

Original Article

## The Law and Ethics of Switching from Biologic to Biosimilar in Canada

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### Abstract

Governments and financial institutions in several jurisdictions are planning or implementing nonmedical/‘forced’ switches by cutting drug coverage for reference biologics and funding only less expensive biosimilars. Switches raise numerous ethical and legal challenges, as the drugs are framed as not being identical and, despite strong evidence for noninferiority of some biosimilars, there is controversy over whether switching can sometimes lead to adverse events. Canadian law generally requires physicians to give precedence to their patients’ best interests over social interests such as cost containment. The primacy of patients’ interests is also clearly reflected in professional policies and codes of ethics. Moreover, physicians are obligated to disclose everything a reasonable person in the patient’s position would want to know when obtaining informed consent for treatment, including addressing not only scientific information but also relevant social controversy about nonmedical switches. Under Canadian law, physicians may be obligated to tell patients about the ability to access unfunded biologics, even if patients lack the resources to obtain them. In sum, while there is no inherent right to funding for reference biologics in Canada, physicians in some circumstances may have a legal obligation as fiduciaries to advocate on behalf of patients to remain on a reference biologic. At a minimum, the controversy surrounding switching will necessitate, as part of the consent process, a robust and thorough disclosure of relevant risks, benefits and reasonable alternatives.

**Keywords:** *Biologics and biosimilars; Health law; Physician obligation*

### INTRODUCTION

Biologics have been life changing. Indeed, this class of drugs could be considered one of the most significant biomedical developments of the past few decades. While the therapeutic benefits have been truly impressive, biologics are, relatively speaking, expensive products. Indeed, the federal Patented Medicine Prices Review Board reported that in 2017 biologics comprised 7 of the top 10 medicines contributing to growth in patented drug sales, with ‘annual treatment costs ranging from \$2,948 to \$57,928’ (1,2). Given that Canadian prices for more common prescription drugs are also among the highest in the world (3,4), drug costs are a serious concern for the sustainability of the health care system.

Drug coverage varies by province (5,6), and biologics may be funded publicly or through private prescription drug plans (7). Because of the significant cost of biologics, there has been a push to move to less expensive biosimilars. In May 2019, British Columbia announced it would be expanding use of certain biosimilars and cutting funding to analogous biologics in order to reduce PharmaCare costs by an estimated \$96.6 million over the first 3 years alone (8,9). Despite carefully crafted language stating that the move will ‘offer coverage for more treatment options’ (8), some consider these kinds of ‘forced’ or ‘nonmedical switches’ to biosimilars to be problematic—especially for patients in remission currently being treated with a biologic (10,11).

Rightly or not, there is controversy regarding the degree to which biologics are interchangeable with their biologic corollaries (12). As a result, switching from a biologic to a biosimilar, or otherwise selecting a biosimilar over a biologic based on cost alone, can raise a number of legal and ethical challenges for physicians and health care providers. Here, we assess these challenges in a Canadian legal, bioethical and policy context. The conclusions are also informative for other jurisdictions with similar legal norms in the context of the physician–patient relationship.

## BIOLOGICS AND BIOSIMILARS

Biologics “include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.” (13) In Canada, biologics are listed under Schedule D of the *Food and Drugs Act* (14), and their review and authorization are governed by Health Canada’s Biologics and Genetic Therapies Directorate (15).

A biosimilar is also a biologic drug under Canadian regulation, but one “demonstrated to be highly similar to a brand name drug already authorized for sale”—the latter often being referred to as the ‘reference’ biologic drug (16). Due to the complexity and variability in the production process, biosimilars are not identical to the reference drug (17) and it is possible for some of them to differ in immunogenicity (18).

Health Canada states that in order to receive authorization for use a biosimilar’s drug manufacturer must “provide information to Health Canada to show that the biosimilar and the reference biologic drug are highly similar, and that there are no clinically meaningful differences in terms of safety and efficacy between them” (16). Health Canada also states that their decision to authorize is “based upon a benefit/risk assessment after considering all of the data submitted” (16). Of course, funding decisions lie in provincial jurisdiction, so Health Canada’s decisions relate solely to licensing. Health Canada states in its biologics fact sheet that “[p]atients and health care providers can have confidence that biosimilars are effective and safe for each of their authorized indications” (17).

Indeed, there is strong evidence of ‘noninferior’ efficacy and safety—when compared to the reference biologic—for several internationally used biosimilars (19–23). In some areas, such as rheumatology, many clinicians have endorsed switches to biosimilars (22). However, controversy remains concerning the robustness of certain jurisdictions’ approval processes and the potential for differential effects on a patient-to-patient basis (24). For example, the ‘extrapolation’ method of approving biosimilars, which has been used by the European Medicines Agency to approve a biosimilar for all indications of its reference drug, was in the past criticized by some as having insufficient

evidentiary requirements (24,25). Health Canada has also engaged in extrapolation of biosimilars for multiple indications, though this occurred after more evidence was generated and in some cases, such as for infliximab products, it required applicants to submit additional risk management and minimization plans (26–28). Some clinicians and scientific societies have in the recent past indicated a lack of confidence in prescribing biosimilars (29–31), though more recent additional evidence for their safety and efficacy may have altered these perspectives.

