CANADIAN STRATEGY FOR PATIENT-CENTRED, COST-EFFECTIVE, SUSTAINABLE BIOSIMILARS ACCESS

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Regulatory Basis for Biosimilar Uptake

Across regulators, the US FDA, EMA, Health Canada, and Swissmedic, all approve biosimilars if they are “sufficiently similar” in their structure, activity, efficacy, safety, and immunogenicity, that is, there be no clinically meaningful differences between biosimilars and their references. However, while some regulators say that a “one-time” switch is acceptable for most patients, no regulator has designated a biosimilar as identical or “interchangeable” with its originator reference product. Moreover, regulatory approval of one biosimilar as similar to the originator product does not mean it is approved as similar to a second biosimilar to the same reference drug. There is no clinical evidence as to the safety of switching from one biosimilar to another. [1], [2], [3]

Canada’s Biosimilars Policies

Across Canada, as older biologics come off patent and increased numbers of manufacturers launch biosimilars, drug programs, both public and private, are developing strategies to increase the utilization of biosimilars, aimed toward reducing biologic drug expenditures. While Canada has lagged the European Union countries in access to biosimilars, at the end of 2019, Health Canada had approved 18 biosimilars for 11 different biologics. Twelve are actively marketed. [4]

Canadian uptake has been tepid, for various reasons. On the prescriber side, physicians who are comfortable with original biologics may nevertheless lack experience with their biosimilars and lack confidence in prescribing them based on lack of quality evidence and lack of practice guidelines, especially with respect to switching patients. Patients are understandably reluctant to be moved from a familiar product to one with unknown effects. Moreover, patients who receive their biologics and supportive care at a manufacture-sponsored clinic, may be required to change clinics if switched to a biosimilar.

On the supply side, penetration of biosimilars in the Canadian market has also been hampered for several reasons. Initial price reductions were not as steep as anticipated, about 20% for biosimilars as compared to 75% for generics. Moreover, the brand manufacturers launched various strategies to retain market share, including confidential discounts and rebates as well as "bundled" pricing that included newer therapies.

While most stakeholders agree there "new starts" could be prescribed biosimilars with little risk, there is controversy as to the safety or desirability of nonmedical switching of patients who are stabilized on a brand biologic. [5] In May 2019, with almost no patient or physician consultation, British Columbia introduced a mandatory nonmedical switch policy from the original biologics (etanercept, infliximab, or insulin glargine) to an approved biosimilar for patients with specific conditions (ankylosing spondylitis, diabetes, plaque psoriasis, psoriatic arthritis or rheumatoid arthritis); patients with Crohn's Disease and ulcerative colitis were included later. [6] Alberta announced a similar nonmedical switching policy In December 2019. [7], [8] Offers by the brand manufacturers to "match" biosimilar prices with discounts and rebates were apparently refused.

European Biosimilars Policies

With over a decade of experience and access to nearly 50 approved biosimilars, European countries have adopted a variety of strategies, indicating there is no one right approach to integrating biosimilars into biologics use. While a few reimbursement programs are driven by a singular goal of lowering drug budgets, most funders utilize both supply-side mechanisms to promote a competitive market for originators and biosimilars as well as user incentives to support the uptake of biosimilars while preserving clinician-patient choice. [9]

Across Europe, one or more access practices may be employed, at national or subnational levels, directed at managing supply and/or utilization. Some (for example, Spain, Norway, Denmark, France and Italy), have established a reference pricing scheme (as used with generics) with expected or mandated discounts for the biosimilar and sometimes the original biologic). Others have developed a competitive purchasing process (a.k.a. tendering) at national level (Norway and Denmark) or subnational or institutional levels (France, Italy, Spain). Although many pricing and reimbursement arrangements are confidential, there has been no discernible "straight-line" correlation between pricing and biosimilar uptake (market share). [10]

To promote biosimilar uptake, jurisdictions have also adopted a variety of practices to increase utilization, some of which have raised considerable controversy and resistance. Prescribing guidelines, for some conditions, reference the molecule

and not the brand, thus putting the original and biosimilar on equal footing, specifically for new starts. Facilities may be charged to achieve a targeted percentage of biosimilar use (France). Financial incentives (or disincentives) may direct the prescriber to the "best price" drug; similarly, patients may choose to pay the cost differential if they do not want the "lowest cost" option. Another Incentive for prescribers is to redirect savings back to the institution or clinic, a practice also known as "gain-sharing" (UK). Only Norway and Denmark have policies which require physicians to switch all patients with specific diagnoses.

