

AT A GLANCE

STATE OF KNOWLEDGE

Safety of Switching Biologics and their Interchangeability

This AT A GLANCE document presents the highlights of the state-of-knowledge report (in French) entitled *Innocuité de la substitution et de l'interchangeabilité des médicaments biologiques*, recently published by the Institut national d'excellence en santé et en services sociaux (INESSS). The significant increase in the use of biologic drugs is putting an unsustainable financial strain on public drug insurance plans that may compromise access to innovative therapies. The Ministère de la Santé et des Services sociaux (MSSS) therefore asked INESSS to produce a state-of-knowledge report on the risks associated with switching biologics and their interchangeability.

The purpose of introducing biosimilar drugs, whose greatest uptake is observed in Europe, is to reduce the economic burden associated with biologics and thereby facilitate access to this type of therapy. In Québec, despite the fact that in 2017 the MSSS introduced restrictive rules promoting the expansion of the biosimilar market, their uptake remains low. Even so, biosimilars seem to be widely accepted by clinicians who generally have little reluctance to initiating this treatment for a patient who has never taken the reference product (patients who are treatment naïve). However, there are still concerns for patients already receiving treatment with a reference biologic drug, in particular with regard to the immunogenicity that could be caused by a switch.

This AT A GLANCE first discusses what biosimilar drugs are, the types of switching, and the concept of a biologic's immunogenicity. It then presents the findings drawn from the scientific literature on the safety of switching biological drugs and the features of policies put in place to promote the uptake of biosimilars, as well as position statements from learned societies and the perspectives of Québec clinicians consulted as part of the project.

The complete state-of-knowledge report is available at inesss.qc.ca

JUNE 2020

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BIOSIMILAR DRUGS

A biosimilar drug is a replica of a biological drug whose patent has expired. It cannot be considered identical to the original molecule because of the nature of the production processes using living organisms (cells or tissues) that can introduce variations in the glycosylation profile or other post-translational modifications of the protein produced. Thus, even if it has an identical amino acid sequence and efficacy and adverse effects similar to those of the reference biologic drug, a biosimilar drug is not a generic.

TYPES OF SWITCHING

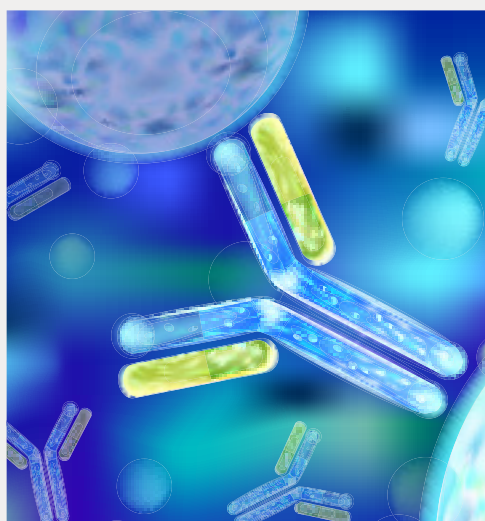
Switching refers to replacing a reference biologic drug with a biosimilar, replacing a biosimilar with another biosimilar, or replacing a biosimilar with a reference biologic. There are two types of switching:

Medical switching (physician led)	Non-medical switching
A switch is made following a decision of the physician who has discussed it with the patient.	A switch is made following an administrative policy. The decision to switch is thus made by the state, province, or country concerned without requiring the approval of the physician.



WHAT NEEDS TO BE KNOWN ABOUT IMMUNOGENICITY

- Immunogenicity refers to a molecule's ability to induce an immune response in a person.
- In the case of biologics, it usually results in a formation of antibodies against the drug or in a hypersensitivity reaction when the immune system recognizes the biologic as an allogeneic molecule.
- The loss of a biologic's efficacy over time is not caused entirely by immunogenicity. It can be caused by the natural progression of a disease or by a more rapid elimination of the drug.
- Health Canada approval of a biosimilar is based on the quality of the safety and efficacy data. In addition, a biologic's immunogenicity must be re-evaluated each time the manufacturing process is changed in any way.



SAFETY OF SWITCHING BIOLOGICS: WHAT THE SYSTEMATIC REVIEWS ARE FINDING

Systematic literature reviews were carried out to determine if there is a statistically significant difference, in terms of loss of therapeutic efficacy, in immunogenicity, in retention rate, and regarding adverse effects, between persons whose treatment was switched and those who remained on the reference biologic.

