BPC Better Pharmacare Coalition

Assessment of a non-medical switch health policy

Background on biologics/biosimilars and considerations for policy makers

Note: rather than non-medical switch the term "transition" is used by some in the public sector.

Background:
As the number of biosimilar drugs available in Canada grows, so will the list of disease areas affected by health policies that mandate prescribing practices around their use. Therefore, creating responsible, evidence-based policies that consider the different impact on patients in each of the disease areas is required to effectively maximize cost savings to public drug and health care budgets, while ensuring optimal health outcomes for patients.

Biologics are complex and highly specific medicines that are created in living cells or organisms and infused or injected into the patient.[1] Due to the complexity of their production and the extensive clinical research required in their development, they come with a substantial cost (Table 1).[2] Given the sophisticated biotechnology processes required for the production of biologics, it is not possible to create an exact copy when its patent expires.[1,3] Health Canada does not consider biosimilars to be identical or bioequivalent to their originator reference biologic and states that ***biosimilars are not the same as generic drugs***.[1,4] However, approved biosimilars are **safe, effective, and highly similar** to the reference originator biologic.[1] The decreased costs associated with biosimilar development and clinical validation present a valuable opportunity for cost-savings in public drug budgets.[1,3]

Table 1. Biologics and biosimilars available in BC being considered for switch policy:

molecule	originator biologic	biosimilar		BC PharmaCare reimbursement[2]
infliximab	Remicade®	Inflectra®		$78.62 million
etanercept	Enbrel®	Brenzys	Erelzi™	$26.97 million
			Total	**$105.59 million**
Reimbursement including adalimumab (Humira®)				$162.29 million

Treatment areas (or *Indications*) that will be impacted under this switch policy*:
Currently being considered:
Rheumatoid Arthritis (& other rheumatoid diseases: Ankylosing Spondylitis, Psoriatic Arthritis?)

Potential for expansion:
Crohn's Disease, Psoriasis, Ulcerative Colitis

*switch policy refers to government requiring all patients within a disease area currently stable on an originator biologic be forced to switch to the available biosimilar, regardless of physicians' treatment decision.

Interest in biosimilars uptake:
Given the potential cost-savings of 12% to 47% for biosimilars as compared to their reference biologic (e.g., **list price**‡ of Remicade® is $925/100g versus Inflectra® $525/100g)[5], there is interest in creating a competitive biosimilars market in Canada.

‡**list price:** the official list price of a pharmaceutical drug currently does not take into account the confidential discounts or rebates offered to public and private payers by the manufacturer, which is negotiated before the drug is listed on the formulary.[6] **Of note: BC is one of the only jurisdictions paying list price for Remicade® in Canada.**

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Current coverage policy:
For biologic-therapy naïve patients, current clinical data support that treatment with biosimilars is as safe and effective as with the originator biologic drug.[1,4] As a result, new-starts (patients receiving biologic therapy for the first time) under the BC PharmaCare program are required to start on the biosimilars for infliximab and etanercept. Unfortunately, there has been lower than expected uptake of biosimilars with this strategy (approximate Canada-wide uptake 1.5 years after listing on public formularies = 3.1% of market share for infliximab biosimilar, Canada-wide etanercept biosimilar uptake after 5 months = 1.9% (16.2% of new starts)).[7] Therefore, a non-medical switch policy is being considered to strengthen the biosimilars market in BC to facilitate cost savings in the public drug budget.

Non-medical (government-mandated) switch policy:
Instituting a non-medical switch policy relies on a level of confidence that the originator biologic and biosimilar may be interchangeable for those stable on their current biologic therapy. Canadian Agency for Drugs and Technologies in Health (CADTH) defines interchangeability as "products that are so alike that the drug is expected to have the same clinical result as the reference drug in *any given patient*."[4] A switch generally refers to a one-time change in a patient's medication.[4] At this time, Health Canada recommends that any **decision to switch to a biosimilar should be made by patients in consultation with their prescribing physicians**, using available clinical evidence.[1]

