on accumulated clinical experience or by providing relevant pre-clinical or clinical data, somewhat like the approval process for biosimilars.

2.2.3. Immunogenicity risk factors

Characteristics of the molecule

As previously mentioned, the characteristics of biologics are optimized *in silico* and *in vitro* to minimize immunogenic risks. However, certain essential characteristics of biologics cannot be modified and may increase their immunogenic risk. First, the complexity and size of the biologic allow the immune system to quickly identify it as a foreign substance. Monoclonal antibodies (adalimumab, infliximab, rituximab, etc.) are the most complex and have the highest immunogenic potential. Fusion proteins such as etanercept, followed by growth factors (filgrastim, epoetin, etc.) and the various forms of insulin show a gradually decreasing immunogenic profile [EMA-CE, 2019; Vermeire *et al.,* 2018].

Secondly, the more different the molecular structure is from that of humans, the more likely the immune system will recognize the drug as a foreign molecule and react against it. A chimeric monoclonal antibody with a non-human part (e.g. infliximab) produces higher immunogenicity than an entirely human monoclonal antibody (e.g. adalimumab) [Vermeire *et al.,* 2018]. In addition, biologic products interacting with a cellular component (e.g. receptor) are more immunogenic than those targeting soluble proteins [EMA, 2017] or immune cells [Doevendans and Schellekens, 2019]. Immune tolerance, which is the immune system's ability to accept minimal differences in self molecules, is also greater for abundant endogenous proteins. Therefore, the risk of immunogenicity is higher for a biologic that targets or replaces a type of protein found in small amounts (e.g. cytokine or growth factor) or in a patient with complete or partial lack of an endogenous molecule that the drug is intended to replace [Tovey and Lallemand, 2011]. Finally, some chemokines are associated with a high incidence of ADA development such as the recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) used in the treatment of cancer patients. This immunogenicity is related to the adjuvant properties of GM-CSF [Rini *et al.,* 2005].

Patient characteristics

One of the least predictable risk factors for the induction of immunogenicity is the "patient-specific" aspect that contributes to inter-patient variation in clinical studies [EMA, 2017]. Firstly, genetic polymorphism plays a role in the development of immunogenicity, since the latter can develop in some individuals with a genetic variation of human leukocyte antigens (HLA) that encode the major histocompatibility complex (MHC). The quality of interaction between the MHC expressed by the accessory cells and the T-cell receptor expressed by the T-cells can affect the evolution and intensity of the immune response. ADA formation would also be more likely depending on ethnic group (double in African Americans compared to Caucasians) and in the case of hemophilia associated with a specific genetic mutation, reinforcing the significance of genetic polymorphism [Kuriakose *et al.,* 2016]. Age, too, is involved in the immunogenicity profile. The immune system evolves with age by adapting and becoming more complex, then decreases in older adults and gradually displays a reduction in the quantity of plasma cells (antibody factories) [Simon *et al.,* 2015]. As a result, newborns and infants (under 2 years of age), pregnant women and the elderly show a weaker immune response with little recognition

of non-self peptides, rendering them vulnerable to various infections. Therefore, the data observed in one group of school-aged children cannot be automatically extrapolated to other age groups due to the differences in immune response [Ebina *et al.*, 2019; Simon *et al.,* 2015]. In addition, the possible window for biotherapy differs between age groups, being shorter for children than for adults. Furthermore, the use of biologic drugs in young children with Crohn's disease must be be closely monitored as they are at higher risk of relapse of its symptoms [Panaccione *et al.,* 2019].

Characteristics of the disease or other concomitant clinical conditions

As discussed in previous sections, the state of a patient's immune system plays a central role in the immunogenicity of a biologic drug. Consequently, patients with immune deficiency, regardless of the cause (e.g. medical condition or pharmacological treatment), have a greater non-self immune tolerance which should reduce the risk of ADA development: those undergoing solid organ transplantation, which requires simultaneous use of immunosuppressive drugs to prevent graft rejection [Jasiak and Park, 2016], individuals with chronic and severe alcohol consumption [Szabo and Saha, 2015; Barr *et al.,* 2016], and people with acquired immunodeficiency syndrome (AIDS), for example. Cancer patients receiving monoclonal antibody therapy are also less likely to produce ADAs. However, co-administration of monoclonal antibodies with an immunosuppressant such as methotrexate (MTX) is necessary in some cases to control ADA production during treatment [Tovey and Lallemand, 2011].

On the other hand, patients with an immune system activated by underlying conditions that create a pro-inflammatory environment (viral infections, allergies, autoimmune diseases, and chronic infections) may be more likely to develop an immunogenic response to biologics. The solicitation of the immune system during a viral infection could strengthen the immunogenic response against a biologic drug like an adjuvant would, leading to abundant production of ADA [Hall *et al.,* 2018]. In the case of allergies, the ratio between effector cells (allergic response) and suppressor cells is unbalanced, resulting in the production of IgE antibodies. It is the CD4+CD25+ suppressor cells that determine the development of a healthy or excessive immune response to an allergen or other non-self molecule [Palomares *et al.,* 2017]. A deficiency of these suppressor cells results in the development of autoimmune diseases (multiple sclerosis, type 1 diabetes, psoriasis and rheumatoid arthritis). In these patients, ADA production can be facilitated by the lack of suppressor cells. The same mechanism is also proposed to explain the decrease in the efficacy of biologic anti-TNF drugs in the treatment of arthritis, axial spondyloarthritis, Crohn's disease, psoriasis, and psoriatic arthritis in obese people, conditions associated with chronic inflammation [Shan and Zhang, 2019]. Abundant ADA production could be specific to the advanced stage of inflammation of certain diseases, with the incidence of an immunogenic response to infliximab possibly higher in patients with rheumatoid arthritis compared to patients with vasculitis and seronegative spondyloarthritis [Vultaggio *et al.,* 2008]. In addition, patients with lymphoma (a cancer of the lymphatic system affecting immune cells) would appear to develop far fewer ADAs in response to rituximab than patients with lupus (a chronic autoimmune disease) [Van Walle *et al.,* 2007].

Treatment characteristics

Certain characteristics of a biologic drug treatment, including the frequency and route of administration and the dose administered, can affect immunogenicity [Schreitmüller *et al.,* 2019]. On the one hand, repeated administration of infliximab in the same patient usually leads to a loss of efficacy [Dziechciarz *et al.,* 2016]. On the other hand, the incidence of NAb appears to be lower in continuous and long-term treatment [Sethu *et al.,* 2012], while re-exposure to the same biologic drug after a long period of no treatment (or intermittent treatment) may increase the risk of a significant immunogenic reaction, similar to a vaccine, suggesting that regular or intermittent short-term treatments are less immunogenic [EMA, 2017; Vultaggio *et al.,* 2008]. In addition, the administration of high concentrations of biologic products (more specifically, monoclonal antibodies) may result in immune tolerance in patients with rheumatoid arthritis for whom the incidence of immunogenicity in response to infliximab is lower at high doses [Wasserman *et al.,* 2004].

Finally, the route of administration may also affect the immunogenicity of a biologic product, oral administration being the least immunogenic. However, this route of administration is not feasible for biologic drugs since they can easily be denatured by the acidic environment of the digestive system. The size and sensitivity of biologics therefore requires administration via injection, inhalation or infusion, all of which are administration routes under high immune surveillance that increase the risk of an immunogenic reaction. Due to the fact that the skin's layers contain a large quantity of immune system accessory cells, mucosal or intravenous treatment administration may result in a lower risk of immunogenicity than subcutaneous administration [Doevendans and Schellekens, 2019; Meritet *et al.,* 2001a; Meritet *et al.,* 2001b; Nagler-Anderson *et al.,* 2001].

In summary…

- The development process for biologic drugs and approval by regulatory agencies minimizes their immunogenicity.
  - Prior to approving a biosimilar, Health Canada requires demonstration that its immunogenicity is not greater than that of the reference biologic.
  - The immunogenicity of a biologic drug should be reassessed in the event of any change to the manufacturing process.
- Immunogenicity may vary depending on the characteristics of the patient, molecule, disease and treatment.
- However, the immunogenicity risk of a biologic is generally higher for:
  - larger molecules (e.g. monoclonal antibodies);
  - molecules of foreign or hybrid origin (human sequence combined with a foreign sequence);

- molecules that target a cell receptor (rather than a soluble molecule);
- molecules for which the corresponding endogenous protein is found in low quantities (or is absent).

- The immunogenicity risk of a biologic drug may be greater in patients:
  - with a genetic polymorphism that increases the intensity of the immune response (e.g. HLA);
  - who have a mature and fully functional immune system (e.g. healthy adult) and who present with a pro-inflammatory state.

2.3. Safety of switching – Comparative studies

The majority of the studies retained for this report cover a single specialty with respect to one or more pathologies. However, the Norwegian study by Jorgensen *et al.* (NOR-SWITCH) involves several specialties and conditions: gastroenterology (CD, UC), rheumatology (RA, AS, PsA), and dermatology (Ps) [Jorgensen *et al.,* 2017]. In the present report, the results of this study regarding loss of efficacy are presented separately for each of the three specialties, but its results on immunogenicity, safety and retention represent the six pathologies combined.

2.3.1. Gastroenterology – inflammatory bowel disease

The systematic search for scientific information identified the following documents relating to inflammatory bowel disease (IBD): two double-blind RCTs [Ye *et al.,* 2019; Jorgensen *et al.*, 2017], two prospective cohorts [Kang *et al.*, 2018; Ratnakumaran *et al.*, 2018], one retrospective cohort [Lukas *et al.*, 2020] and two prospective cohorts compared to retrospective cohorts [Van Hoeve *et al.*, 2019; Guerra Veloz *et al.* , 2018] (Appendix E, Tables E1 to E11, E28, E29, E30). In total, the RCTs included 345 participants, 298 of whom had CD and 47 had UC, while the cohorts had 708 participants, 568 of whom had CD, 134 had UC, and six had undefined IBD. It should be noted that Kang *et al.* and Van Hoeve *et al.* conducted their work with paediatric populations. Six of the studies included subjects whose treatment with the RBD infliximab (Remicade®) was switched with the biosimilar CT-P13 [Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Ratnakumaran *et al.*, 2018; Jorgensen *et al.*, 2017], while one assessed switching an RBD adalimumab (Humira®) treatment with the biosimilar SB5 [Lukas *et al.*, 2020]. Studies were primarily conducted in Europe and South Korea.

The reported results for loss of efficacy are similar in both treatment groups for the seven studies assessing this parameter [Lukas *et al.*, 2020; Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Ratnakumaran *et al.*, 2018; Jorgensen *et al.*, 2017]. No statistically significant difference in the proportion of patients in clinical remission was observed between the two treatment groups after a 54-week follow-up for the Ye *et al.* study (RBD/RBD 53.7% vs RBD/BS 60.0%, p = 0.564 and BS/BS 62.5% vs BS/RBD 58.2%, p = 0.700); a 52-week follow-up for Jorgensen *et al.* (CD: aRD: 6.1 [-9.6 to 21.9]; UC: aRD: -5.0 [-18.6 to 10.0]); a 12-month follow-up for Guerra Veloz *et al.* (CD: RBD/RBD 69.2% vs RBD/BS 67.7%, p = 0.992; UC: RBD/RBD 75.0% vs RBD/BS 69.2%, p = 0.866); Kang *et al.* (RBD/RBD 90.3% vs RBD/BS 88.6% p = 1.000), Ratnakumaran *et al.* (RBD/RBD 47.4% vs RBD/BS 58.1% p = 0.370). The study by Lukas *et al.* showed no difference in disease activity (CD, HBI p = 0.179; UC, pMayo p = 0.670). The Jorgensen *et al.* non-inferiority study indicates that treatment with CT-P13 is not inferior to infliximab after switching due to disease worsening in the treatment of ulcerative colitis or Crohn's disease. However, it should be noted that, for the latter, the observed difference in disease worsening is at the 15% tolerance limit set by the authors, i.e. -14.3%.

Several biochemical parameters (e.g. C-reactive protein (CRP), albumin, platelets, hemoglobin, etc.) were also assessed in the various studies retained and no clinically significant differences were observed.

Immunogenicity results are presented in four studies [Lukas *et al.*, 2020; Ye *et al.*, 2019; Kang *et al.*, 2018; Jorgensen *et al.*, 2017]. No statistically significant differences were detected in three studies [Lukas *et al.*, 2020; Kang *et al.*, 2018; Jorgensen *et al.*, 2017]. Only the number of new subjects with ADAs showed a statistically significant difference in one of the retained studies [Ye *et al.*, 2019].

- The proportion of ADA-positive subjects at the end of follow-up in the two treatment groups in the Ye *et al.* RCT varied as follows: RBD/RBD 38.9% vs RBD/BS 54.5%, p = 0.126; BS/BS 39.3% vs BS/RBD 32.7%, p = 0.554. The difference was RBD/RBD 90.3% vs RBD/BS 94.3%, p = 0.888 in the Kang *et al.* cohort and RBD/RBD 2.2% vs RBD/BS 2.2%, p = 1.000 in the Lukas *et al.* adalimumab study.
- The difference in the proportion of new ADA-positive subjects between the two treatment groups in the RCT by Ye *et al.* was significant for RBD/RBD 0% vs RBD/BS 12.7%, p = 0.012, but not significant for BS/BS 3.6% vs BS/RB 5.4%, p = 0.679. This result is also not statistically significant in the Kang *et al.* cohort: RBD/RBD 5.6% vs RBD/BS 2.6%, p = 0.610.
- A single study assessed the presence of NAb in subjects at the end of the observation period and found no statistically significant difference: RBD/RBD 10.7% vs RBD/BS 12.5%, p = 0.573 [Jorgensen *et al.*, 2017].
- Two studies assessed the presence of new NAbs in subjects during the observation period and reported results varying from 0 to 7.9% with no statistically significant differences [Ye *et al.*, 2019; Jorgensen *et al.*, 2017].

With respect to the occurrence of adverse events, no statistically significant differences could be detected between the two treatment groups in the six studies that assessed this parameter [Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Ratnakumaran *et al.*, 2018; Jorgensen *et al.*, 2017].

