Generic Drugs and Biosimilars

Innovator Liability in Canada[1]

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Jurisprudence in Canada regarding innovator liability is sparse. The few cases that have directly examined the issue have rejected the contention that an innovator (brand name) manufacturer can be liable for injuries caused by a generic manufacturer's drug.

With the impending expiration of patents for many biologic drugs, and the onslaught of biosimilars, similar issues involving innovator liability in the biologic context will inevitably arise. (Biosimilars were previously referred to by Health Canada as subsequent entry biologics. *See* Draft – Revised Guidance Document: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (2010) available from http://www.hc-sc.gc.ca, [2010 *SEB*

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Guidance], which was replaced by the 2016 *Biosimilars Guidance*, *infra*). While there are no cases yet in Canada examining whether the manufacturer of a reference biologic (i.e., the original biologic) can or should owe a duty of care to consumers of biosimilars, on the principles underlying the brand/generic drug cases, an equally strong or stronger argument can be made to reject such a duty of care to consumers of biosimilars.

Innovator Liability in the Brand/Generic Drug Cases

The first reported case in Canada to consider the issue of innovator liability was *Goodridge v Pfizer*, 2010 ONSC 1095, a 2010 decision of the Ontario Superior Court of Justice. In that case, the plaintiffs sought damages for a proposed class action that included persons who ingested not only brand name Neurontin, but also generic gabapentin not manufactured or sold by the Pfizer defendants. The plaintiffs pleaded that the Pfizer defendants were negligent and caused harm to consumers of Neurontin and generic gabapentin, by designing and distributing a drug that had a harmful side effect—namely, propensity for suicidal behavior. Furthermore, the plaintiffs pleaded that the Pfizer defendants negligently promoted the off-label use of Neurontin, and that it was foreseeable to the Pfizer defendants that physicians would rely on their statements about Neurontin in prescribing the generic version of the drug for these off-label uses.

The court in *Goodridge* conducted its analysis from first principles to determine whether the innovator manufacturer owed users of the generic drug a duty of care. Because the relationship between the innovator manufacturer and generic users did not fall into a category that was already recognized as giving rise to such a duty, the court considered whether the relationship passed the two-stage test for establishing a duty of care developed in Canadian case law:

> (a) Do the facts disclose a relationship of proximity in which failure to take reasonable care might foreseeably cause loss or harm to the plaintiff (and thereby create a prima facie duty of care)?
>
> (b) If so, are there any policy reasons why the prima facie duty of care should not be recognized?

Anns v Merton London Borough Council, [1978] A.C. 728 (U.K.H.L.) and *Cooper v. Hobart*, 2001 SCC 79.

On the question of proximity, while the court accepted that foreseeability was established, that alone was not enough to establish proximity. The court held that the relationship between the Pfizer defendants and the consumers of generic gabapentin was more remote than the relationship between consumers of generic gabapentin and the manufacturer of generic gabapentin. *Goodridge* at para 90. The court held that it would be unfair to impose a duty of care on an innovator manufacturer for another manufacturer's conduct when the innovator cannot control, qualify, or stop that conduct:

> …the innovator is not in a position to give any warnings about the uses being made by consumers of a copied version of the innovator's product. A drug innovator cannot issue warnings about the hazards of a drug manufactured and sold by another pharmaceutical company, particularly when the hazards may be associated with off-label uses. Although the drug innovator can control the manufacture of its own product, monitor for adverse reactions to its product and give warnings about its own product, the innovator is not in a position to stop the generic manufacturer from releasing the generic drug or to stop physicians from prescribing the generic drug for off label uses. This conduct is not the innovator's conduct, and, in my opinion, *it would be unfair to impose a duty of care on the innovator for another's conduct when the innovator cannot control, qualify or stop that conduct. In my opinion, it would not be fair or just to make the innovator liable for failing to do something that should and can only be done by others.*

Goodridge at para 98(emphasis added).

The court in *Goodridge* further held that it would be unfair to make the defendants, as innovators, liable simply for releasing an idea that is copied.