Comparison of Canadian and European Biologics Policies (ASBM BC vs EU)

The Canadian provincial approach to integrating biosimilar utilization stands in stark contrast to those of all other countries. [11] As noted by the Alliance for Safe Biologic Medicines "The vast majority of countries leave the decision on choice of biologic medicine with the treating physicians in consultation with their patients. In most European countries switching from an originator to a biosimilar remains a clinical decision made by the treating physician; furthermore, physicians are in charge of treatment protocols regarding switching between protocols." [12]

The BC and Alberta non-medical mandatory switch is the LEAST patient-centered, even in comparison to policies of Norway and Denmark, which previously had the strongest biosimilar biases. However, neither Norway nor Denmark, which use national tender to select the provider, have processes that preclude physicians from prescribing the originator nor are originators precluded from submitting to a competitive tender.

There are several elements that are key to successful prescriber uptake of biosimilars. These are: confidence in the biosimilars, ability to provide patient-centred care, prescribing guidelines based on quality evidence of biosimilar use in the real world over time, education and tools for communications with patients, and feedback based on appropriate monitoring and evaluation.

Nocebo effect

In addition, the very real risk of the nocebo effect cannot be discounted. A recent review confirmed "new or worsening symptoms and adverse events arise from patients' negative expectations and not the pharmacologic action of the drug itself—in biosimilar therapy…" The review identified contributing factors to the nocebo effect as "gaps in patients' and providers' awareness, understanding, and perception of biosimilars, reducing their clinical benefits. Other research has demonstrated that patients who are not given a choice in their medication are more likely not to comply or even to abandon their therapy, despite its effectiveness, leading to negative clinical outcomes. [13]

"This evidence suggests that nocebo effects associated with switching patients from originator biologics to biosimilars can have unfavorable consequences for patients as well as healthcare systems. Non-adherence to or discontinuation of treatment, and perceived increases in adverse events and suboptimal efficacy, can substantially impair quality of life, lead to higher treatment costs, and damage the patient–clinician relationship." [14]

Competitive Bidding (Tendering)

It is also important to note that Canada also has adopted the LEAST transparent competitive bidding process. In those few European countries where either national or hospital-driven single-winner tenders exist and where, as a result, the choice of products is limited, the process is transparent and non-discriminatory against either originator or biosimilar manufacturers but based on competition and the price offered. The same is true in multi-winner tender environments that allow for multiple winners, preserve physician treatment choice and protect against any supply shortages. Most policies do not allow for substitution of a biosimilar for the original biologic at the pharmacy level (except France). In Canada, we have absolutely no evidence that the drug programs have secured the lowest price biologic NOR do we have assurance of security of supply.

Biosimilar Sustainability Assessment Framework: Qualitative & Quantitative Metrics

The following table presents an assessment of key elements of a sustainable biosimilar environment. [15]

POLICY AREAS	AREA SUBTYPE	#	Metric	DE	NL	FR	IT	ES	NO	DK
ACCESS	ACCESS TO BIOLOGICS	0.	Increased molecule use by biosimilar entry	~	~	~	-	~	~	+
REGULATORY ENVIRONMENT AND CLINICAL GUIDELINES	TIME TO ACCESS THE MARKET	1.	Time to first sales	+	+	~	+	+	+	+
	TREATMENT GUIDELINES	2.	Treatment guidelines	~	+	~	-	~	~	+
	SWITCHING POLICIES	3.	Physician switching policies	+	+	+	+	+	+	+
	SUBSTITUTION POLICIES	4.	Pharmacist automatic substitution policies	+	~	~	+	+	+	~
PRODUCT	SAFETY AND QUALITY	5.	Safety and / or quality control alerts	+	+	+	+	+	+	+
	SUPPLY CONTINUITY	6.	Presence / absence of supply shortages	+	+	+	+	+	+	+
INCENTIVES	PATIENT FACTORS	7.	Patient incentives	-	-	+	~	~	-	-
	PROVIDER & PRESCRIBER INCENTIVISATION	8.	Existence of prescription quotas	-	~	~	~	~	-	~
		9.	Provider financial incentives	~	-	-	-	-	-	-
		10.	Physicians quotas linked with financial incentives	~	-	~	-	-	~	-

COMPETITIVE PRESSURE	LEVEL OF COMPETITION	11.	Biosimilar penetration	~	~	~	~	~	+	+
		12.	Biosimilar competitor concentration	-	-	-	-	-	-	-
	PRICING RULES AND DYNAMICS	13.	Mandatory price cut policy for originator	O-B+	+	+	O-B+	+	+	+
		14.	Price reference policy at molecule level	+	+	+	+	-	-	-
		15.	Price erosion vs. originator	~	~	+	-	+	+	+
		16.	Price evolution of biosimilars over time	~	+	+	-	-	~	~
		17.	Price evolution of originators over time	-	+	+	+	+	+	+
	PURCHASING MECHANISMS	18.	Length of contracts	+	+	+	+	+	+	+
		19.	Number of winners	+	+	~	+	+	-	~
		20.	Winner decision criteria beyond price	-	-	~	~	-	-	-

Key threats to long-term sustainability

In summary, IQVIA articulates the following key threats to long-term sustainability of biosimilars