- The total proportion of subjects who experienced AEs or treatment-emergent adverse events (TEAEs) during the observation period was similar among groups in four studies, varying from 25.9 to 72.7% (Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Kang *et al.*, 2018; Jorgensen *et al.*, 2017]. Although still not statistically different, such results were much lower in one cohort study, varying from 9.2 to 11.2% [Guerra Veloz *et al.*, 2018].
- The total proportion of subjects who experienced serious adverse events (SAEs) or treatment-emergent serious adverse events (TESAEs) during the observation period was similar among the groups in the five studies assessing this parameter and varied from 0 to 10.0% [Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Jorgensen *et al.*, 2017].

No statistically significant differences were observed between the two treatment groups in the four studies that assessed the subject retention rate at the end of the observation period. Retention varied from 83.9 to 97.0% in the studies that assessed this parameter [Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Jorgensen *et al.*, 2017]. It should be noted that no statistically significant difference in the treatment discontinuation rate due to adverse events was observed in the studies concerned, with this rate varying from 0 to 6.5% [Van Hoeve *et al.*, 2019; Ye *et al.*, 2019; Guerra Veloz *et al.*, 2018; Kang *et al.*, 2018; Ratnakumaran *et al.*, 2018].

Subsequent to the systematic search, ten systematic reviews (SR) aimed at assessing the effect of switching a RBD to a BS, and that included studies on IBD, were retained (Moayyedi *et al.*, 2020; Bakalos and Zintzaras, 2019; Feagan *et al.*, 2019; Cohen *et al.*, 2018a; Gisbert and Chaparro, 2018; McKinnon *et al.*, 2018; Numan and Faccin, 2018; Inotai *et al.*, 2017; Moots *et al.*, 2017; Radin *et al.*, 2017]. Several of these SRs conclude that the cumulative results from published data do not demonstrate any significant difference for loss of efficacy, immunology or safety [Feagan *et al.*, 2019; Cohen *et al.*, 2018a; Gisbert and Chaparro, 2018; Radin *et al.*, 2017], and the difference reported in some studies can likely be explained by subjective worsening of the disease and treatment safety [Bakalos and Zintzaras, 2019; Inotai *et al.*, 2017]. Other SRs conclude that the absence of clinical effect in switching to these biosimilars has not yet been fully demonstrated in terms of long-term efficacy, safety and immunogenicity [McKinnon *et al.*, 2018; Numan and Faccin, 2018; Moots *et al.*, 2017], and that additional longer-term studies are required. An SR including studies on Crohn's disease and ulcerative colitis presents a meta-analysis with statistically significant results in favour of the reference biologic due to loss of response or disease progression (RR 0.64 [95% CI: 0.44 to 0.94]) [Moayyedi *et al.*, 2020]. One of the studies included in this meta-analysis is published only as a conference abstract [Röder *et al.*, 2018]. It could not be retained for the present SR since the lack of details precluded assessment of its methodological quality.

The publications retained for this section have some methodological limitations. Ye's RCT was not designed with enough statistical power to analyze the study extension period, during which treatment was switched to the biosimilar. Jorgensen's RCT was not designed to have the statistical power to demonstrate non-inferiority within each condition analyzed, but rather across all conditions. In addition, there is some heterogeneity among the different study populations: adult subjects with active or stable disease, paediatric subjects, imbalance in the different conditions analyzed and presence of comorbidity and comedication. The analysis of results for efficacy and ADA was carried out with various diagnostic tools. In the cohort studies, the distribution of groups was non-random and often according to participant choice. Significant variation in study group size and small population sizes were also noted.

In summary…

According to the results reported in the documents retained, for subjects with inflammatory bowel disease (see Table F1 in the appendices):

- No statistically significant difference in the risk of loss of treatment efficacy is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low
- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate

- No statistically significant differences are observed in retention rates when comparing subjects who received a biosimilar to those in whom the reference biologic drug was maintained.
  Level of scientific evidence: Moderate

2.3.2. Rheumatology – inflammatory arthritis

The systematic search for scientific information identified 16 primary studies that assessed the effect of switching a biologic drug in people with inflammatory arthritis: nine double-blind RCTs [Yamanaka *et al.*, 2020; Alten *et al.*, 2019; Genovese *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.*, 2019; Cohen *et al.*, 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.*, 2017], two prospective cohorts [Kaltsonoudis *et al.*, 2019; Vergara-Dangond *et al.*, 2017], one retrospective cohort [Yazici *et al.*, 2018], one prospective cohort compared to a retrospective cohort [Scherlinger *et al.*, 2018], one prospective cohort compared to a historical cohort [Tweehuysen *et al.*, 2018] and two retrospective cohorts compared to historical cohorts [Glintborg *et al.*, 2019; Glintborg *et al.*, 2017] (Appendix E, Tables E12 to E23, E28, E29, E30).

Of the seven RCTs, three addressed treatment with infliximab (RBD Remicade® to BS CT-P13) [Alten *et al.*, 2019; Smolen *et al.*, 2018; Jorgensen *et al.*, 2017], four related to treatment with adalimumab (RBD Humira® to BS BI695501 [Cohen *et al.*, 2018b], BS SB5 [Yamanaka *et al.*, 2020; Weinblatt *et al.*, 2018] or BS FKB327 [Genovese *et al.*, 2019]) and two addressed treatment with rituximab (RBD Rituxan® or MabThera® to BS CT-P10 [Shim *et al.*, 2019] or BS GP2013 [Tony *et al.*, 2019]). In addition, the majority of the participants included in these studies had RA.

Of the seven cohorts, five studied subjects who underwent infliximab treatment switching (RBD Remicade® to BS CT-P13) [Kaltsonoudis *et al.*, 2019; Scherlinger *et al.*, 2018; Yazici *et al.*, 2018; Glintborg *et al.*, 2017; Vergara-Dangond *et al.*, 2017] and two studied those who underwent etanercept treatment switching (RBD Enbrel® to BS SB4 [Glintborg *et al.*, 2019; Tweehuysen *et al.*, 2018]).

In total, the RCTs included 4,274 participants, 4,153 of whom had RA, 91 had AS and 30 had PsA. The cohorts included 969 participants, 729 of whom had RA, 227 had AS, none had PsA, and 13 had unspecified arthritis. The three cohorts that were compared to historical groups included 3,488 participants, 2,055 of whom had RA, 778 had AS, and 655 had PsA. Two of the historical cohorts [Glintborg *et al.*, 2019; Tweehuysen *et al.*, 2018] included 2,615 participants, 1,641 of whom had RA, 481 had AS, and 473 had PsA. The description of the Glintborg *et al.* historical cohort [2017] is missing. The follow-up duration across all of the retained studies varied from 12 weeks to 18 months, with the majority of studies having a follow-up period of more than 24 weeks. The studies were primarily conducted in Europe, North America and Latin America, but also in the Asia-Pacific region, Australia, Russia, Israel and North Africa.

Of the studies retained, 12 investigated whether switching the biologic treatment led to a loss of treatment efficacy and no statistically significant differences were observed between the two treatment groups in 11 of these studies [Alten *et al.*, 2019; Glintborg *et al.*, 2019; Kaltsonoudis *et al.*, 2019; Shim *et al.*, 2019; Cohen *et al.*, 2018b; Scherlinger *et al.*, 2018; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Glintborg *et al.*, 2017; Jorgensen *et al.*, 2017; Vergara-Dangond *et al.*, 2017]. Only the Tweehuysen *et al.* NRCT (comparison with a historical cohort) demonstrated a statistically significant difference in efficacy, in favour of the RBD group in people with RA or PsA (DAS28-CRP, DRA 0.15 [95% CI: 0.05 to 0.25]). The authors state that these results are not considered clinically relevant. It should also be noted that the parameters analyzed to assess the loss of treatment efficacy differed between studies and according to the condition involved. In the Smolen *et al.* study it is indicated that a certain degree of reduction in treatment response, based on the ACR20, is observed in subjects who switched treatment (RBD/BS) and did not experience any dosage increase during the follow-up period, compared to subjects who were always treated with the RBD (RBD/RBD) or the BS (BS/BS). This difference, however, is not statistically significant.

No statistically significant differences in immunogenicity rates were observed between the two treatment groups in the eight retained RCTs that assessed this parameter [Yamanaka *et al.*, 2020; Alten *et al.*, 2019; Genovese *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.*, 2019; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.*, 2017].

- The proportion of ADA-positive subjects at the end of the observation period varied from 42.0 to 50.5% in the infliximab studies [Alten *et al.*, 2019; Smolen *et al.*, 2018], from 0 to 61.0% in the adalimumab studies [Yamanaka *et al.*, 2020; Genovese *et al.*, 2019; Weinblatt *et al.*, 2018] and from 0 to 12.9% in the rituximab studies [Shim *et al.*, 2019; Tony *et al.*, 2019].
- The proportion of positive subjects who developed new ADA at the end of the observation period varied from 14.6 to 14.9% in the infliximab study [Smolen *et al.*, 2018], from 6.3 to 12.6% in the adalimumab study [Weinblatt *et al.*, 2018] and from 0 to 1.9% in the rituximab studies [Shim *et al.*, 2019; Tony *et al.*, 2019].
- The proportion of NAb-positive subjects at the end of the observation period varied from 10.7 to 34.3% in the infliximab studies [Alten *et al.*, 2019; Jorgensen et al., 2017], from 0 to 12.6% in the adalimumab study [Yamanaka *et al.*, 2020] and was 0% in the rituximab studies [Shim *et al.*, 2019; Tony *et al.*, 2019].
- The proportion of positive subjects who developed new NAb at the end of the observation period varied from 7.1 to 7.9% in the infliximab study [Jorgensen *et al.*, 2017].

With respect to the number of subjects who experienced adverse events, no statistically significant differences were observed between the two treatment groups in the 11 studies that assessed these parameters [Yamanaka *et al.,* 2020; Alten *et al.*, 2019; Glintborg *et al.*, 2019; Kaltsonoudis *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.,* 2019; Cohen *et al.,* 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.,* 2017; Vergara-Dangond *et al.*, 2017].

- The total proportion of subjects who experienced AEs or TEAEs during the observation period varied from 21.3 to 69.8% in the nine studies that assessed this parameter [Yamanaka *et al.*, 2020; Alten *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.*, 2019; Cohen *et al.*, 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.*, 2017; Vergara-Dangond *et al.*, 2017].
- The total proportion of subjects who experienced SAEs or TESAEs during the observation period varied from 0 to 16.7% in the 11 studies that assessed this parameter (Yamanaka *et al.*, 2020; Alten *et al.*, 2019; Glintborg *et al.*, 2019; Kaltsonoudis *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.*, 2019; Cohen *et al.*, 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.*, 2017; Vergara-Dangond *et al.*, 2017].

No statistically significant differences in the subject retention rate at the end of the observation period were observed between the two treatment groups in eight of the 12 studies that assessed this parameter [Genovese *et al.*, 2019; Kaltsonoudis *et al.*, 2019; Shim *et al.*, 2019; Cohen *et al.*, 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Glintborg *et al.*, 2017; Jorgensen *et al.*, 2017], this rate varying between 86.1 and 100%.

A statistically lower retention rate is observed in the BS group compared to the RBD group in the Scherlinger *et al.* cohort (RBD/RBD 87.8% vs RBD/BS 71.9%, $p = 0.013$), and in the Yazici *et al.* cohort (RBD/RBD 66.1% vs RBD/BS 13.0%, $p < 0.001$). In their 2017 and 2019 studies, Glintborg *et al.* demonstrated a statistically significant difference in the adjusted retention rate between the RBD/BS group and a historical cohort (HRBD) (2017: HRBD 86.8% [95% CI: 84.8 to 88.8] vs RBD/BS 83.4% [95% CI: 80.8 to 86.2], $p = 0.03$; 2019: HRBD vs RBD/BS aHR = 1.76 [95% CI: 1.39 to 2.23], $p<0.0001$). Specific factors that could lead to the discontinuation of treatment with the biosimilar product were identified in these four articles: use of MTX, CRP level, overall disease activity score (PGS, PGA), less than one year of treatment with the RBD and obtaining remission with treatment switching. Two studies also indicate that retention rates would be lower in patients who switched to the biosimilar when they have RA rather than AS or PsA [Glintborg *et al.*, 2019; Scherlinger *et al.*, 2018].

With respect to the treatment discontinuation rate due to AEs or TEAEs, no statistically significant differences were observed in 10 out of 11 studies that assessed this parameter [Yamanaka *et al.*, 2020; Alten *et al.*, 2019; Kaltsonoudis *et al.*, 2019; Shim *et al.*, 2019; Tony *et al.*, 2019; Cohen *et al.*, 2018b; Smolen *et al.*, 2018; Weinblatt *et al.*, 2018; Jorgensen *et al.*, 2017; Vergara-Dangond *et al.*, 2017]. However, a statistically significant increase in the treatment discontinuation rate due to AEs or TEAEs was observed in the Tweehuysen *et al.* study (RBD/RBD 2.2% vs RBD/BS 4.5%, $p = 0.026$).

Subsequent to the systematic search, nine SRs were retained that aimed at assessing the effect of a RBD-to-BS treatment switch and included studies on inflammatory arthritis [Bakalos and Zintzaras, 2019; Feagan *et al.*, 2019; Cohen *et al.*, 2018a; Declerck *et al.*, 2018; McKinnon *et al.*, 2018; Numan and Faccin, 2018; Inotai *et al.*, 2017; Moots *et al.*, 2017; Radin *et al.*, 2017]. Several of these SRs conclude that the cumulative results from published data do not demonstrate any significant difference between the two treatment

groups in terms of loss of treatment efficacy, immunogenicity or safety [Feagan *et al.*, 2019; Cohen *et al.*, 2018a; Radin *et al.*, 2017], and the difference reported in some studies can likely be explained by subjective worsening of the disease and treatment safety, or by the nocebo effect [Bakalos and Zintzaras, 2019; Inotai *et al.*, 2017]. Other SRs conclude that the absence of clinical effect in switching treatment to a biosimilar has not yet been fully demonstrated in terms of long-term efficacy, safety and immunogenicity [Declerck *et al.*, 2018; McKinnon *et al.*, 2018; Numan and Faccin, 2018; Moots *et al.*, 2017], and that additional longer-term studies are required.