There is some concern that switching a patient currently in remission on a biologic to a biosimilar could potentially have uncertain or adverse results (11,32), especially in cases of comorbidity or other complex patient or disease-specific characteristics (33). Two 2018 meta-analyses of research into clinical outcomes of switching to biosimilars came to different conclusions regarding safety: one concluded that “there are important evidence gaps around the safety of switching” (34), while the other claimed their results provided reassurance that “the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.” (35) And another review of 29 studies concerning switching for patients with inflammatory bowel disease concluded that “scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars” (36). Given such inconsistencies, and since many patients in remission on a reference biologic are likely to have experienced multiple failed treatments in the past, some patients may want to remain on the same drug (37). For these reasons, some have argued that the decision to switch should be made by the physician and patient on a case-by-case basis (33).

## THE LAW

### Competing Interests

Physicians and other health care professionals can often be faced with difficult decisions regarding competing obligations to patients and to the greater health care system (38,39). Though a biosimilar may save a health care system millions of dollars, the existing legal and ethical framework largely directs physicians to focus on the interests of the patient, even when considering cost containment measures that would benefit the broader health care system.

Clinicians are fiduciaries to their patients (40). The physician–patient relationship is fiduciary in nature because the physician has ‘scope for the exercise of some discretion or power’ and ‘can unilaterally exercise that power or discretion so as to affect the beneficiary’s legal or practical interests’, while the patient is ‘peculiarly vulnerable or at the mercy of’ the physician’s power (41). Canadian fiduciary law means that physicians must treat patients with ‘utmost good faith and loyalty’ (40,41).

As such, existing jurisprudence generally requires physicians to give precedence to their patients' needs over the needs of the health care system. *Law Estate v. Simice* sets out that, in the face of "budgetary problems", "if it comes to a choice between a physician's responsibility to his or her individual patient and his or her responsibility to the medicare system overall, the former must take precedence" (42).

In other words, physicians' efforts at economic restraint must be secondary to patients' interests (43–47). This remains the dominant common law principle in relation to competing interests of this nature.

It follows that a physician-ordered switch from reference biologic to biosimilar for a patient who is stable or in remission could, in certain circumstances, constitute a breach of the physician's legal obligations to the patient. Specifically, it could be viewed as contrary to existing legal norms if a physician has concerns about the switch but makes the move based on a policy aimed solely at system cost savings. This may also be relevant in cases where a patient not on a biologic is provided a biosimilar over a biologic solely for cost savings. The likelihood of such actions constituting fiduciary breaches may increase if adverse effects are subsequently observed. Of course, there is no general legal right to specific forms of health care in Canada (48), and the decision of what drugs should receive funding rests largely with provincial governments (49).

### Informed Consent

Since 1980, physicians have been required by law to consider and disclose all information and risks a reasonable person in their patient's position would want to know when obtaining informed consent (50). In determining what to disclose, a physician must consider both objective factors, such as scientific and medical evidence, and subjective considerations of the patient and their expectations (51). In the context of biologics and biosimilars, this could include disclosing recent research showing the safety and efficacy of some biosimilars (19–22). Moreover, given that there is significant public debate and controversy around switching, and these would reasonably affect the patient's expectations, a physician recommending a switch will likely need to address dominant public discourse. This disclosure could include addressing perspectives popularized by industry groups, patients and medical professionals who oppose nonmedical switches.

While emerging research on the safety of biosimilars may eventually quell debates, as long as there is controversy associated with switching physicians will likely have an obligation to discuss it with patients. As noted, disclosure obligations are not limited to or determined solely by scientific fact (52). The mere existence of a controversy that is so central to the relevant clinical decision, whether scientifically justified or not, may trigger an obligation to address it (52). However, if in the future there

is no evidentiary basis to the controversy, physicians could also incorporate this information into their disclosures.