On the public policy question, the court held that there were two public policy factors that ought to negate any prima facie duty of care to generic users. First, the imposition of a duty of care to the competitor's consumers would impose strict liability for defective products and make an innovator an insurer against all harm from its innovation, which would be a radical change in Canadian law and one for the legislature, not the courts, to make. Second, the imposition of liability on the innovator would discourage medical advances and innovative technologies that could be beneficial to society. *Goodridge* at para 102.

The court in *Goodridge* ultimately struck all claims relating to Pfizer's alleged liability for generic drugs manufactured by its competitors, concluding that it was plain and obvious that a defendant innovator manufacturer owes no duty of care to purchasers of the generic version of the drug. *Goodridge* at para 65. It is noteworthy that *Goodridge* was a motion to strike based on the pleadings, heard at the same time as the class certification motion.

Six years later, in *Brown v Janssen*, (April 7, 2016), Toronto 06-CV-321585CP (ONSC), Belobaba J, another judge of the Ontario Superior Court of Justice had occasion to reconsider the issue on a more specific pleading. The plaintiffs' proposed class action against Janssen alleged that the antipsychotic medicine Risperdal causes gynecomastia, a condition of male breast growth, and that the defendants failed to adequately warn consumers of both Risperdal and generic risperidone about the risk of developing gynecomastia. The plaintiffs pleaded that the defendants knew or ought to have known that manufacturers of generic risperidone "would be bound by Health Canada's regulations to reproduce exactly in the product monographs for

generic risperidone the safety data in the product monographs for Risperdal, such that prescribers and consumers of generic risperidone would necessarily be relying on safety data presented by the defendants in the product monographs for Risperdal."

The plaintiffs in *Brown* attempted to distinguish *Goodridge* on the basis that the pleadings in *Goodridge* did not allege that manufacturers of the generic drug were bound by Health Canada's regulatory regime to copy the warnings authored by the manufacturers of the brand name drug. They argued that the "requirements" of "Health Canada's regulatory regime" provided the causal link necessary to find a proximate relationship between an innovator manufacturer and generic consumers to establish a duty of care with respect to a failure to warn claim.

The relevant regulations are described in more detail below. However, and by way of summary, nothing in Canada's *Food and Drugs Act*, or its corresponding regulations, require the labeling for generic drugs to be identical to the labeling of the brand name drug. R.S.C. 1985, c. F-27 [*Food and Drugs Act*]; Food and Drug Regulations, C.R.C. c. 870 [Food and Drug Regulations]. Nothing in either prohibits a generic manufacturer from asking Health Canada to approve labeling for its products that is different from the innovator manufacturer's labeling. Nothing in either gives the innovator manufacturer any legal control over the labeling of the generic product. Only Health Canada has legal authority over changes to, and approval of, product labeling. As more fully described below, a generic manufacturer is subject to the same post-approval safety monitoring requirements as an innovator manufacturer, the same post-approval reporting obligations, and the same obligations to ensure that its product labeling is up to date and supports safe conditions of use. Nothing requires the innovator manufacturer to continue to sell its product after expiry of its patent protection (or at all), or to monitor safety of

or labeling for its products after it stops selling. Generic manufacturers could be selling their products long after the innovator manufacturer has stopped.

Under the provisions of the *Food and Drugs Act* and its regulations, before a new drug (a defined term under the Food and Drug Regulations) may be advertised or sold in Canada, the drug manufacturer, whether "originator" or "generic," must obtain a notice of compliance (NOC) for that drug from the Minister. *Apotex Inc. v Ontario (Minister of Health & Long-Term Care*), [2004] O.J. No. 1728 (Ont. S.C.) at para 10. To seek an NOC, a manufacturer must file a drug submission with the Minister. *Reddy Cheminor Inc. v Canada (AG),* 2003 FCT 542 at para 7. Specifically, subsection C.08.002(1) of the Food and Drug Regulations provides that no person can sell a new drug unless the manufacturer has filed a new drug submission (NDS), an extraordinary use new drug submission, an abbreviated new drug submission (ANDS), or an abbreviated extraordinary use new drug submission that is satisfactory to the Minister and has obtained an NOC in respect of the submission.