The retained publications have some methodological limitations. With respect to the RCTs, some studies were not designed to assess secondary criteria on the basis of a formal hypothesis and the interpretation of the results is based on descriptive statistics. In addition, these studies were not designed to provide statistical comparisons between the two treatment groups, but rather consisted of study extension periods. This means that the statistical power was potentially insufficient to detect a difference between the treatment groups by the end of the observation period. The results obtained must therefore be analyzed accordingly. Moreover, the Jorgensen study was not designed to demonstrate non-inferiority within each diagnostic group, and the small sample size may have led to selection bias. In addition, study populations were not homogeneous, including adult subjects with active or stable disease and a preponderance of subjects with RA.

The cohort studies also contain several limitations. The distribution of groups was non-random and often according to participant choice. Variations in the study group size and the baseline characteristics of the subjects were noted, as well as a small sample population size. The duration of pre-treatment with the reference biologic varied between cohorts within the same study and between studies. Comedications could vary for the same disease (e.g., methotrexate, folic acid). Some studies had short follow-up periods and in several cases no reason was provided for discontinuation. The use of historical cohorts can lead to selection, temporal and performance biases.

In summary…

According to the results reported in the retained documents, for subjects with inflammatory arthritis (see Table F2 in the appendices):

- No statistically significant difference in the risk of loss of treatment efficacy is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: High
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who received a

biosimilar to those for whom the reference biologic was maintained.
Level of scientific evidence: Moderate

- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the retention rate is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate

2.3.3. Dermatology – plaque psoriasis

The systematic search for scientific information identified five primary studies, all of which were double-blind RCTs that assessed the effect of switching a treatment with a biologic drug in people with plaque psoriasis [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017] (Appendix E, Tables E24 to E27, E28, E29, E30).

Of these five RCTs, one addressed infliximab treatment (RBD Remicade® to BS CT-P13 [Jorgensen *et al.*, 2017]), three were related to adalimumab treatment (RBD Humira® to BS ABP501 [Blauvelt *et al.*, 2018; Papp *et al.*, 2017] or BS MSB11022 [Hercogova *et al.*, 2020]) and one looked at etanercept treatment (RBD Enbrel® to BS GP2015 [Griffiths *et al.*, 2017]). A total of 1,824 subjects with Ps were included in these studies, which were primarily carried out in Europe, North and South America, but also in Australia and South Africa. Follow-up duration for the retained studies varied from 48 to 66 weeks for the total study length and from 32 to 52 weeks for the period after the treatment was switched to a biosimilar. In addition, two of the selected RCTs involved multiple switches [Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017], alternating treatments three or four times every six weeks.

Of the studies retained, three investigated whether switching the biologic would lead to a loss of treatment efficacy. No statistically significant differences were observed between the group whose treatment was switched to a biosimilar and the group that remained on the reference biologic (% of PASI 75: RBD/RBD 87.1% vs RBD/BS 81.2% [Papp *et al.*,

2017]; variation in PASI: RBD/RBD -94.0 ± 9.7 vs RBD/BS -94.8 ± 9.7 [Hercogova *et al.*, 2020]; PASI: -0.28 (95% CI: -1.10 to 0.55] [Jorgensen *et al.*, 2017]).

In addition, no statistically significant differences in immunogenicity were observed between the two treatment groups in the five RCTs that assessed this parameter [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017].

- The proportion of ADA-positive subjects at the end of the observation period varied from 35.8 to 88.5% in adalimumab studies [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Papp *et al.*, 2017] and between 0 and 1.1% in the etanarcept study [Griffiths *et al.*, 2017].
- None of the studies reported results for new ADA.
- The proportion of NAb-positive subjects at the end of the observation period varied from 10.7 to 12.5% in the infliximab study [Jorgensen *et al.*, 2017], between 20.3 and 39.3% in adalimumab studies [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Papp *et al.*, 2017] and was 0% in the etanarcept study [Griffiths *et al.*, 2017].
- The proportion of new NAb-positive subjects at the end of the observation period varied from 7.1 to 7.9% in the infliximab study [Jorgensen *et al.*, 2017].

With respect to the number of subjects who experienced adverse events, no statistically significant differences were observed between the two treatment groups in the five studies that assessed this parameter [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017].

- The total proportion of subjects who experienced AEs or TEAEs during the observation period varied from 46.0 to 77.3% in the five studies that assessed this parameter [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017].
- The total proportion of subjects who experienced SAEs or TESAEs during the observsation period varied from 2.4 to 10.0% in the five studies that assessed this parameter [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017].

No statistically significant differences in the subject retention rate at the end of the observation period were observed between the two treatment groups in the five studies that assessed this parameter [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017], this rate varying between 74.6 and 100%.

With respect to the discontinuation of treatment due to AEs or TEAEs, no statistically significant differences were observed for this parameter in the five studies [Hercogova *et al.*, 2020; Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017; Jorgensen *et al.*, 2017; Papp *et al.*, 2017]. The results varied from 1.3 to 11.1%.

Subsequent to the systematic search, four SRs were retained that aimed at assessing the effect of RBD-to-BS treatment switching and included studies on plaque psoriasis [Ebbers *et al.*, 2019; McKinnon *et al.*, 2018; Numan and Faccin, 2018; Moots *et al.*, 2017]. Ebbers *et al.* conclude in their SR that the cumulative results from published data show no significant differences for loss of efficacy, immunology or safety. Nevertheless, the other SRs conclude that the effect of switching to these biosimilars has not yet been fully demonstrated in terms of long-term efficacy, safety and immunogenicity [McKinnon *et al.*, 2018; Numan and Faccin, 2018; Moots *et al.*, 2017] and that additional longer-term studies are required.

The retained publications contain some methodological limitations. Some studies were not designed to assess treatment switching and the statistical power for secondary parameters could be insufficient to detect a difference between the treatment groups by the end of the observation period. The scope of the results obtained must therefore be analyzed accordingly. Moreover, Jorgensen's study was not designed to demonstrate non-inferiority within each diagnostic group, but rather across all conditions combined. The study populations were homogeneous and may not be representative of clinical practice. The small sample size could have led to selection bias.

In summary…

According to the results reported in the documents retained, for subjects with plaque psoriasis (see Table F3 in the appendices):

- No statistically significant difference in the risk of loss of treatment efficacy is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate

- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the retention rate is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate

2.3.4. Oncology – breast cancer (neutropenia prevention, HER2 positive)

The systematic search for scientific information identified two primary studies, double-blind RCTs, which assessed the effect of substituting treatment with a biologic drug in people with breast cancer [Blackwell *et al.*, 2018; Von Minckwitz *et al.*, 2018] (Appendix E, Tables E31 to E34).

Of these two RCTs, one studied treatment with filgrastim (RBD Neupogen® to BS EP2006 Zarxio®) for the prevention of severe neutropenia [Blackwell *et al.* 2018] and the other studied treatment with trastuzumab (RBD Herceptin® to BS ABP980) in people with HER2-positive early stage breast cancer [Von Minckwitz *et al.*, 2018]. These international studies included 939 participants in total. Follow-up was carried out over six cycles of chemotherapy for filgrastim and 52 weeks for trastuzumab.

Of the studies retained, only that on filgrastim sought to determine whether switching a biologic treatment to a biosimilar led to a loss of efficacy. No statistically significant difference was observed for this parameter between the group switched to the biosimilar treatment and the group that remained on the reference biologic drug (difference in febrile neutropenia: -3.4; 95% CI: -9.65 to 4.96) [Blackwell *et al.*, 2018].

In addition, no statistically significant difference in the level of immunogenicity rate was observed between the two treatment groups in the study that assessed this parameter since all subjects were NA-b negative [Blackwell *et al.*, 2018].

With respect to the number of subjects who experienced adverse events, no statistically significant differences were observed between the two treatment groups in the two studies retained [Blackwell *et al.*, 2018; Von Minckwitz *et al.*, 2018].

- The total proportion of subjects who experienced AEs or TEAEs during the observation period varied from 95.3 to 96.1% in the Blackwell study and from 32.2 to 38.6% in the Von Minckwitz study.
- The total proportion of subjects who experienced SAEs or TESAEs during the observation period varied from 2.0 to 4.7% in the Blackwell study and was 3.5% in both treatment groups in the Von Minckwitz study.

No statistically significant differences in the subject retention rate at the end of the observation period were observed between the two treatment groups in the two studies retained [Blackwell *et al.*, 2018; Von Minckwitz *et al.*, 2018]. This rate varied from 86.4 to 96.0%.

With respect to the rate of treatment discontinuation due to AEs or TEAEs, no statistically significant differences were observed for this parameter in the two studies retained [Blackwell *et al.*, 2018; Von Minckwitz *et al.*, 2018]. No subjects experienced a TEAE leading to the discontinuation of treatment in the Blackwell study, whereas this rate varied from 1.8 to 2.3% in the Von Minckwitz study.

Subsequent to the systematic search, two SRs were retained that aimed at assessing the effect of switching an RBD treatment to a biosimilar, and included studies on cancer patients [Declerck *et al.*, 2018; McKinnon *et al.*, 2018]. These two SRs conclude that switching to a BS has not yet been fully demonstrated in terms of long-term efficacy, safety and immunogenicity, and that additional longer-term studies are required.

The retained publications have some methodological limitations. Both studies concern breast cancer, but one focuses on the prevention of neutropenia while the other on HER2-positive breast cancer treatment. The generalization of the results may be limited by the selection of a specific patient population.

In summary…

Based on the results reported in the documents retained, for subjects who received neutropenia prevention and HER2-positive breast cancer treatments (see Tables F4 and F5 in the appendices):

- No statistically significant difference in the risk of loss of treatment efficacy is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low and insufficient, respectively
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low and insufficient, respectively
- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was

maintained.
Level of scientific evidence: Low

- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low
- No statistically significant difference in the retention rate is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low

2.3.5. Endocrinology – diabetes

The systematic search for scientific information identified three primary studies that assessed the effect of switching treatment to a biologic drug in people with diabetes, including one double-blind RCT (ELEMENT 2 study [Rosenstock *et al.*, 2015]), one open-label RCT (INSTRIDE 3 study [Blevins *et al.*, 2019]) and a post-hoc analysis of two RCTs, i.e. the ELEMENT 1 and ELEMENT 2 studies [Hadjiyianni *et al.*, 2016] (Appendix E, Tables E35 to E38). The ELEMENT 1 and ELEMENT 2 studies recruited subjects who were previously treated with the RBD Lantus® at the time of study inclusion, as well as subjects who were not receiving treatment with a biologic. However, the results were not presented according to the drug status of the subjects at inclusion in the original publication of the ELEMENT 1 study [Blevins *et al.*, 2015], while this distinction was only made for some results in the original publication of the ELEMENT 2 study. Nonetheless, the post-hoc analysis by Hadjiyianni *et al.* allows for this distinction in the results of these two studies, without combining them. To avoid duplication of results in the present systematic review, only data that do not appear in the original publication of the ELEMENT 2 study as well as all data related to the ELEMENT 1 study were extracted from the post-hoc analysis reported by Hadjiyianni. To simplify the presentation of results, the names of the studies will be used for further analysis rather than that of the authors of the publication.

The ELEMENT 1 and ELEMENT 2 studies focused on insulin glargine treatment (RBD Lantus® to BS LY IGlar) in people with type 1 diabetes (T1D) or type 2 diabetes (T2D), respectively [Hadjiyianni *et al.*, 2016; Rosenstock *et al.*, 2015], whereas the INSTRIDE 3 study dealt with the treatment of T1D with insulin glargine (RBD Lantus® to BS MYL-1501D [Blevins *et al.*, 2019]). A total of 878 subjects with diabetes participated in these studies, including 579 with T1D and 299 with T2D. The studies were primarily conducted in Europe and North America, but also in Korea, Taiwan and Japan. Follow-up duration for the retained studies varied from 28 to 52 weeks. In addition, Blevins *et al.* carried out multiple switching in their RCT, alternating treatments three times, every 12 weeks.

With respect to loss of treatment efficacy, no statistically significant differences in HbA1c levels were observed in the group switched to a biosimilar treatment compared to the group that remained on the reference biologic (INSTRIDE 3: 0.01, 95% CI: −0.085 to 0.101, p > 0.05; ELEMENT 2: -0.004, 95% CI: -0.193 to 0.185, p > 0.05; ELEMENT 1: -0.018, 95% CI: -0.149 to 0.112, p > 0.05) [Blevins *et al.*, 2019; Hadjiyianni *et al.*, 2016; Rosenstock *et al.*, 2015].

In addition, no statistically significant difference in the immunogenicity rate was observed between the two treatment groups in the ELEMENT 1, ELEMENT 2, and INSTRIDE 3 studies (p > 0.05) [Blevins *et al.*, 2019; Hadjiyianni *et al.*, 2016].

- The proportion of ADA-positive subjects at the end of the observation period varied from 9.8 to 12.4% in the ELEMENT 1 study and from 2.8 to 5.8% in the ELEMENT 2 study [Hadjiyianni *et al.*, 2016].
- The proportion of new ADA-positive subjects at the end of the observation period varied from 14.1 to 14.3% in the INSTRIDE 3 study [Blevins *et al.* 2019] and from 3.8 to 6.8% in the ELEMENT 1 study [Hadjiyianni *et al.*, 2016].
- None of the studies reported results for NAb.
- None of the studies reported results for new NAbs.

With respect to the number of subjects who experienced adverse events, no statistically significant differences were observed between the two treatment groups in the studies retained (p > 0.05 in the ELEMENT 1 and 2 studies; p = 0.853 in the INSTRIDE 3 study) [Blevins *et al.*, 2019; Hadjiyianni *et al.*, 2016]. However, a statistically significant reduction in the rate of TESAEs was observed in the group that was switched to a biosimilar treatment compared to the group that remained on the reference biologic in the ELEMENT 2 study (RBD/RB 8.3% vs RBD/BS 2.6%, p = 0.038) [Hadjiyianni *et al.*, 2016].

- The total proportion of subjects who experienced AEs or TEAEs during the observation period varied from 61.5 to 66.7% in the studies involving subjects with T1D (INSTRIDE 3 and ELEMENT 1) and from 47.9 to 48.4% in the study involving subjects with T2D (ELEMENT 2) [Blevins *et al.*, 2019; Hadjiyianni *et al.*, 2016].
- The total proportion of subjects who experienced SAEs or TESAEs during the observation period varied from 3.1 to 4.8% in the INSTRIDE 3 study [Blevins *et al.*, 2019] and from 7.8 to 9.4% in the ELEMENT 1 study [Hadjiyianni *et al.*, 2016].