US regulator, the Food and Drug Administration (FDA), released draft guidelines in 2017 outlining additional clinical data that must be presented by biosimilar manufacturers prior to being granted interchangeable status.[8] This includes conducting a switching study or studies for biosimilars to determine "risk in terms of safety or diminished efficacy of alternating or switching between use of proposed interchangeable product and reference product that is not greater than the risk of using the reference product without such alteration or switch."[8]

Brief clinical research summary:
To date, the clinical research available examining the impact of switching suggests that a switch from originator biologic to biosimilar is likely safe and does not carry a significant risk of adverse drug reactions.[9, 10] The majority of studies that have been carried out, however, have not been set up to conclusively determine patient health outcomes in specific disease areas.[10] It is worth noting, that the chronic diseases in the biologics treatment space have varying amounts of clinical data available regarding the impact of switch, and the therapeutic options available should the treatment response after switch fail differ for different disease areas as well. This means that failure after switching might be inconsequential for some disease areas and consequential for others.

Notably, in a relatively large-scale, much anticipated study (482 patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, or psoriasis) published last year referred to as the NOR-SWITCH trial, it was concluded that switching from originator infliximab (Remicade®) to its biosimilar (Inflectra®) was not inferior to continuing on the originator.[11] Non-inferiority trials determine whether a new treatment is unacceptably less efficacious than the treatment already in use.[12] These types of trials can be difficult to set up and interpret, with complications that can make them less reliable than typical trials assessing superiority of a

novel therapy.[12] Further, the number of patients in each disease area were not enough, *i.e*. the study was not powered, to show that switching from originator biologic to the biosimilar was non-inferior within the individual diseases.[11]

There is lack of conclusive data on the effects of switching from originator biologics to biosimilars on patient outcomes in all disease areas. Therefore, a sweeping mandated prescribing policy is inappropriate at this time.

Policy considerations:

(1) Monitoring after switch (pharmacovigilance):

It is necessary to capture patient health outcomes. These have not been successfully captured in Europe, given anecdotally there have been 11 years of experience with 26 biosimilars and "zero safety concerns."[13] Although "zero safety concerns" speaks to the issue of adverse drug reactions, patient health outcomes and retention rates post-switch have not been adequately captured and reported in all disease areas affected.

- **Public policy makers must play a role in holding manufacturers accountable by asking for monitoring, especially in cases where clinical data to support the policy is lacking or incomplete.**

(2) Development of exclusion criteria:

Factors including disease history, complications, and co-morbidities should be considered if a non-medical switch policy is implemented in a disease area (*e.g.*, rheumatology).

- Exclusion criteria determined by expert physician associations (*e.g.*, Canadian Rheumatology Association, Canadian Dermatology Association, Canadian Association of Gastroenterology) must be included in the non-medical switch policy to protect vulnerable patients from potential complications or treatment failure post-switch. **Until appropriate patient-exclusion criteria for the specific disease areas have been defined, a non-medical switch policy should not be considered.**

(3) Number of therapeutic options available in specific disease areas:

The number of originator treatment options, as well as the consequences of treatment failure vary drastically from one disease to another. Examples of this include:

- Rheumatoid arthritis: 12 approved biologics available in Canada, resulting in several other therapeutic options available to combat the debilitating effects of disease progression should there be complications or treatment failure post-switch.[14]
- Crohn's disease or ulcerative colitis: only 4 biologics are available to patients in each of these disease areas.[15] The consequences of failing to achieve a therapeutic response can lead to surgical removal of sections of the small or entire large intestine or, in extreme cases, death. This demonstrates the unique natures of the diseases that rely on biologics.

(4) Patient Support Programs: Canada is unique.

- In Europe and most other locations, biologics and biosimilar infusions or injections are primarily administered and supported through hospitals or some private physicians' clinics. In Canada, biologics and biosimilars are administered at specialized infusion clinics and patient support programs are delivered and funded by the manufacturer. This is an important factor in patient care that can impact patient adherence to their medication, as well the potential of achieving remission for their disease (Figure 1) .