In addition, in provinces where reference biologics are no longer funded by public or private prescription drug plans, physicians may be obligated to tell their patients about the ability to access them, even if they lack the resources to obtain them (45). While some may be concerned that disclosing such options could be psychologically harmful to some patients, past case law has held that paternalistic withholding of health-related information by physicians is usually a breach of fiduciary and consent obligations (40,53–57). This sort of withholding can only be acceptable in circumstances where sharing the information will "undoubtedly trigger an adverse reaction that will cause further unnecessary harm to the patient" (58), circumstances which would not apply in relation to disclosing information about drug alternatives. Case law has generally held that "[a] patient should be advised of a known treatment which others in the same specialty consider superior, even if the doctor does not agree." (59–62)

### PROFESSIONAL ETHICS

Physicians are bound by the ethical and practice standards set by their self-regulating bodies, and, to some degree, by the norms and standards of the international medical community. Failure to meet those standards can result in disciplinary action. In physicians' codes of ethics, a dominant consideration has always been the best interest of the patient. The World Medical Association International Code of Medical Ethics states "A physician shall act in the patient's best interest when providing care." (63) The American Medical Association's Principles of Medical Ethics states "[a] physician shall, while caring for a patient, regard responsibility to the patient as paramount." (64) Most importantly, the Canadian Medical Association's *CMA Code of Ethics and Professionalism* states that physicians must "[c]onsider first the wellbeing of the patient", and "always act to the benefit of the patient and promote the good of the patient." (65) The contents of this code have been formally adopted by some provincial colleges of physicians and surgeons through standards of practice (66,67), rendering them binding on members. Some other colleges have their own codes and policies, though they generally reflect the same principle of "[a]dvocating for patients" (68).

As noted, there are tensions that arise in any physician's practice between the duty to society and to individual patients. Switches from biologics to biosimilars for cost containment purposes are great examples of this. However, the lack of any statement in the relevant professional codes and standards indicating physicians can prioritize public health or health economic interests over those of a current patient underscores the primacy of patients' interests in the existing ethical paradigm.

Thus, where a significant difference in effectiveness or risk exists between a biologic and biosimilar, physicians will have a professional obligation to advocate for the option that prioritizes their patients' interests and wellbeing.

## PUBLIC PERSPECTIVES AND REPRESENTATIONS

The perspectives of patients and the general public on controversial health care changes can both frame policy debates and impact the trajectory of health technologies. Research has found that patients, the general public, health care providers and policymakers can all have different views on the value and attractiveness of health interventions (69). Members of the public now look online and to social media for health information (70), and the quality and reliability of health information on the dominant platforms can often be low because false information spreads quickly (71,72). Individuals are also potentially susceptible to echo chambers of confirmation bias that can polarize likeminded groups (73). These groups could be susceptible to lobbying and marketing from corporations and special interests.

Direct and indirect or veiled marketing representations can also impact public perceptions. Former FDA Commissioner Scott Gottlieb has stated that there are "deliberate or unintentional efforts by branded [biologic] companies to create confusion" about biosimilars' safety and efficacy (74). Industry trade groups representing biologic manufacturers have lobbied governments and undertaken campaigns to publicize claimed potential risks of switching (74,75). This creates the potential for undue influence by corporations that stand to profit from preventing the use of biosimilars.

In addition, mass media portrayals of health care issues can shape public discourse, and subsequently, potentially policy and utilization (76–79). In Canada, the media places a strong emphasis on patient interests (80). When the issue is about price, Canadian media reporting generally favours patient access and government funding (80).

Ultimately, it is clear that the public discourse around switching is complex and shaped by a variety of interests. Notably, public representations can also drive legal action. More media coverage, marketing or public discussion of a topic—whether accurate or not—can heighten public awareness and change patient expectations, affecting the likelihood of legal action (81). Changes to patient expectations will also have a significant impact on the physician/patient relationship and consent obligations in Canada. Given physicians' disclosure requirements for informed consent are expanded on the basis of patient expectations and dominant social discourses (50,51), such that physicians must address key points of the public discourse even if they are unscientific (52), public advocates can indirectly have a significant influence on

clinical practice. While discussion of the various mechanisms for restraining such influence is highly complex and beyond the scope of this research, regulatory bodies such as the Competition Bureau (82) and Health Canada (83) have some jurisdiction to intervene.

## CONCLUSION

The reasons governments implement switches from biologics to biosimilars are important. These switches can generate immense savings for both health care systems and individual patients, potentially allowing for better overall medical care (8). Indeed, there is a large opportunity cost in both dollars and public health to continuing to pay for biologics if equally safe and effective biosimilars are available. Additionally, as there is no general legal right to access specific forms of health care in Canada (48), provincial governments are typically free to make the funding decisions they see fit.

Regardless, the push toward the use of biosimilars—even if justified on the basis of cost and sound science indicating highly similar performance—will raise legal and ethical challenges. And news and social media coverage of the topic may play a significant role in shaping the public debate, impacting interactions between physician and patient. Where patients with complex chronic disease are in remission on a biologic, there may be pushback from both physicians and patients against potentially disrupting that status quo. Some biologic users, such as those with severe and complex inflammatory bowel disease, may be hesitant to switch. If a physician has concern about switching, there may be legal obligation as a fiduciary to advocate for whatever is viewed to be in the patient's best interest, which may include remaining on a reference biologic. At a minimum, the controversy surrounding switching will necessitate, as part of the consent process, a robust and thorough disclosure of relevant risks, benefits and reasonable alternatives.

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