No statistically significant difference in the subject retention rate at the end of the observation period (RBD/RBD 92.1% vs RBD/BS 95.3%, p = 0.49) or in the treatment discontinuation rate due to AEs or TEAEs (RB/RB 1.6% vs RBD/BS 0%, p = 0.496) was observed between the two treatment groups in the only study that assessed these parameters [Blevins *et al.*, 2019].

Subsequent to the systematic search, a sole systematic review aimed at assessing the effect of switching a RBD to a BS and which included studies on diabetes, was retained [McKinnon *et al.*, 2018]. The authors of this SR conclude that the effect of switching

treatment to a biosimilar on long-term efficacy, safety and immunogenicity has not yet been fully demonstrated, and that additional longer-term studies are required.

The retained publications contain some methodological limitations. Some studies were not designed to assess the effect of treatment switching and the statistical power could be insufficient to detect a difference between the treatment groups by the end of the observation period. Generalization of the findings may be limited by the selection of a patient population that is potentially less heterogeneous than in clinical practice. One of the RCTs was open in design, which can lead to detection bias.

In summary…

According to the results reported in the documents retained, for subjects with type 1 or type 2 diabetes (see Table F6 in the appendices):

- No statistically significant difference in the risk of loss of treatment efficacy is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: High
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low
- No statistically significant difference in the retention rate is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Low

2.3.6. Haematology/Nephrology – Anaemia caused by chronic kidney disease

The systematic search for scientific information identified four primary studies that assessed the effect of switching treatment with a biologic drug with epoetin in patients on hemodialysis due to anemia caused by chronic kidney disease: one double-blind RCT [Haag-Weber *et al.*, 2009], one open-label RCT [Thadhani *et al.*, 2018] and two retrospective cohorts [Belleudi *et al.*, 2019; Minutolo *et al.*, 2017] (Appendix E, Tables E39 to E42).

The epoetin-type biologic drugs of interest varied in these four studies according to the following treatment switches: from RBD Epogen® or Procrit® to BS Retacrit® in the Thadhani *et al.* study; from RBD Eprex®/Erypo® to BS Binocrit® in the Haag-Weber *et al.* study; from RBD epoetin alpha Eprex®, epoetin beta NeoRecormo® or Aranesp® darbepoetin to BS Binocrit® or Retacrit® in the Minutolo *et al.* study; and from RBD Eprex® to BS Abseamed®, Retacrit® or Binocrit® in the Belleudi *et al.* study. The last study also assessed switching a BS with its RBD. These studies included 5,402 participants in total and were conducted in Europe and the United States. Follow-up duration for the studies varied from 24 to 52 weeks.

The four retained studies assessed the loss of efficacy following the switching of a treatment with a biologic drug. No statistically significant differences were observed in three of these studies between the group whose treatment was switched to a biosimilar compared to the group that remained on the reference biologic [Belleudi *et al.*, 2019; Thadhani *et al.*, 2018; Haag-Weber *et al.*, 2009]. No statistically significant difference was obtained when the BS was switched with the RBD in the Belleudi study. However, a significant difference in favour of no substitution was observed in the time-weighted average concentration of hemoglobin (TWA_{Hb}) in the Minutolo study (TWA_{Hb}: -0.20; 95% CI: -0.33 to -0.06; p<0.001).

In addition, no subjects developed NAbs in the only study that evaluated this parameter [Haag-Weber *et al.*, 2009]. Subjects with ADAs, new ADAs or NAbs were not evaluated in any of the retained studies.

With respect to the number of subjects who developed adverse events, no statistically significant differences were observed between the two treatment groups in either of the studies that evaluated this parameter [Belleudi *et al.*, 2019; Thadhani *et al.*, 2018].

- In the study by Thadhani *et al.*, the overall proportion of subjects who developed AEs or TEAEs during the observation period varied from 59.2 to 63.7% (p = 0.367), while the aHR was 1.18 [95% CI: 0.49 to 2.83] for RBD/RBD vs RBD/BS and 1.52 [95% CI: 0.54 to 3.90] for BS/BS vs BS/RBD [Belleudi *et al.*, 2019] in the two studies that evaluated this parameter.
- The overall proportion of subjects who developed SAEs or TESAEs during the observation period was evaluated in just one study and was found to vary between 15.5 and 16.0% (p = 0.894) [Thadhani *et al.*, 2018].

No statistically significant differences in subject retention rate at the end of the observation period were observed between the two treatment groups in either of the studies that evaluated this parameter (p varying from 0.356 to 0.498) [Thadhani *et al.*, 2018; Haag-Weber *et al.*, 2009]. The rate varied from 73.6 to 86.6%.

With respect to the rate of treatment discontinuation due to AEs or TEAEs, no statistically significant differences were observed between the two treatment groups in the only study that evaluated this parameter (RBD/RBD 4.4% vs RBD/BS 6.1%, p = 0.656) [Thadhani *et al.*, 2018].

Subsequent to the systematic research, two SRs were included, both of which aimed to assess the effect of switching treatment from a RBD to a BS and involved studies of anaemia and chronic kidney disease [McKinnon *et al.*, 2018; Inotai *et al.*, 2017]. Inotai *et al.* conclude in their SR that the cumulative findings of the published data show no significant differences in terms of loss of efficacy, immunogenicity or safety between the group whose treatment was switched to a BS and the group that remained with the RBD. They further state that the difference reported by some studies likely represents a subjective worsening of disease and safety [Inotai *et al.*, 2017]. In the SR by McKinnon *et al.*, the authors conclude that long-term efficacy, safety and immunogenicity when switching from an RBD to a BS have not yet been fully demonstrated, and that additional longer-term studies are required.

There are some methodological limitations of the retained publications. Generalization of the findings may be limited by the selection of a patient population that is potentially less heterogeneous than in clinical practice. One of the RCTs was open label, which can lead to detection bias. Some studies present a certain imbalance in the size of the groups compared. There is a lack of information on the study populations, particularly regarding disease severity, such as levels of hemoglobin and iron. Subjects were treated with the RBD for different periods depending on the study, varying from 24 weeks to one year.

In summary…

According to the results reported in the documents retained, for subjects on hemodialysis as a result of anaemia caused by renal disease (see Table F7 in the appendices):

- No statistically significant differences are observed in the risk of loss of treatment efficacy when comparing subjects who received biosimilars with those in whom the reference biologic drug was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of developing anti-drug antibodies or neutralizing anti-drug antibodies is observed when comparing subjects who

received a biosimilar to those for whom the reference biologic was maintained.
Level of scientific evidence: Low

- No statistically significant difference in the risk of experiencing adverse events or treatment-emergent adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant difference in the risk of experiencing serious adverse events or treatment-emergent serious adverse events is observed when comparing subjects who received a biosimilar to those for whom the reference biologic was maintained.
  Level of scientific evidence: Moderate
- No statistically significant differences are observed in retention rates when comparing subjects who received biosimilars with those in whom the reference biologic drug was maintained.
  Level of scientific evidence: High

2.4. Multiple switching

The systematic search for scientific information identified four primary studies that evaluated the effect of multiple switching between a reference biologic drug and a biosimilar: two double-blind RCTs in plaque psoriasis sufferers [Blauvelt *et al.*, 2018; Griffiths *et al.*, 2017], one open-label RCT in patients with T1D [Blevins *et al.*, 2019], and one double-blind RCT on the prevention of neutropenia in breast cancer patients [Blackwell *et al.*, 2018]. Data from these articles have already been included in the analyses in the previous sections and have shown no statistically significant differences in terms of loss of efficacy, immunogenicity, adverse events or retention rates. However, given the highly heterogeneous nature of the conditions being studied and the findings presented in these articles, no conclusions could be drawn on the safety of multiple switching and the level of evidence was deemed insufficient (Table F9 in the appendices).

In summary…

According to the results reported in the documents retained, for subjects who have undergone multiple switching of a biologic drug (see Table F9 in the appendices):

- There are insufficient data to draw any conclusions on the safety of multiple switching with respect to the risk of loss of treatment efficacy, the risk of emergence of anti-drug or neutralizing anti-drug antibodies, the risk of developing adverse events or treatment-related adverse events, the risk of developing serious adverse events or serious treatment-related adverse events and the rate of retention of treated individuals.
  Level of scientific evidence: Insufficient

2.5. Safety of switching – Non-comparative studies

Several primary articles evaluating the switch from a reference biologic drug to a biosimilar have been published by various health facilities internationally. However, in the large majority of these studies, there is no comparator (continuation of treatment with the RBD evaluated over the same period or in a historical cohort) and at the time of treatment switching, only baseline values are available. In the absence of a comparator, it is difficult to interpret the findings of these publications, which do not meet the selection criteria set out in this SR. However, the AEs/TEAEs and SAEs/TESAEs that led to the discontinuation of treatment in the populations that switched their medication to a biosimilar were still extracted for information purposes (Table E43 in the appendices).

A quick analysis of these data shows major variations in the number of subjects who experienced adverse events when switching from an RBD to a BS, with proportions from 0 to 82.8% of subjects. These variations are possibly related to the lack of uniform definitions of AEs/TEAEs in these studies. In addition, few of these articles compiled treatment-related AEs/TEAEs, which could have reduced the rates of AEs observed. The percentage of subjects who experienced SAEs/TESAEs after switching treatment varies from 0 to 9.1%. Fewer SAEs/TESAEs are seen in cases of IBD, with rates from 0 to 5.2%, while rates for inflammatory arthritis vary from 1.7 to 9.1%. The rate of AEs/TEAEs resulting in discontinuation never exceeded 10% in any of the studies.

2.6. Features of implemented switching policies

The main source of information on the switching policies implemented worldwide is a 2018 document by CADTH, which was supplemented by consultation of 25 government websites by the project team. Most of these switching strategies offer multiple incentives to encourage the breakthrough of biosimilars in the market, while interchangeability was only the concern of a few countries. The specific features of these strategies are summarized in Table 4.

2.6.1. Regulatory context

The public health agencies consulted, including Health Canada, are in favour of switching when it is a physician's decision to use a biosimilar for a patient (medical switching). However, none of the agencies stated a position on switching imposed by an administrative policy (non-medical switching), leaving this decision up to the government, region or country concerned [Biosimilar Medicines, 2019; Santé Canada, 2019; HIS, 2018; Baumgärtel, 2017; EMA, 2017; FDA, 2017; HAS, 2017; SAMAC, 2017; NICE, 2016].

Nonetheless, the FDA, the South Australia Medicines Advisory Committee (SAMAC), Germany's Paul-Ehrlich-Institute, and the French national health authority (Haute Autorité de Santé, HAS) have introduced regulatory processes that allow for recognition of the interchangeability of biosimilars. Currently, no biosimilars have been recognized as interchangeable by the FDA. However, SAMAC has allowed this practice since 2019 for the etanercept reference biologic drug, except for children with severe idiopathic juvenile arthritis and severe plaque psoriasis, and for infliximab and pegfilgrastim [PBS, 2020; SAMAC, 2017]. In addition, biologic drugs (both RBD and BS) within the same group can be considered interchangeable in Germany and France. In France, however, this is only the case at the start of treatment [CADTH, 2018], whereas in Turkey, Estonia, Poland and Serbia, such a practice takes place due to a lack of regulation [GaBI, 2017; Roediger *et al.*, 2017].

2.6.2. International switching policies

In accordance with public health agency guidelines, several governments, regions and countries strongly recommend medical switching for reference biologic drugs (Table 4) in all patients [Center for Biosimilars Staff, 2019; CADTH, 2018; FDA, 2017; GaBI, 2017; Roediger *et al.*, 2017]. However, Portugal and Italy require that the patient has been treated with the reference biologic drug for at least six months before it can be replaced with a biosimilar, and that adequate time has been allowed for clearance of the drug, respectively [Biosimilar Medicines, 2019; Genazzani *et al.*, 2017]. The use of biosimilars is not mandatory but is encouraged by the implementation of strategies that influence treating physicians or hospitals by restricting market availability. These strategies are explained in the following sections.

Financial incentives

To stimulate the advancement of biosimilars in Ireland, the government gives hospitals back a proportion of the savings generated for each patient whose reference biologic drug has been replaced by a biosimilar [Center for Biosimilars Staff, 2019]. In the United States, France and the United Kingdom, meanwhile, prescribing physicians receive money when they prescribe the least expensive biologic [CADTH, 2018].

Setting quotas

Some countries, such as France, Germany, Greece, Italy, Denmark, Latvia and Lithuania have adopted quota policies whereby they set a maximum percentage of patients who can be prescribed the reference biologic drug [CADTH, 2018; Roediger *et al.*, 2017]. In France, physicians are free to prescribe reference biologic drugs for patients who need them, up to a maximum of 30% of prescriptions, with the remainder of prescriptions being made for biosimilars [CADTH, 2018]. Elsewhere, such as in Germany, physicians would have to pay any amount exceeding a fixed budget, which encourages them to prescribe the least expensive drug [CADTH 2018].

National purchasing policy

Other European countries (see Table 4) purchase the least expensive biologic, often a biosimilar, while maintaining limited availability of reference biologic drugs. This gives doctors the freedom to refuse the drug proposed by the government [Roediger *et al.*, 2017]. As for Denmark, the government negotiates the price of biologics through a centralized system, purchases the drug that wins the call for tender and distributes it to hospitals, thereby imposing non-medical switching for all patients receiving treatment in a hospital setting. There are exceptions, however, such as for patients with cognitive disorders and those showing a lack of efficacy after at least three months of use, who can then resume their initial treatment [Davio, 2019]. Denmark's success is unequivocal, with 90% of patients switching from adalimumab to a biosimilar in just three weeks [Torgny, 2019]. Poland, Bulgaria, Serbia, and Turkey also have a national policy of buying the least expensive biologic drug; theirs is more radical, though, as there are no possible medical exceptions. In addition, when calls for tenders are made on a regular basis, as in Bulgaria (every 12 months), Denmark (every 12 to 24 months) or Finland (every 24 to 36 months), patients may be forced to switch multiple times during their treatment course [CADTH, 2018; Roediger *et al.*, 2017].

