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

by

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**Abstract**

Governments and financial institutions in several jurisdictions, including British Columbia, are planning or implementing non-medical / "forced" switches by cutting drug coverage for reference biologics and funding only less expensive biosimilars. Switches raise numerous ethical and legal issues, as the drugs are not identical and, despite strong evidence for non-inferiority of some biosimilars, there is evidence that 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 non-medical switches. Under Canadian law, physicians are also 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 the switch will necessitate, as part of the consent process, a robust and thorough disclosure of relevant risks, benefits and reasonable alternatives.

## Introduction

Biologics drugs have been a truly life changing development. 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 in 2017 that biologics comprised seven of the top ten 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 healthcare 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.[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 "non-medical switches" to biosimilars to be problematic – especially for patients in remission currently being treated with a biologic.[10,11] Recent research has shown that Denmark's recent switch for arthritis nevertheless resulted in about 20% of patients not switching after one year.[12]

Biosimilars are not entirely identical to their biologic corollaries.[13] As a result, switching from a biologic to a biosimilar can raise a number of legal and ethical challenges for physicians and healthcare providers. Here, we assess these challenges in a Canadian legal, bioethical and policy context.

**Biologics and Biosimilars**

Biologics "include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins."[14] As such, it is difficult to neatly define them, but they can be described as drugs made using living organisms or containing components of organisms. In Canada, biologics are listed under Schedule D of the *Food and Drugs Act*,[15] and their review and authorization are governed by Health Canada's Biologics and Genetic Therapies Directorate.[16]

A biosimilar is also a biologic drug under Canadian regulation, but one "demonstrated to be similar to a brand name drug already authorized for sale" – the latter often being referred to as the "reference" biologic drug.[17] Due to the complexity and variability in the production process (often made in living cells), biosimilars are not identical to the reference drug[18] and it is possible for them to differ in immunogenicity.[19]

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 similar and that there are no clinically meaningful differences in terms of safety and efficacy between them".[17] Yet, despite this statement that there cannot be clinically meaningful differences, Health Canada also states that their decision to authorize is "based upon a benefit/risk assessment after considering all of the data submitted."[17] These two statements do not necessarily accord. Given that switching between two drugs with clinically meaningless differences would likely not impose additional risk, the reason or reasons for needing additional risk/benefit analysis are unclear. Likely, it is in relation to assessing the strength of the research forming the evidentiary basis supporting a biosimilar. Of course, funding decisions lie in provincial jurisdiction, so Health Canada's decisions relate solely to the licensing of the drug.

There is strong evidence of "non-inferior" efficacy and safety – when compared to the reference biologic – for several internationally used biosimilars.[20,21,22,23,24] In some areas, such as rheumatology, many clinicians have endorsed switches to biosimilars.[23] However, controversy remains concerning the robustness of certain jurisdictions' approval processes and the potential for differential effects on a patient-to-patient basis.[25] For example, the "extrapolation" method of approving biosimilars, which has in the past been used by the European Medicines Agency to approve a biosimilar for all indications of its reference drug, has been criticized as having insufficient evidentiary requirements.[25,26] Health Canada has also engaged in extrapolation of biosimilars for multiple indications, though in some cases, such as for infliximab products, it required applicants to submit additional risk management and minimization plans.[27,28,29]

Some clinicians and scientific societies have in the recent past indicated a lack of confidence in prescribing biosimilars,[30,31,32] though more recent evidence for their safety and efficacy may have improved these perspectives and more research is needed.

There is some concern that switching a patient currently in remission on a biologic to a biosimilar could potentially have uncertain or adverse results[11,33], especially in cases of comorbidity or other complex patient or disease-specific characteristics.[34] Many patients in remission on a reference biologic are likely to have experienced multiple failed treatments in the past, and may want to remain on the same drug.[35] 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.[34] It is also important to note that there are other forms of switching beyond merely biologic to biosimilar. One 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]

**The Law**

*Competing Interests*

Physicians and other health care professionals in a clinical context can often be faced with difficult decisions regarding competing obligations to patients and to the greater healthcare system.[37,38] Though a biosimilar may save a healthcare system millions of dollars, a physician acting without supporting legislative authority may be breaching ethical and legal obligations when switching a patient on a cost basis.

Clinicians are fiduciaries to their patients.[39] 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.[40] Canadian fiduciary law means that physicians must treat patients with "utmost good faith and loyalty."[39,40]

As such, existing jurisprudence generally requires physicians to give precedence to their patients' needs over the needs of the healthcare 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."[41]

In other words, physicians' efforts at economic restraint must be secondary to patients' interests.[42,43,44,45,46,47] 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. The likelihood of this constituting a breach 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.[20,21,22,23] 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 forced switches.

Existing and future scientific research indicating biosimilars are non-inferior in safety and efficacy to reference biologics is not likely to affect physicians' obligations to discuss the controversy of switching with patients, as long as such public debate persists and patients could reasonably want it addressed. As noted, disclosure obligations are not limited to or determined solely by scientific fact.[52] The mere existence of a controversy, whether scientifically justified or not, may trigger disclosure obligations.[52]

In addition, in provinces where reference biologics are no longer funded by public or private prescription drug plans, physicians will still likely be obligated to tell their patients about the ability to access them, even if they lack the resources to obtain them.[44] 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.[39,53,54] Though two older cases held physicians were not negligent in exercising "therapeutic privilege" and withholding information to prevent harm to their patients,[55,56] these decisions have been criticized by legal scholars as improper applications of the law.[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."[59,60,61,62]

**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 and loss of station. 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 very 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 on social media.[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 – a concern relevant to biosimilars that we discuss further below.

How the mass media portrays healthcare issues can shape public discourse, and subsequently, potentially policy and utilization. [74,75,76,77] In Canada, the media places a strong emphasis on patient interests.[78] When the issue is about price, Canadian media reporting generally favours patient access and government funding.[78] This could potentially work in favour of reference biologics that are at risk of being defunded in favour of biosimilars.

Marketing representations can also affect 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.[79] Industry trade groups representing biologic manufacturers have lobbied governments and undertaken campaigns to publicize claimed potential risks of switching.[79,80] While these efforts should not be conflated with well-intentioned patient-focused advocacy raising issue with forced switches,[10] it does mean that the public discourse around switching is highly complex and underlaid by a variety of interests.

It is worth noting that 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 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] influential public advocates can indirectly have a significant influence on clinical practice.

## Conclusion

The reasons governments implement forced switches from biologics to biosimilars are important. These switches can generate immense savings for both healthcare 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 healthcare in Canada,[48] provincial governments are typically free to make the funding decisions they see fit.

Yet, it should be recognized that a push toward the use of biosimilars – even if justified on the basis of cost and sound science indicating similar performance – will still raise a host of legal and ethical challenges. Mass and social media may help shape debate on the topic, and this will affect interactions between physician and patient. Where patients with complex chronic disease are stably in remission on a biologic, there may sometimes 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 only show effectiveness with a certain drug in a manner that is not easily scientifically explainable. Even with evidence of biosimilar equivalence, a switch may sometimes have the potential to disrupt remission and cause patient regression.[11] This possibility could mean that physicians in some circumstances would have a legal obligation as fiduciaries to advocate against a switch in keeping with the prioritization of their patients' best interests. At a minimum, the controversy surrounding the switch will necessitate, as part of the consent process, a robust and thorough disclosure of relevant risks, benefits and reasonable alternatives.

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