These systematic reviews did not reveal a statistically significant difference, for all study end points, between patients whose treatment was switched and those who remained on the reference biologic.

The following table presents the levels of evidence associated with the outcomes observed in the literature, according to the type of disease investigated.

	Inflammatory arthritis	Diabetes	Anemia/ chronic kidney disease	Plaque psoriasis	Inflammatory diseases	Neutropenia	Oncology (HER2 positive)	Substitutions multiples
Loss of therapeutic efficacy	H	H	M	M	L	L	I	I
Immunogenicity	M	M	L	M	L	L	I	I
Retention rate	M	L	H	M	M	L	L	I
Adverse effects	M	M	M	M	M	L	L	I
Severe adverse effects	M	L	M	M	M	L	L	I

No significant difference at level of evidence indicated

H = High

M = Moderate

L = Low

I = Insufficient

FEATURES OF POLICIES IMPLEMENTED IN OTHER COUNTRIES OR CANADIAN PROVINCES TO PROMOTE THE UPTAKE OF BIOSIMILARS

Most of the policies reviewed favour switching patients being treated with a reference biologic drug to a biosimilar but do not impose this for all patients. Some policies rely on financial incentives, quotas, or other measures.

Only a few European countries and two Canadian provinces, British Columbia and Alberta, have policies that lead to **mandatory non-medical switching** for the vast majority of patients. In these cases, a national tendering process or reimbursement only for biosimilars is favoured.

IN BRIEF: THE PERSPECTIVES OF QUÉBEC CLINICIANS AND LEARNED SOCIETIES

- The preferential use of biosimilars in patients who are treatment naive is generally **accepted**.
- **Medical (physician-led) switching** in patients who are treatment experienced is generally **accepted**.
- **Non-medical switching** in patients who are treatment experienced is generally **not accepted** by the learned societies or Québec clinicians mainly because of the following concerns:
 - There are few quality clinical trials that evaluate the effects caused by switching a reference biological drug to its biosimilar.
 - The therapeutic options are limited in the event of a loss of efficacy of the biologic, particularly in gastroenterology.
 - There is a lack of studies involving persons with comorbidities or co-medication.
 - The important effect of loss of therapeutic efficacy (e.g., blindness, major surgery, death) in the case of some conditions must be considered.
- If a **non-medical switch** policy were to be implemented, the clinicians' wishes would be for:
 - a gradual roll-out of the policy, focussing first on patients who are stable with no particular condition;
 - an initial exclusion from any non-medical switch policy of pediatric populations, those who are pregnant, and persons who are at high risk;
 - the establishment of a review committee mandated to hear appeals in certain specific cases;
 - the authorization to revert to the reference biologic drug in the event of an adverse effect or reduced therapeutic efficacy;
 - a registry for the purposes of pharmacovigilance and long-term follow-up of persons whose treatment has been switched.

Elements to consider when establishing a switch policy:

- Non-medical switching at the pharmacy level is not accepted
- The possibility of multiple switches among biosimilars and the reference drug
- The likely loss of patient assistance programs
- The increased risk of intra-institutional errors resulting from the storage of two or more molecules with a shared generic name



METHODOLOGY NOTES

Systematic Reviews

INESSS conducted systematic reviews to assess the safety of switching biologics. The main outcomes reported in the selected studies were presented as summary statements of scientific evidence. An overall level of scientific evidence was assigned to each statement according to a four-level scale (high, moderate, low, insufficient).

Québec Clinicians' Perspectives

INESSS formed a panel of 19 health experts to obtain the perspectives of Québec clinicians on switching biologic drugs. The panel represented the main professional associations concerned with the use of biologics.

Literature search period	January 2006 to December 2019
Evidence sources	Systematic reviews, randomized controlled trials, and cohort studies listed in Medline (Ovid), Embase (Ovid), and Evidence-Based Medicine Reviews (EBMR; Ovid)
Population	Persons being treated with a biologic drug
Intervention	A switch from a reference biologic drug to a biosimilar drug (or vice versa) or from one biosimilar drug to another
Comparators	No switch (continued treatment)
Outcomes (primary end points)	Safety (loss of efficacy, immunogenicity, adverse effects, retention rate) Position statements from learned societies

This *At a Glance* document and the state-of-knowledge report titled *Innocuité de la substitution et de l'interchangeabilité des médicaments biologiques* can be found in the [Publications](#) section at inesss.qc.ca.

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