2.6.3. Switching policies in Canada

In Canada, there is no federal policy governing non-medical switching of biologics. In contrast, treatment-naive patients are strongly encouraged to start their treatment with a biosimilar since several provinces, including Québec, no longer cover new prescriptions for reference biologic drugs for these patients, except for indications not covered by the biosimilar. Regarding patients already undergoing treatment, two Canadian provinces have adopted or announced the forthcoming implementation of a strategy to promote switching from the reference biologic drugs listed in Table 5 to a biosimilar. Thus, British Columbia has introduced a policy whereby the reference biologic drug will no longer be

reimbursed when a biosimilar has been approved by Health Canada for the same indication (see Table 4) [BC PharmaCare, 2019]. This policy applies to patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or diabetes (since November 25, 2019) and to Crohn's disease or ulcerative colitis patients (since March 5, 2020). The measure currently only applies to adults, with the policy for children still being discussed. Pregnant women treated with Remicade™ and patients treated with Lantus could also be exempted from this policy, based on a case-by-case assessment, in addition to First Nations diabetic patients who are exempted under their Plan W insurance coverage (grandfather clause).

Alberta has also announced a similar policy to British Columbia which will take effect on July 1, 2020 but has expanded its application to include people with plaque psoriasis and neutropenic patients treated for cancer [Alberta Blue Cross, 2020]. Currently, Alberta's policy excludes people under the age of 18 and pregnant women.

Ontario is currently involved in consultations on the appropriateness of a non-medical switching policy like those in British Columbia and Alberta. However, the current strategy in Ontario, which promotes the use of biosimilars in treatment-naive patients, suggests some exceptions that could also be applied to a possible non-medical switching policy. These include children with neutropenia and patients beginning stem cell transplant therapy [Wojtyra, 2019; OPDP, 2018; OPDP, 2016].

Table 4 Description of switching strategies adopted by several countries to facilitate or enforce the breakthrough of biosimilars in their territory

Switching policy	Country	Special features
Medical switching strongly encouraged in patients already being treated	• Germany • Australia • Spain • United States • Finland • France • Italy • Norway • New Zealand • The Netherlands • Portugal • United Kingdom	*No information available*
Financial incentives	• United States	Savings shared with the physician
	• France	Additional remuneration for the physician for at least 20% of prescriptions for insulin biosimilars
	• Ireland	An amount for each patient switched
	• United Kingdom	Savings shared with the physician (1% share for 80% of prescriptions for the least expensive biologic drug)
National purchasing policy	• Germany • Belgium • Croatia • Spain • Estonia • Finland • France • Italy • Norway • The Netherlands • Portugal • Czech Republic • United Kingdom • Sweden	**With** the option for prescribers to refuse
	• Bulgaria • Denmark (hospital)* • Poland • Serbia • Turkey	**Without** the option for prescribers to refuse
Setting quotas	• Germany	A certain percentage of prescriptions must be written for biosimilars; associated with penalties
	• France	70% of prescriptions for biosimilars
	• Lithuania	No prescriber refusal
	• Denmark • Greece • Italy • Latvia	*No information available*
Interchangeability accepted	• Germany	Biosimilars considered to be bioidentical
	• Australia	Specific *a-flag* list
	• United States	Unless the physician documents “no switching” and with biosimilars approved for interchangeability
	• France	At the start of treatment only, unless the doctor writes “no switching”
	• Poland	Unless the doctor documents “no switching”
	• Estonia • Czech Republic • Turkey	*No information available*
Non-medical switching without influence	• British Columbia	*No information available*
	• Alberta	

*The program excludes patients with cognitive disorders and those whose switch treatment is not effective after three months of use.

Table 5 Description of mandatory switching for patients being treated with Enbrel™, Remicade™, Lantus™, Neupogen™ or Neulasta™ in certain Canadian provinces

Province	Pathology	Mandatory switching from reference biologic drugs		Exceptions (no enforced switching)	
British Columbia		**Enbrel™**	**Remicade™**	**Enbrel™**	**Remicade™**
	Rheumatoid arthritis	✓	✓		Pregnant women and assessment on a case-by-case basis for all pathologies
	Psoriatic arthritis	✓	✓		
	Ankylosing spondylitis	✓	✓		
	Psoriasis		✓	✓	
	Crohn's disease		✓		✓ Patients ‹ 18 years
	Ulcerative colitis		✓		✓Patients ‹ 18 years
		Lantus™		**Lantus™**	
	Type 1 diabetes	✓		Exemption for medical reasons, or First Nations patients	
	Type 2 diabetes	✓			
		Neupogen™		**Neupogen™**	
	Neutropenia	No obligation		✓ Treatment-naive patients ‹ 18 years who have had adverse events with other drugs ✓ Treatment-naive patients with latex allergies ✓ Treatment-naive patients treated with stem cell transplant therapy	
Alberta		**Enbrel™**	**Remicade™**	**Enbrel™**	**Remicade™**
	Rheumatoid arthritis	✓	✓	✓Patients ‹ 18 years and pregnant women	Patients ‹ 18 years and pregnant patients, for all pathologies
	Psoriatic arthritis	✓	✓	✓Patients ‹ 18 years and pregnant women	
	Ankylosing spondylitis	✓	✓	✓Patients ‹ 18 years and pregnant women	
	Psoriasis		✓		
	Crohn's disease		✓		
	Ulcerative colitis		✓		
		Lantus™		**Lantus™**	
	Type 1 diabetes	✓		✓Patients ‹ 18 years and pregnant women	
	Type 2 diabetes	✓		✓Patients ‹ 18 years and pregnant women	
		Neupogen™	**Neulasta™**	**Neupogen™**	**Neulasta™**
	Neutropenia	✓	✓	✓Patients ‹ 18 years and pregnant women	✓Patients ‹ 18 years and pregnant women

In summary…

The 17 sources of information that describe strategies to stimulate the use of biosimilars bring several practices to light:

- Most of the jurisdictions examined are in favour of switching patients being treated with a reference biologic drug to a biosimilar, **but do not impose this on all patients (via financial penalties or incentives, quotas, etc.).** Some countries support the following principles:
  - the physician should have some freedom in choosing patients whose treatment should be switched to a biosimilar;
  - the patient should have been treated for at least six months prior to switching;
  - the patient should have had time for clearance of his or her biologic drug.
- Only a few European countries (Denmark, Bulgaria, Poland and Serbia) and two Canadian provinces have adopted policies for **mandatory non-medical switching for the vast majority of patients (national tendering processes or reimbursement of biosimilars only)**. These policies, however, have the following limits:
  - the policies in British Columbia and Alberta do not generally apply to children nor to pregnant women;
  - in Denmark, people with cognitive disorders and those for whom the substitute treatment is observed to be ineffective after at least three months of use may continue to use their initial treatment.

2.7. Position statements from learned societies

Consultation of learned societies and national and international organizations identified 33 documents outlining positions on switching from biologics to biosimilars, each of which could involve several specialties: a total of 13 documents in the field of rheumatology, 12 in gastroenterology, five in dermatology, four in oncology and four in endocrinology. The remaining ten position statements come from international specialist groups or from pharmacist groups and government agencies. The present SR also identified four CPGs with recommendations for non-medical switching from a reference biologic drug to a biosimilar.

Table 6 presents the position statements from the various learned societies on medical and non-medical switching from a reference biologic drug to a biosimilar and their interchangeability. Where Table 6 mentions the word “conditional”, the position statement has specific features discussed in the paragraphs that follow.

2.7.1. Use of biosimilars in treatment-naive patients

All the learned societies consulted, except for the Working Group of the Polish National Consultant in Gastroenterology (PNCG) [Mularczyk *et al.*, 2014], agree on the preferential use of biosimilars in treatment-naive patients. However, the Canadian Gastroenterology Association (CAG) and Crohn’s Colitis Canada (CCC), two Canadian specialist gastroenterology groups, recommend that people with ulcerative colitis begin therapy with the reference biologic drug (infliximab), given the lack of available evidence on biosimilars [Moayyedi *et al.*, 2020]. In addition, the European League Against Rheumatism-People with Arthritis and Rheumatism (EULAR) recommends that a biosimilar be given to a treatment-naive patient on the basis of a medical decision rather than an administrative one [Wiek, 2018].

2.7.2. Single switching in patients already undergoing treatment

Rheumatology

Rheumatology societies are generally in favour of switching a patient already being treated to biosimilars when this involves an informed discussion between the patient and the physician (medical switching). In contrast, the position statements consulted raise some concerns and specific points with regards to non-medical switching. Firstly, the Canadian Rheumatology Society (CRA) and the National Rheumatoid Arthritis Society of the United Kingdom (NRAS) recommend that the patient and the physician be given six months’ notice in advance of any non-medical switching [NRAS, 2019; CRA, 2019]. In addition, they recommend that a patient can return to the reference biologic drug if switching to a biosimilar is associated with important side effects within the first six months of use. The CRA also has reservations regarding paediatric patients for whom switching must only take place for indications authorized by Health Canada. Along the same lines, the Brazilian Society of Rheumatology (BSR), the Saudi Food and Drug Authority (SFDA) and the NRAS [NRAS, 2019; Halabi *et al.*, 2018; Azevedo *et al.*, 2015] recommend that switching only take place in patients who have been treated in a stable manner for at least six months. The American College of Rheumatology (ACR) and the Spondylitis Association of America (SAA) are strongly opposed to non-medical switching to biosimilars when treatment with the reference biologic drug (specifically, monoclonal antibodies), is effective [Ward *et al.*, 2019]. The ACR also recommends that the prescriber have the option of refusing non-medical switching for a patient by documenting “dispense as prescribed” on the prescription. Lastly, the Portuguese Society of Rheumatology (SPR) takes issue with medical and non-medical switching owing to a lack of evidence on the subject [Araujo *et al.*, 2017].

Endocrinology

Diabetes Canada has a firm position against non-medical switching in patients already being treated, a position shared by the International Diabetes Federation Europe (IDF) and the Association of British Clinical Diabetologists (ABCD). However, these organizations are not against switching when the physician and the patient make this decision by mutual agreement (medical switching), according to Diabetes Canada [Diabetes Canada, 2019], or there is a benefit related to improved disease control, as per IDF and ABCD [Biosimilar Medicines, 2019; Diabetes Canada, 2019]. In addition, ABCD opposes non-medical switching to biosimilars in patients who have achieved their HbA1c target without hypoglycemia [Biosimilar Medicines, 2019]. Diabetes Canada adds that certain populations, such as children, pregnant women, the frail elderly and those with a history of mental illness can be seriously affected by drug switching [Diabetes Canada, 2019].

Gastroenterology

Except for CAG, most of the learned societies that have expressed an opinion on medical switching to biologic drugs favour this practice. Such is the case for the Belgium Inflammatory Bowel Disease Research and Development Group (BIRD), the British Society of Gastroenterology (BSG), CCC, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (IBD Porto Group of ESPGHAN), the Danish Council for the Use of Expensive Hospital Medicines (RADS), the Brazilian Federation of Gastroenterology (FBG) and the Brazilian Study Group on Inflammatory Bowel Disease (GEDIIB). They specify, however, that medical switching is acceptable only after a period of at least six months of stable symptoms. In contrast, there is uniform opposition to non-medical switching, with CAG citing the increased risk of disease worsening and the need to increase the dose or of having to switch to an alternative therapy [Moayyedi *et al.*, 2020; Biosimilar Medicines, 2019; De Ridder *et al.*, 2019; Franchimont *et al.*, 2018; Danese *et al.*, 2017; Azevedo *et al.*, 2015]. Nevertheless, the European Crohn's and Colitis Organisation (ECCO) takes a positive stance on non-medical switching, while specifying that the patient should be in a stable state before non-medical switching can be considered, and that it is important to take patient preferences into account [Danese *et al.,* 2017]. In pediatric patients, IBD Porto Group of ESPGHAN supports switching only when children have received at least three injections of the reference biologic drug and are in stable clinical remission [De Ridder *et al.*, 2019].

Dermatology

All the learned dermatology societies that have expressed an opinion on the subject are opposed to non-medical treatment switching in psoriasis sufferers [Biosimilar Medicines, 2019; ACD, 2013]. Nevertheless, they are all in favour of medical switching from a reference biologic drug to a biosimilar, taking the view that the treating physician should be free to choose the treatment for his or her patient. The Portuguese College of Dermatology & Portuguese Society of Dermatology and Venereology (PCD/PSDV) has not issued an opinion on medical switching, while awaiting evidence on the matter.

Oncology

The Brazilian Health Surveillance Agency (SBOC) only approves of medical switching when the reference biologic drug is contraindicated (administration route, allergies, etc.) [Fernandes *et al.*, 2018], while the other four societies (see Table 6) accept it in hospitals, in order to ensure adequate medical supervision [Nakashima, 2019; Tabernero *et al.*, 2016]. While non-medical switching is not unanimously accepted among the societies consulted, the International Society of Oncology Pharmacy Practitioners (ISOPP) supports the practice, provided that it is partially implemented for patients who meet all the safety criteria for biosimilar use; British Columbia Cancer (BC Cancer) can accept it if ongoing treatment is not interrupted and if the first drug can be retained in the event of relapse [ISOPP, 2019; Nakashima, 2019]. The American Society of Clinical Oncology (ASCO) supports medical switching from a reference biologic drug to a biosimilar, taking the view that the treating physician should be free to choose the treatment for his or her patient [Lyman *et al.*, 2018].

Other groups

The British Oncology Pharmacy Association (BOPA), a group of pharmacists, believes that monoclonal antibodies are safe and well tolerated by patients because their side effects are more to do with batch differences than with the molecules themselves. BOPA considers biosimilars to be clinically identical to reference biologic drugs and therefore supports all forms of switching, either between reference biologic drugs and biosimilars or between different biosimilars [Biosimilar Medicines, 2019]. However, the Portuguese Association of Hospital Pharmacists (APFH) proposes that the patient maintain his or her therapy for at least nine months before any switching is considered [Biosimilar Medicines, 2019]. The Sociedad Espanola de Farmacia Hospitalaria (SEFH) supports non-medical switching in hospital settings, while recommending that the implementation policy take the opinions of patients, physicians and pharmacists into account [Martinez-Lopez de Castro *et al.*, 2018]. Elsewhere, drug and technology assessment agencies, including the Austria Medicine and Medical Devices Agency (AGES), the National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland (HIS), and SAMAC, take a clear stance against non-medical switching of biologic drugs, arguing for the importance of the patient and the physician in the decision [HIS, 2018; Baumgärtel, 2017; SAMAC, 2017; NICE, 2016].