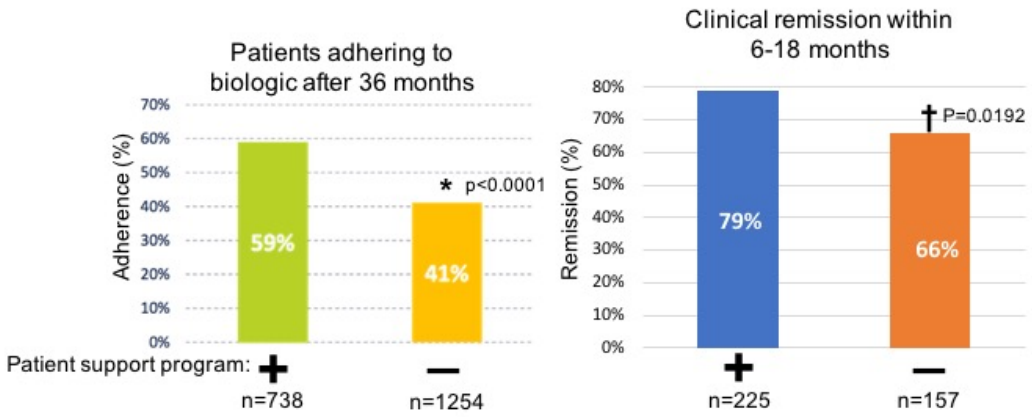

Figure 1. Impact of patient support programs on drug adherence and disease outcome.
*graphs representative of data from references (16) and (17).

- If a patient is forced to switch, rather than coming to the decision with their prescriber, and the location of their infusion clinic, the nurses administering their medication, patient coaching, and other supports in place change dramatically – this may in turn impact their drug adherence and disease outcomes. **If a non-medical switch is mandated, will biosimilar manufacturers be required to ensure robust and effective patient support programs are in place to minimize these stresses associated with switching?**

(5) Is a forced non-medical switch policy the only option?

Many European jurisdictions have significant biosimilar uptake, most of them without government mandated non-medical switching. Germany is one such example where biosimilars for infliximab and etanercept have captured 43% (28 months after market entry) and 31% (15 months) of the market share for their molecule, respectively.[7]

Tactics employed in Germany include:[7]

- Originator biologic manufacturer can compete on price.
- Naïve patients can start on the originator or biosimilar.
- Biosimilar prescription quotas for physicians.
- Position statements, but not mandated policy, on non-medical switch published by national regulator support switching only if it happens in consultation with the physician and is well monitored.

Government should require mandatory and incremental price reductions during price negotiations with originator biologic manufacturers to take effect upon entry of biosimilar to the market. BC should not be paying list price for Remicade® because of an unwillingness from government to negotiate a reduced price for patients.

(6) Retention rates post-switch:

Are there concerns about retention rates if a non-medical switch is introduced?

Recent data out of Germany suggests that patients who remain on their initial biologic (n=301) have 48% greater retention on their therapy as compared to those who were switched to the biosimilar (n=42).[18]

- Although this study did not capture the reasons for higher discontinuation of therapy after switch, it highlights the need to consider and mitigate contributing factors.

Have ramifications to other sectors of the health care budget been considered?

- Potential consequences of increased discontinuation after switch include surgical interventions if an alternate therapy is not available or resulting in a therapeutic response. University of Western Ontario hospital estimates for colectomy costs: $10,445- $11,147 per patient.[19] This does not include follow up post-surgery, treating complications, or the impact on quality of life of having an ostomy bag into which bowel contents are emptied, in some cases, for the rest of an individual's life.
- Nocebo effect: where negative thoughts or experiences may, in part, drive a less than optimal response. This is likely affected by the physician's opinions on a mandated prescribing policy around switching. A 2017 survey of over 400 Canadian physicians indicated that 64% of respondents were not comfortable with a third-party switch of patient's medications.[20] In addition, 83% felt it was critical that the prescribing physician decide the suitable biologic therapy for their patient.[20]

(7) Will the savings from biosimilars go back into the public drug budget?

- Savings realized from increased uptake of biosimilars, should be returned to the public drug budget. Incentivizing or "gain sharing" for physicians and/or select patient groups to facilitate biosimilars uptake creates further uncertainty and mistrust among patients regarding a forced non-medical switch.

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