- Payer-driven incentives to increase switching critical importance, i.e., quotas, financial incentives; however concentrated (single) biosimilar: high savings in short term but sustainability risk.
- Physicians lack confidence in biosimilars and resist switching to a single biosimilar based on cost factors. Multiple winner tenders and contracting with less aggressive price erosion allow physicians to gain experience with biosimilars and to maintain choices
- Tendering (single winner) restrict physician prescription choice, forcing patients to switch, as well as threatening supply and introducing instability in both originator and biosimilar manufacturer
- Payer-driven switch, especially if enforced though negative physician incentives, provides a means to manage healthcare budgets in the short term but jeopardizes sustainability by reducing physician prescription choice, limiting or changing therapy for the patient, reducing patient involvement in treatment decisions, disrupting market forces and bringing uncertainty to manufacturers.
- Payer-driven switch potentially leads to loss of a therapy option currently working for patients, and the impact is estimated to be greater for patients whose disease requires chronic treatment.
- Single-winner tenders with price as the only selection criterion exert maximum pressure on price but jeopardize sustainability.
- By reducing physician prescription choice, limiting or changing therapy for the patient and minimizing patient involvement in treatment decisions, single-winner tendering mechanisms with price as the only selection criterion fail to meet the needs of all stakeholders.

- Single-winner tendering mechanisms with price as the only selection criterion also disrupt market forces, thereby bringing uncertainty to manufacturers about continued market participation and investment profitability; jeopardizing long-term competition and eliminating the incentive for manufacturers to innovate in areas to support patients and providers, hence putting long-term budget sustainability at risk.

Ideal Scenario for Biologics Access Policy

There are several key elements to an ideal biosimilars access policy.

Patients have access to options that meet personal expectations

Patients must have confidence that the drug is safe, quality, and the personal best option for their individual situation. Moreover, there should be no disruption to current users if they are stabilized and doing well on their product of choice. With the premise of lower prices, there should also be Improved access for new starts (based on evidence and best practice guidelines), especially those who may have been denied or delayed access because of cost considerations. All patients on whatever type of biologic should have access to support for optimal usage, monitoring and adverse effects reporting that is linked to the specific biologic. Finally, all patients must be provided with the education and support to fully engage in decision making, at the individual choice level but also at policy levels.

Physicians have choice of safe, quality products

Physicians must have confidence in all products available, including all biosimilars available based on robust regulatory review, manufacturer assessment, evidence-based guidelines, and unbiased, transparent reimbursement review. The range of options available must assure that physicians can provide patient-centered care, that is, they can meet individual patient needs, expectations and preferences. Physicians should be provided with prescribing guidelines that are based on quality assessment of the evidence of biosimilar use in real world over time and they should have the means to contribute to on-going data collection and evaluation to improve practice. Patients say they rely on their physicians for information and guidance, so the physicians must be afforded the education and tools for communicating with patients. All clinicians should be provided with the means for appropriate monitoring and evaluation for use of either the brand or similar biologic. Finally, to the degree feasible and desirable, all physicians should be afforded opportunity and means to engage in policy making. In essence, if a physician decides to switch a patient [with informed consent], economic value should not guide medical decision.

Optimal savings to healthcare budgets (drugs and other costs; short and long-term impacts)

While there may be immediate advantage of lower price for off-patent biologics with approved biosimilars, it is important that policies and strategies also take a long-term perspective. To assure low prices into the future, the only viable approach is unbiased and transparent competition that includes both the originator and all approved biosimilars. To assure that the cost-savings and budget impacts do reflect reality, it is necessary to identify, calculate, and collect all costs, especially when a patient is switched from his/her originator to a biosimilar. These costs must include physician education and support for each new biosimilar, additional patient visits to the physician, patient support services that have been assumed by the originator, patient monitoring, assessment of adverse effects, including nocebo effects and nonadherence, and ALL real costs to the patient and family.

Support for development of biosimilars and innovation in biologic medicines

Assuring a "healthy level" of competition among originators and biosimilars is not only the strategy to supporting development of further biosimilars but also to supporting innovation and on-going improvement in biologic medicines.

According to analysts, to "achieve steady price erosion across competitors", it is important to avoid over-concentration, with no single product (either originator or one biosimilar) dominating the market or securing long-term contracts (e.g., more than 24 months).

Conclusion

Canada has the opportunity but more importantly the responsibility to create a biosimilars access program that is not just directed toward short-term cost savings but is based on best practice guidelines toward long-term sustainable. This approach assures physicians are able to supply individual patient needs and preferences, without risk to those who are responding well to their current therapies and do not wish to switch products. Patients have the right to informed consent but, as importantly, only if they feel secure in the products, they are taking will monitor symptoms, adhere to their treatment regimen and indeed derive optimal benefits from the therapy (which is essential for cost effectiveness). Moreover, supporting transparent and unbiased competition in suppliers, including the originators and biosimilars, assures best pricing and security of supply. There is indeed an optimal strategy that benefits all stakeholders if everyone has a genuine voice in policy making.

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