2.7.3. Multiple switching

Few societies have issued an opinion on multiple switching. EULAR-PARE, a group of professionals and patients with rheumatism and rheumatoid arthritis in Europe, the Hong Kong Society of Rheumatology (HKSR), ECCO, and the Italian Group for Inflammatory Bowel Disease (IG-IBD) are of the opinion that there is a lack of scientific evidence allowing for multiple switching or switching between biosimilars [Fiorino *et al.*, 2019; Ho *et al*, 2019; Wiek, 2018; Danese *et al.*, 2017]. ISOPP is also opposed to this practice in oncology, while other oncology societies have not adopted a position on the matter [ISOPP, 2019]. The international multidisciplinary working group, the Task Force on the Use of Biosimilars to Treat Rheumatologic Diseases (TFUBTRD), proposes that a data registry be established to facilitate monitoring of multiple switching [Kay *et al.*, 2018]. The

importance of investing in pharmacovigilance is addressed and promoted by all of the learned societies. There is general agreement on the need to gather as much information as possible on biologic drugs (including biosimilars) that are used in treatment-naive and already-treated patients.

Lastly, IBD Porto Group of ESPGHAN does not recommend multiple switching in children with inflammatory bowel disease due to a lack of evidence [De Ridder *et al.*, 2019].

2.7.4. Interchangeability

Most of the organizations consulted classify interchangeability as an unacceptable practice because it excludes the physician and the patient from the decision to change a treatment with a biologic drug. APFH, the European Association of Hospital Pharmacists (EAHP) and SEFH support interchangeability (without requiring the advice of the prescriber) in a hospital pharmacy setting when there are no contraindications [Biosimilar Medicines, 2019; Martinez-Lopez de Castro *et al.*, 2018]. ACR accepts interchangeability provided that the reference biologic drugs and the interchangeable biosimilars are clearly identified by the FDA [ACR, 2018]. ACR highlights the fact that some biologic drugs must be given at short intervals, which increases the number of doses a patient receives and can increase the risk of side effects. It is therefore important that the treatment be monitored by the treating physician [ACR, 2018].

Table 6 Positions of learned societies and various groups on medical (by the physician) and non-medical (by the government) switching from a reference biologic drug to a biosimilar in patients already being treated and on pharmacy interchangeability of reference biologic drugs and biosimilars (without medical consent)

Specialty	Society or organization	Medical switching	Non-medical switching	Interchangeability	Reference
Rheumatology	CRA (Canada)	Yes	Conditional [4,5]	No	CRA, 2019
	ACR (USA)	Yes	Conditional [6]	Conditional [12]	ACR, 2018
	ACR/SAA (USA)	Conditional [1]	No (mAb) [1]	No	Ward *et al.*, 2019
	CMR (Mexico)	Yes	No	No	Xibille *et al.*, 2018
	TFUBTRD (international)	Yes	No	No	Kay *et al.*, 2018
	DGRh (Germany)	Yes	No	No	Biosimilar Medicines, 2019
	EULAR-PARE (Europe)	Yes	No	No	Wiek, 2018
	GRL (Germany)	Yes	No	No	Biosimilar Medicines, 2019
	HKSR (Hong Kong)	Yes	No	Not available	Ho *et al.*, 2019
	NRAS (England)	Yes	Conditional [4,5,7]	No	NRAS, 2019
	BSR (Brazil)	Yes	No	No	Azevedo *et al.*, 2015
	SFDA (Saudi Arabia)	Yes	No	No	Halabi *et al.*, 2018
	SPR (Portugal)	No	Conditional if imposed [4,6]	No	Araujo *et al.*, 2017
Endocrinology	Diabetes Canada (Canada)	Yes	No	No	Diabetes Canada, 2019
	AACE/ACE (USA)	Yes	No	No	Fonseca *et al.*, 2017
	ABCD (England)	Yes	No	No	Biosimilar Medicines, 2019
	IDF (Europe)	Yes	No	No	Biosimilar Medicines, 2019
Gastroenterology	CAG-CCC (Canada)	No (CAG)/Yes (CCC)	No	No	Moayyedi *et al.*, 2020
	BIRD (Belgium)	Yes [7,8]	No	No	Franchimont *et al.*, 2018
	BSG (England)	Yes [8]	No	No	Biosimilar Medicines, 2019
	DCCV (Germany)	Yes	No	No	Biosimilar Medicines, 2019
	ECCO (Europe)	Yes	Conditional [9]	No	Danese *et al.*, 2017

Specialty	Society or organization	Medical switching	Non-medical switching	Interchangeability	Reference
	FBG/GEDIIB (Brazil)	Yes [8,9]	No	No	Azevedo *et al.*, 2015
	IBD Porto Group of ESPGHAN (Europe)	Yes, with an exception for children [8,13]	No	No	De Ridder *et al.*, 2019
	IG-IBD (Italy)	Yes	No	No	Fiorino *et al.*, 2019
	PNCG (Poland)	No	No	Not available	Mularczyk *et al.*, 2014
	SEPD (Spain)	Yes	No	Not available	Biosimilar Medicines, 2019
	SNFGE (France)	Yes	No	Not available	Biosimilar Medicines, 2019
Dermatology	ACD (Canada)	Yes	No	No	ACD, 2013
	AAD (USA)	Yes	No	No	AAD, 2013
	AEDV (Spain)	Yes	No	Not available	Biosimilar Medicines, 2019
	PCD/PSDV (Portugal)	Pending studies	No	No	Biosimilar Medicines, 2019
	SBD (Brazil)	Yes	No	No	Azevedo *et al.*, 2015
Oncology	BC Cancer (Canada)	Yes	Conditional [2]	Not available	Nakashima, 2019
	ESMO (Europe)	Yes [7]	No	No	Tabernero *et al.*, 2016
	ISOPP (International)	Yes	Conditional [11]	No	ISOPP, 2019
	SBOC (Brazil)	No [3]	No	No	Fernandes *et al.*, 2018
	ASCO (USA)	Yes	No	No	Lyman *et al.*, 2018
Others	AGES (Austria)	Yes	No	No	Baumgärtel, 2017
	APFH (Portugal)	Yes	Not available	Conditional [12]	Biosimilar Medicines, 2019
	BOPA (England)	Yes	No	No	Biosimilar Medicines, 2019
	EAHP (Europe)	Yes	Conditional [10]	Yes (hospitals)	Biosimilar Medicines, 2019
	NICE (England)	Yes	No	No	NICE, 2016
	HIS (Scotland)	Yes	No	No	HIS, 2018
	Polish Expert Group (Poland)	Yes	No	No	Jahnz-Rozyk, 2019
	RADS (Denmark)	Yes [8]	Conditional [8]	Not available	Biosimilar Medicines, 2019

Specialty	Society or organization	Medical switching	Non-medical switching	Interchangeability	Reference
	SAMAC (Australia)	Yes	No	Conditional [12]	SAMAC, 2017
	SEFH (Spain)	Yes	Yes [10]	Yes (hospitals) [10]	Martinez-Lopez de Castro *et al.*, 2018

Notes

1. Switching not recommended when initial treatment is effective.
2. Biologic drug reserved for patients already undergoing treatment and those in relapse.
3. No switching in a patient already being treated unless there is a contraindication for the reference biologic drug (route of administration or allergies).
4. With prior notice of switching.
5. The patient must be allowed to return to his or her reference biologic drug in the case of a clinically significant flare-up within the first six months after a switch.
6. Option for the prescriber to refuse a switch.
7. Under medical supervision.
8. Patients with stable symptoms.
9. After six months of treatment.
10. The decision to make a non-medical switch should always take the patient's preferences into account.
11. Partial implementation of non-medical switching, in a target population.
12. With clear instructions on interchangeability from the government agency.
13. Children: at least three injections of the reference biologic drug and stable clinical remission.

AACE/ACE, American Association of Clinical Endocrinologists and American College of Endocrinology; AAD, American Academy of Dermatology Association; ABCD, Association of British Clinical Diabetologists; ACD, Association canadienne de dermatologie; AEDV, Psoriasis group of Spanish Academy of Dermatology and Venereology; ACR, American College of Rheumatology; APFH, Portuguese Association of Hospital Pharmacists; ASCO, American Society of Clinical Oncology; BIRD, Belgium Inflammatory Bowel Disease Research and Development Group; BOPA, British Oncology Pharmacy Association; BSG, British Society of Gastroenterology; BSR, Brazilian Society of Rheumatology; CAG, Canadian Gastroenterology Association; CCC, Crohn's Colitis Canada; CMR, Colegio Mexicano de Reumatologia; CNFGE, Société Nationale Française de Gastro-Entérologie; DCCV, Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung; DGRh, German Society of Rheumatology; EAHP, European Association of Hospital Pharmacists; ECCO, European Crohn's and Colitis Organisation; ESMO, European Society for Medical Oncology; EULAR-PARE, European League Against Rheumatism-People with Athritis and Rheumatism; FBG, Brazilian Federation of Gastroenterology; GEDIIB, Brazilian study Group on Inflammatory Bowel Disease; GRL, German Rheumatism League; HKSR, Hong Kong Society of Rheumatology; IBD Porto Group of ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; IDF, International Diabetes Federation Europe; BCCancer, British Columbia Cancer; IG-IBD, Italian Group for Inflammatory Bowel Disease; ISOPP, International Society of Oncology Pharmacy Practitioners; NRAS, National Rheumatoid Arthritis Society; PCD/PSDV, Portuguese College of Dermatology & Portuguese Society of Dermatology and Venerology; PNCG, Working Group of the Polish National Consultant in Gastroenterology; RADS, Denmark Council for the use Expensive Hospital medicines; SAA, Spondylitis Association of America; SBD, Brazilian Society Dermatology; SBOC, Brazilian Health Surveillance Agency; SCR, Société canadienne de rhumatologie; SEFH, Sociedad Espanola de Farmacia Hospitalaria; SEPD, Sociedad Espanola de Patologia Digestiva; SFDA, Saudi Food and Drug Authority; SPR, Portuguese Society of Rheumatology; TFUBTRD, Task Force on the Use of Biosimilars to Treat Rheumatologic Diseases.

In summary…

The 33 documents retained that present the positions of learned societies and the four clinical practice guidelines consulted provide the following key findings:

- The preferential use of biosimilars in treatment-naive patients is generally **accepted**.
- **Medical** switching in patients already being treated is generally **accepted,** with some societies raising a few specific points.
- **Non-medical** switching in patients already being treated is generally **not accepted**.

For countries in the process of implementing a non-medical switching strategy, however, the learned societies suggest:

- In rheumatology:
  - effective treatment should not be disrupted;
  - the patient and the physician should be given enough notice to allow for an informed discussion between the two parties;
  - the option of resuming the initial therapy should be given if significant side effects are reported with the biosimilar;
  - a mechanism for refusing a switch in certain cases should be established;
  - the switch should be made under medical supervision.
- In gastroenterology:
  - no switch should be made before the end of the first six months of treatment.
- In oncology:
  - non-medical switching policies should be applied selectively, for example, only for certain groups of patients who meet all the safety criteria for biosimilar use (same route of administration or same disease tested as with the reference biologic drug).

Generally, learned societies **do not accept the interchangeability** of reference biologic drugs with biosimilars, except where regulatory agencies have established clear processes to recognize the interchangeable nature of a biosimilar and a reference biologic drug.

Pharmacovigilance is essential in implementing non-medical switching and interchangeability.

2.8. Clinician perspectives

2.8.1. Level of confidence in biosimilars

First, several clinicians underline that it should not be assumed that biosimilars are necessarily less effective than reference biologics. Moreover, the clinicians consulted did not generally raise any objections to starting treatment with a biosimilar in treatment-naive patients. In oncology, concerns have been raised about patients using biosimilars following a switch and even for treatment-naive patients, mainly because of a lack of long-term data on their effectiveness, especially in the context where a failing regimen can have significant impact on the patient's survival. There are currently no data to indicate whether the same effect will be achieved in the long term, and the American Society of Clinical Oncology (ASCO), whose oncologists generally follow its recommendations, points to a lack of evidence on this matter [Lyman *et al.*, 2018]. Few clinicians use biosimilars for treatment-naive patients in gastroenterology and rheumatology. Just one biosimilar (Erelzi®) is used, but only in patients diagnosed with juvenile arthritis and weighing more than 63 kg. Therefore, there is limited expertise in biosimilars in this population which often presents with more severe disease.

However, in line with the findings of the systematic reviews carried out for the present project, all of the clinicians consulted highlighted the lack of high-quality clinical trials assessing the effects of switching from a reference biologic to its biosimilar in patients already being treated with a biologic drug. They point out, nevertheless, that the improvement in the development processes for biologic drugs has led to a decrease in the production of ADAs with the latest molecules. These drugs have much better immunological tolerance (fewer chimeric molecules or molecules of non-human animal origin), which reduces their risk of immunogenicity. The literature shows comparable levels of ADAs, but the variable sensitivity of screening techniques makes it difficult to interpret the findings. However, the loss of efficacy of a biologic drug over time is not exclusively the result of immunogenicity (ADAs and Nabs); it can also be caused by natural progression of the disease being treated or by faster elimination of the drug.

The principal factors fuelling clinician concerns about non-medical switching of a biologic drug are the few alternatives available for certain conditions and the risk of relapse in patients with multiple treatment failures or who have been difficult to stabilize. The main concerns were raised in the area of gastroenterology, while there appear to be no such issues for rheumatology. The clinicians consulted worry that switching will result in a loss

of treatment response in some cases. They make the point that none of the randomized trials in adult gastroenterology, particularly in Crohn's disease, have had the statistical power needed to assess loss of treatment efficacy following a switch of medication. They also point out that in 2019, the Canadian Association of Gastroenterology and Crohn's and Colitis Canada published a systematic review with a meta-analysis that shows a statistically significant loss of efficacy in individuals with Crohn's disease or ulcerative colitis when switching from a reference biologic drug to a biosimilar (many of the data in this meta-analysis, however, come from a conference abstract that could not be retained for the purposes of the present report) [Moayyedi *et al.*, 2020]. Nevertheless, the reasons for this difference need to be explored in more detail to eliminate the possibility of nocebo effects. In addition, treatment options in gastroenterology are very limited, and the clinicians consulted emphasize the importance of proper assessment of an individual's health state before considering switching from a drug that is still effective, since it is very difficult to switch back if the patient's health deteriorates. They add that reagent assays are frequently given to patients with poor treatment response to allow better adjustment of medication and to monitor the emergence of ADAs and NAbs. If a patient has been given the wrong dose of medication prior to switching, this will continue after the switch and he or she could lose their response. Furthermore, the clinicians consulted point out that similar assays could also be used for certain conditions when switching treatment, enabling a prompt, proactive response to reduce the risk of deterioration in a patient's health.

Other specialty-specific concerns have been raised about a possible loss of therapeutic efficacy associated with biosimilars. Many dermatology patients suffer from a co-morbidity or receive concomitant treatments (e.g., biotherapy using phototherapy or topical treatments) and there are little data available for these populations. Nonetheless, concerns about non-medical switching mainly relate to adverse reactions since treatment efficacy can be easily observed in dermatology. In diabetes, insulin levels can be increased rapidly and almost without limit, but this kind of increase may lead to side effects such as hypoglycemia or weight gain. The studies in nephrology focus on dialysis patients who are also considered immunosuppressed due to senescence of the immune system. However, there are no studies available on pre-dialysis patients, who have a higher level of immune function, and the concern is greater for these patients. Clinicians also stress that caution is required before data obtained on switching from biologic drugs is extrapolated to the field of ophthalmology, since the doses used differ from those for other pathologies and a decrease in treatment efficacy for certain eye diseases can have irreversible effects, such as blindness.

Nonetheless, some medical specialties exhibit a variety of context-specific features that can reassure clinicians in many cases, particularly in rheumatology. As highlighted in section 2.3.2 of this report, rheumatology is the specialty for which evidence on the effects of switching from biologic drugs to their biosimilars is most readily available, for several drugs (infliximab, etanercept, adalimumab, and rituximab). These studies show no statistically significant difference when switching from treatment with a biologic drug. In addition, there are several treatment options available in case of failure.

2.8.2. Factors influencing acceptability of a strategy promoting the use of biosimilars

As mentioned in section 2.7, all the learned societies are of the opinion that switching from a biologic drug should take place on the advice of a physician. The clinicians consulted agree with this approach and want to be able to decide which treatment is right for their patients. Most of the clinicians consulted are in favour of a gradual switch to biosimilars, starting with stable patients presenting with no particular condition and individuals affected by one of the diseases for which there is the most evidence and a larger number of treatment options. According to the clinicians consulted, the gradual implementation of a switching program could help increase their confidence in the use of biosimilars and make them less hesitant to switch treatments in other patients.

All the clinicians consulted are of the opinion that the paediatric population and pregnant women should be excluded from non-medical switching policies. In addition, they underline their concerns for complex cases in which non-medical switching would be more risky, especially in patients having had multiple treatment failures and for whom treatment stability has taken a long time to achieve, patients who have experienced significant adverse reactions to a biologic drug (e.g. allergic reactions, immunogenicity) or severe infections, or those with mental health difficulties. For example, medication should not be switched in a patient who has taken five years to be stabilized and has already undergone three procedures for their medical condition. According to the clinicians consulted, such situations should be considered on a case-by-case basis with guidelines to follow and recourse to an expert committee for contentious cases.

Each specialty has its own specific criteria for identifying high-risk patients presenting with factors associated with poor prognosis. Gastroenterology clinicians have indicated that good examples of this type of high-risk patient for whom switching should not be carried out would be those with severe intra-abdominal fistulizing disease or with “short gut” syndrome, those who have been resistant to more than two biologic drug agents, those who have already developed immunogenicity with another drug, or those who are not in deep remission. Given that each specialty has its own particularities, the clinicians consulted suggest that a review committee could be established for each specialist area to determine which patients qualify for exemption from non-medical switching. The decision would be based on specific, consistent markers and strict criteria. They believe that establishing these kinds of committees would result in exemption for approximately 5 to 15% of patients already undergoing treatment with a reference biologic drug. Moreover, it would be essential, in their view, to have the option of returning to the previous medication if treatment with biosimilars did not work after either medical or non-medical switching, and to introduce a timely appeals process to assess urgent cases that might warrant exemption from non-medical switching.

The rheumatologists, nephrologists, ophthalmologists and endocrinologists present at the meeting were in favour of switching to biosimilars gradually, citing dialysis patients being treated with erythropoietin as an example of good subjects for introducing a switching policy since they have thrice-weekly follow-up and monthly check-ups. The clinicians would be open to testing biosimilars and even conducting studies on the topic.

Physicians have an obligation to explain switching to the patient, and the clinicians consulted point out that an adequate transition period (about one year) would be required. The idea is that the transition would go more smoothly if the physician had access to tools and if the patient was already informed through advertisements and reading material. The clinicians consulted emphasize that communication is a key factor for successful transition to biosimilars. They deplored the lack of communication in the field, particularly with regard to the arrival of biosimilars on the market, citing, as an example, RAMQ's last-minute announcement about the introduction of a policy encouraging the use of Basaglar® to treat diabetes. They point out that if the ministry develops a policy to promote the use of biosimilars, it will need to take an active role in communicating its strategy to patients and professionals to ensure this takes place in a timely manner, and not at the last minute. According to the clinicians consulted, the ministry should also be involved in the development of educational materials that will assist clinicians in supporting their patients, especially given the significant nocebo effect documented in non-medical switching.

The use of biosimilars is an economic advance but enforced non-medical switching for economic reasons without disclosing the savings can create a certain level of mistrust on the part of clinicians and can undermine the implementation of the chosen strategy. Thus, the clinicians consulted propose that the savings generated by adopting a strategy to encourage the use of biosimilars be reinvested in improving patient services. This would include increasing the number of "pivot nurses", improving infusion clinics or quality of care in outlying regions (which is not the same as in large cities) and could partly compensate for the loss of some of the patient support programs put in place by the manufacturers of biologic reference drugs. For example, if non-medical switching is implemented in dialysis units, the clinicians consulted propose that the money recouped could be used to support the roll-out of self-dialysis (home-based), which costs less and offers patients a better quality of life. In addition, the clinicians consulted stressed that pharmacoeconomic studies are needed to confirm that the savings from the lower costs of the biologic drug outweigh the possible increase in the number of medical visits due to uncertainty or loss of treatment efficacy, hence the importance of setting up a registry for Québec.

The consulted clinicians are of the opinion that establishing a pharmacovigilance program, which would include registries for systematic long-term patient tracking, is a priority. They point out that the use of electronic tools could facilitate collecting data on a large number of patients, providing a more accurate view of the evolution of treatment over time. It was also mentioned that reducing the administrative burden associated with prescribing biosimilars, for example by adding a code that would avoid having to repeat the administrative process of requesting and renewing a biologic drug, would be an advantage for physicians and could in some cases avert interruption in treatment for the patient.

Taking the examples of non-medical switching programs elsewhere in Canada, the clinicians consulted have a positive view of British Columbia's six-month transition period accompanied by the possibility of requesting an exemption if a case is too risky. This

highlights the more progressive and collaborative nature of such a system compared to that implemented in Alberta, where switching has been imposed without opportunity for exemption nor a transition period. It was also noted that since British Columbia adopted its switching policy, the province has added fees for pharmacists to assist patients in making the transition and has removed the requirement to prescribe immunosuppressant therapy before prescribing a biologic drug in gastroenterology, a situation that persists in Québec in order to adhere to RAMQ reimbursement criteria. Such measures were considered to be of value by the clinicians consulted.

2.8.3. Issues related to implementing a biosimilars strategy

Consulted clinicians expressed numerous concerns about the potential loss of patient care programs supported by reference biologics manufacturers in the event of a non-medical switching policy. These programs notably allow for funding for infusion clinics that manage the administration of biologic drugs and patient monitoring by nurses. For the patient, then, switching would apply not only to his or her medication, but also to his or her entire support program. This could be very difficult for some patients and may therefore increase the risk of the nocebo effect. According to the clinicians consulted, this situation could also have major consequences for some patients with a significant disability, particularly neurological, and it could also be difficult to manage switching for patients who do not have access to a nearby biosimilars infusion clinic. The clinicians consulted therefore indicate that an alternative plan would be needed to facilitate administration of biosimilars (infusion site, training, supervision and follow-up).

The approval processes required by RAMQ or private companies are often lengthy. Manufacturers of biologic reference drugs often offer generous patient assistance programs. When access to a biologic drug is urgent, manufacturers will often provide it free of charge to clinicians through these programs, so that they can initiate treatment or avoid its interruption. Biosimilar manufacturers' patient assistance programs are often not as generous, and patients sometimes have to pay deductibles or go to infusion clinics that are not as well managed.

The Québec Order of Pharmacists does not currently support non-medical switching in the pharmacy setting. The clinicians consulted are of the opinion that pharmacy-based switching would rupture the relationship between physician and patient since the physician knows his or her patient's condition best. The possibility that patients may have to deal with multiple drug switching also raises fears and questions among these clinicians. Does Health Canada's approval of a biosimilar and a reference biologic imply that biosimilars can be substituted for each other? Biosimilars are approved based on comparison with the reference biologic drug, but never on the basis of comparison with another biosimilar. This could become a major concern if there are several biosimilars with the same non-proprietary name on the market, increasing the risk that some players will withdraw from a market that has become less profitable. Patients exposed to such molecules would need to change their treatment once again if the drug disappeared from the market. Studies on multiple switching are virtually non-existent (there are only four in the publications retained) and there are unlikely to be any in the future. According to the

clinicians consulted, the only studies that might be available are based on data gathered in some of the Scandinavian countries, where the drug that is reimbursed depends on the offers for tender and patients are at risk of multiple drug switching. They add that there is a need for consistency between the reimbursement criteria of RAMQ and of private insurers to avoid or limit the switching that would result from a change in insurance coverage. Several clinicians are already prescribing an etanercept biosimilar to prevent their patients from being switched if they lose their job or are transferred to RAMQ.

The pharmacists consulted underscore that, even if the public drug insurance plan ceases to reimburse the reference biologic drug, pharmacies still need to stock the drug to allow for treating individuals with a contraindication for the biosimilar or to treat indications for which the biosimilar has not been approved by Health Canada. Having to keep two molecules with the same generic name increases the risk of error and complicates the pharmacist's work, particularly in institutional settings. They therefore anticipate having to juggle support programs, private insurers, latex allergies, the ability to adjust the dosage in children (e.g. syringes that make dose adjustment easy), and the availability of options that do not cause additional pain at the injection site. In the view of the pharmacists consulted, all these concerns should therefore be considered and resolved before a non-medical switching policy can be introduced. They also point out that switching currently takes place in a different manner according to the hospital. There is a fear of creating a divide between hospitals since the use of biosimilars varies from one facility to another. For example, since MSSS published a directive for bevacizumab on November 14, 2019 whereby the use of the reference biologic (Avastin™) can be maintained for previously-started treatment in cases of colorectal or gynaecological cancer, some facilities have introduced mandatory use of the biosimilar for treatment-naive patients only, while others, following consultation with and approval by their pharmacology committee and hemato-oncology subcommittee, have decided to switch patients already undergoing treatment to the biosimilar as well. If informed, patients may feel they are being treated with a second-class drug and may decide to choose where they will be treated based on this criterion. For a policy to be accepted by clinicians, it would need to be applied consistently everywhere

Some clinicians mentioned that moving to a different reference biologic drug that is more effective for some patients would likely be considered in some cases if non-medical switching was introduced. As an example, they cited the case of a dermatology patient who is stable but has not achieved complete remission. Medication switching would not normally be considered for such a patient, due to his or her stability, even if a more effective treatment appeared on the market. If switching is required, however, the clinician can opt for another biologic drug when changing the medication, a drug that could be more effective and could increase the patient's chances of achieving a more complete remission.

In summary…

In the opinion of the clinicians consulted:

- There is little concern about starting treatment with a biosimilar for a treatment-naive patient.
- A patient who is already being treated should always be switched from a biologic drug on the advice of a physician, mainly because of the following concerns:
  - there are few high-quality clinical trials available that assess the effects of switching medication from a reference biologic drug to its biosimilar;
  - therapeutic options are limited in the event of a loss of efficacy of the biologic drug, particularly in gastroenterology;
  - there are few studies in individuals presenting with comorbidities or comedications;
  - the significant impact of a loss of treatment efficacy in certain conditions (e.g. death, blindness, major surgery) must be considered.
- If a non-medical switching policy is introduced:
  - the transition should be gradual and should focus primarily on stable individuals presenting with no particular condition;
  - children, pregnant women and those at high risk, presenting factors associated with poor prognosis, should be excluded from this policy;
  - a review committee could be established for each specialty to determine the type of patients who should be exempt from non-medical switching;
  - it should be possible to return to the reference biologic drug in the event of an observed loss of efficacy with the biosimilar or the onset of significant adverse events;
  - a rapid appeals process will need to be introduced to handle exceptions;
  - effective communication of the policy adopted by the ministry to physicians and patients will be essential for a smooth transition (including the development of educational materials and other tools);

- the savings from implementing a switching strategy should be reinvested in improving patient services (e.g. to increase the number of pivot nurses, to encourage self-dialysis);
- a long-term patient follow-up and pharmacovigilance program should be introduced;
- the administrative burden for prescribing biosimilars should be reduced.

- The following factors should also be considered for the implementation of a non-medical switching policy:
  - the loss of patient support programs provided by manufacturers of reference biologics could have a significant effect (e.g. for infusion clinics, follow-up by nurses, free emergency drugs, or to avoid treatment interruption);
  - in hospitals, storing two or more molecules with the same generic name increases the risk of error and greatly complicates work;
  - the patient could have to deal with multiple switches of their biologic drug treatment;
  - non-medical pharmacy switching is not acceptable.

DISCUSSION

In the systematic reviews of the literature conducted for the purposes of the present report, the safety of switching from a reference biologic to a biosimilar, or vice versa, was evaluated by considering the following main aspects: loss of efficacy, immunogenicity, retention rate, and adverse events. In addition, the published positions of learned societies on this matter, as well as the features of the switching policies adopted in other countries and Canadian provinces, were documented. This information was complemented by consultation with Québec clinicians from most of the fields concerned with the use of biologic drugs, in order to gather their perspectives on the subject. The main findings that arise from the full set of these scientific data are presented below.

Overview of main findings

There is very little clinician opposition to the use of biosimilars in treatment-naive patients. Biosimilars go through a rigorous comparative approval process implemented by Health Canada, by which data must be provided to demonstrate the similarity between the biosimilar and its reference biologic drug. The development process for biologic drugs and approval by regulatory agencies minimizes their immunogenicity. In addition, the efficacy and safety of any biologic, whether reference or biosimilar, must be reassessed whenever there is a change in the manufacturing process.

The picture is different and much more nuanced regarding the use of biosimilars in individuals who are already being treated with a reference biologic drug, in particular because of the risks of immunogenicity posed by the use of biologic drugs and the possible loss of efficacy. In this respect, all the learned societies are clearly opposed to non-medical switching of a biologic drug, and instead favour medical switching, by which the decision to switch a patient's treatment rests with the individual and his or her doctor. This position is shared by all the clinicians consulted for this project, who stress that the physician is the best person to assess the risk of treatment switching in a given patient.

The present evaluation concludes that no statistically significant differences are observed in terms of safety between people whose treatment was switched and those who continued their initial therapy. The same is true for loss of treatment efficacy, immunogenicity, retention rate, and adverse reactions. These findings cover 12 different conditions and eight different biologic drugs. The level of evidence is considered moderate for most pathologies (inflammatory arthritis, plaque psoriasis, diabetes, anaemia), with the exception of inflammatory bowel diseases, for which the level of evidence is considered low. In oncology, the limited number of publications covering few indications (one on preventing neutropenia and one on breast cancer) renders the level of evidence insufficient. In addition, no publications were retained for several medical conditions and reference biologic drugs for which a biosimilar is available (several types of cancers, thrombocytopenic purpura, lupus, multiple sclerosis, growth hormone, eye diseases). Consequently, no level of evidence could be assigned in these cases.

Several concerns raised by the clinicians consulted arise from the limited number of therapeutic options that would be available, particularly in gastroenterology, in the event of a loss of efficacy of the biologic drug, as well as from the lack of studies in people with comorbidities or comedications and when considering the significant consequences (e.g. death, blindness, major surgery) that could result from a decrease in treatment efficacy in certain conditions.

Although most studies include just one treatment substitution, in the ‘real world’ setting, multiple switches could occur if several biosimilars were to be available for the same reference biologic drug, and patients were to have to switch from one biosimilar to another with which it has not been directly compared. In fact, this is one of the concerns raised by the clinicians consulted, who note that there may be an increased risk to patient safety if multiple goings back and forth between the reference drug and the biosimilar were permitted. Moreover, learned societies do not generally accept the interchangeability of reference biologic drugs and biosimilars or automatic switching, and such policies only exist in a few countries. Pharmacists in Québec do not recommend these either. None of the retained publications could be used to evaluate the safety of switching between two biosimilars, and only four studies were designed so that the effect of multiple switching between a reference biologic and a biosimilar could be assessed. Since these studies represent only three distinct diseases (plaque psoriasis, neutropenia, and diabetes), their level of evidence was considered insufficient.

With respect to policies in place in other jurisdictions, the majority of those analyzed favour switching patients already being treated with a reference biologic drug to a biosimilar, without imposing this on all patients. Only a few European countries and two Canadian provinces have policies resulting in mandatory non-medical switching for the vast majority of patients. Should a non-medical switching policy be introduced in a given jurisdiction, the learned societies and the clinicians consulted are of the opinion that the change should be gradual and applied selectively, focusing mainly on stable individuals presenting with no particular condition and pathologies for which there are greater numbers of therapeutic options. It is important to note, however, that children, pregnant women and people with cognitive disorders are generally excluded from non-medical switching policies in the jurisdictions examined, and that the clinicians consulted agree with these exclusions. The clinicians also add that high-risk people presenting with factors associated with poor prognosis, for whom treatment stability has been time-consuming and difficult to achieve, should also be excluded from any non-medical switching policy. It would be preferable to wait until six months of stable treatment has taken place, or even nine months in some cases, before switching is considered. One of the factors influencing policy acceptability according to clinicians is the establishment of specialty-specific review committees that would be responsible for determining the types of patients who could be exempted from non-medical switching. In this regard, both clinicians and the learned societies stress the need for a rapid appeals process to allow for the prompt assessment of urgent cases that could be exempted from switching, as well as the ability to resume the previous therapy if loss of efficacy or significant adverse reactions are reported after switching to a biosimilar.

The learned societies and the clinicians consulted also agree on the importance of establishing a long-term pharmacovigilance and patient follow-up program and of communication to foster a smoother transition, including giving patients and physicians sufficient notice to permit informed discussion between the two parties. It was stressed that the ministry will need to be involved in the development of educational materials that would assist clinicians in supporting their patients. A decrease in retention rates is often seen in observational studies and is generally attributed, at least in part, to a nocebo effect caused by negative patient and physician perceptions of biosimilars.

Lastly, the clinicians consulted emphasized that the savings generated by implementing a switching strategy should be reinvested in improving patient services (e.g., to increase the number of pivot nurses, to promote self-dialysis) and that it would be advisable to reduce the administrative burden associated with prescribing biosimilars. In addition, they are concerned about the loss of patient support programs provided by reference biologics manufacturers. In Québec, switching from a reference biologic drug to its biosimilar involves not just the medication, but the entire patient management system. Such a change could prove difficult for some patients.

Strengths and limitations

One of the main strengths of the set of systematic reviews conducted for the purpose of the present project is that they are based on a rigorous, explicit methodology including systematic literature searching, critical evaluation of relevant publications, and an overview and systematic synthesis of the conclusions. There are, however, limitations to this work that must be mentioned.

An important limitation of this SR report is that, despite the large number of retained publications, several diseases are not represented (e.g., colorectal, ovarian, lung and renal cancer, glioblastoma, lymphoma, multiple sclerosis). In addition, some biologic drugs for which biosimilars are available in Canada (e.g., pegfilgastrim, bevacizumab, somatropin) are also not addressed in the retained studies. Moreover, a wide variety of methods used to detect clinical parameters was observed between the individual studies. The clinical findings of interest presented in the different studies were often heterogeneous, with several different parameters being analyzed to account for a single clinical outcome. In these studies, treatment response could be assessed by calculating, for example, clinical remission, maintenance of clinical remission, disease worsening, or disease activity.

Such variation was also present in the selection of participants in the different studies. The definition of stability for a given disease could vary between studies (e.g., between four and six months). Clinical follow-up periods were also relatively short, varying from 10 weeks to 18 months, which could be insufficient for proper assessment of the real long-term effect of switching. Moreover, there is no consideration of treatment duration with the reference biologic drug prior to substitution, and the majority of the cohort studies had no selection criteria other than treatment with a biologic drug, with the decision to switch to treatment with the biosimilar often being made by the patient, which can lead to

a high risk of bias. Since the evidence is derived mainly from observational studies or RCT extension periods, it is difficult to generalize their findings with confidence.

Of the 76 studies retained, 31 were RCTs, but only six of these were actually conceived to assess the effect of switching. In the other RCTs, switching was included in an extension period that did not permit detection of non-inferiority or equivalence after the switch from biologics. These RCTs show a lack of statistical analyses and process the data in a purely descriptive manner. In addition, one of the studies cited most often, NOR-*Switch* [Jorgensen *et al.*, 2017], presented a significant limitation since six different pathologies were evaluated as a composite study population. The study was therefore not designed to assess efficacy for the individual diseases.

With regards to the systematic review of the 33 position statements of learned societies and the four CPGs on modes of use, certain pathologies were not addressed, although their methodological quality was deemed sufficient for their retention. Moreover, the methodological quality of the primary studies used to formulate the recommendations in these documents has not been evaluated by INESSS.

CONCLUSIONS

This SR report has permitted addressing the five major research questions that were posed during its development. The level of scientific evidence of the parameters assessed by the studies has been determined (see Appendix F) and allows INESSS to conclude the following:

- Immunogenicity can vary depending on the characteristics of the patient, the molecule, the pathology, and the treatment. The loss of efficacy of a biologic drug over time is not solely due to immunogenicity. It can also be caused by natural progression of the underlying disease or by faster elimination of the drug.
- No statistically significant differences in safety are observed between people whose treatment was switched and those who continued with their reference treatment. The same is true for loss of treatment efficacy, immunogenicity, retention rate, and adverse reactions.
- Most jurisdictions favour switching patients already being treated with a reference biologic drug to a biosimilar, without imposing this on all patients. Only a few European countries and two Canadian provinces have adopted policies for mandatory non-medical switching for the vast majority of patients (national tendering process or reimbursement of biosimilars only).
- There is general acceptance among clinicians of the preferential use of biosimilars in treatment-naive patients and medical switching in patients already undergoing treatment with a reference biologic drug. On the other hand, non-medical switching in patients being treated with a reference biologic drug is generally not accepted, owing to a number of specialty-specific concerns.
- If a non-medical switching policy were to be implemented in Québec, clinicians emphasize that the transition would need to be gradual and focus primarily on stable individuals presenting with no particular condition. Clinician concerns include destabilization of complex cases (5-15% of patients depending on the pathology) for whom few treatment options are available, the lack of mechanisms to prevent such patients from being exempted from switching, the absence of any option to switch back in the event of loss of efficacy or significant adverse reactions following switching, and the risks associated with multiple switching. More use could be made of ADA, NAb and biologic drug assays to improve medication control. Furthermore, the experts point out that good communication between the ministry, clinicians and patients will be very important to facilitate the transition. They also stress that the cost savings should be used to improve patient services and thus could offset the loss of patient support programs.

The present SRs have also highlighted certain populations and biologic drugs for which there are very little or no data available regarding the safety of switching from a biologic drug to a biosimilar. There are methodological limitations associated with most of the available scientific data, which raises significant uncertainty. Therefore, it would be useful to conduct adequate clinical studies including more people from these populations, with greater homogeneity of the participants' baseline characteristics, to better determine the effects of biologics switching.

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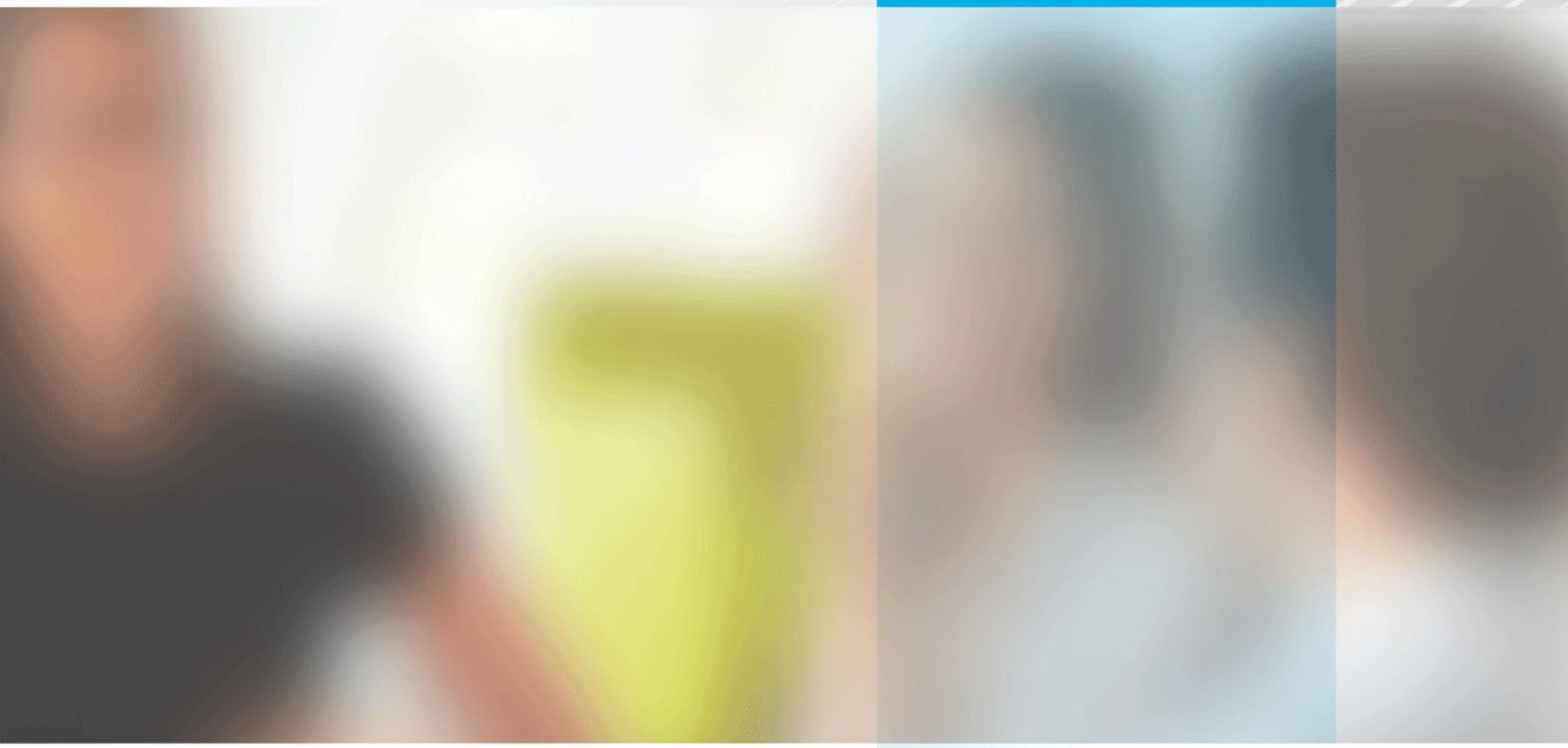

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