Pursuant to C.08.002(2) of the Food and Drug Regulations, a New Drug Submission (NDS) must be submitted for an innovator's drug to enable the Minister to assess the safety and effectiveness of the new drug before issuing a notice of compliance. Some of the requirements of an NDS are set forth below.

> **C.08.002**
>
> (2) A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:
>
> (a) a description of the new drug and a statement of its proper name or its common name if there is no proper name;
>
> (b) a statement of the brand name of the new drug or the identifying name or code proposed for the new drug;

(c) a list of the ingredients of the new drug, stated quantitatively, and the specifications for each of those ingredients;

(d) a description of the plant and equipment to be used in the manufacture, preparation and packaging of the new drug;

(e) details of the method of manufacture and the controls to be used in the manufacture, preparation and packaging of the new drug;

(f) details of the tests to be applied to control the potency, purity, stability and safety of the new drug;

(g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended;

(h) substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended;

(i) a statement of the names and qualifications of all the investigators to whom the new drug has been sold;

…

(j.) in the case of a new drug for human use, mock-ups of every label to be used in connection with the new drug — including any package insert and any document that is provided on request and that sets out supplementary information on the use of the new drug — and mock-ups of the new drug's packages;

(k) a statement of all the representations to be made for the promotion of the new drug respecting

(i) the recommended route of administration of the new drug,

(ii) the proposed dosage of the new drug,

(iii) the claims to be made for the new drug, and

(iv) the contra-indications and side effects of the new drug;

(l) a description of the dosage form in which it is proposed that the new drug be sold;

(m) evidence that all test batches of the new drug used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production;

…

(o) in the case of a new drug for human use, an assessment as to whether there is a likelihood that the new drug will be mistaken for any of the following products due to a resemblance between the brand name that is proposed to be used in respect of the new drug and the brand name, common name or proper name of any of those products:

(i) a drug in respect of which a drug identification number has been assigned,

(ii) a radiopharmaceutical, as defined in section C.03.201, in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01, and

(iii) a kit, as defined in section C.03.205, in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01.

Pursuant to C.08.002.1(1), manufacturers of generic drugs are permitted by Health Canada to submit an abbreviated New Drug Submission (ANDS) if certain conditions are met in relation to the "Canadian Reference Product."

C.08.002.1

(1) A manufacturer of a new drug [here, the generic drug] may file an abbreviated new drug submission or an abbreviated extraordinary use new drug submission for the new drug where, *in comparison with a Canadian reference product*,

(a) the new drug is the *pharmaceutical equivalent* of the Canadian reference product;

(b) the new drug is **bioequivalent** with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;

(c) the *route of administration of the new drug is the same* as that of the Canadian reference product; *and*

(d) the *conditions of use for the new drug fall within the conditions of use for the Canadian reference product* (emphasis added).

(2) An abbreviated new drug submission or an abbreviated extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to *assess the safety and effectiveness of the new drug*, including the following:

(a) the information and material described in

(i) paragraphs C.08.002(2)(a) to (f), (j) to (l) and (o), in the case of an abbreviated new drug submission, and …

(b) information identifying the Canadian reference product used in any comparative studies conducted in connection with the submission;

(c) evidence from the comparative studies conducted in connection with the submission that the new drug is

(i) the pharmaceutical equivalent of the Canadian reference product, and

(ii) where the Minister considers it necessary on the basis of the pharmaceutical and, where applicable, bioavailability characteristics of the new drug, bioequivalent with the Canadian reference product as demonstrated using bioavailability studies, pharmacodynamics studies or clinical studies;

(d) evidence that all test batches of the new drug used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production; …

While the Canadian Reference Product is typically a brand name drug and the proposed generic drug is required to be the pharmaceutical equivalent, a Canadian Reference Product may or may not be currently marketed. *Reddy-Cheminor, supra,* at para 9. It is defined as follows:

> a) a drug in respect of which a notice of compliance is issued under section C.08.004 or C.08.004.01 and which is marketed in Canada by the innovator of the drug,
>
> b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, *where a drug in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01 cannot be used for that purpose because it is no longer marketed in Canada* (emphasis added), or
>
> c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph (a).

Because the Canadian Reference Product does not need to be currently marketed by the innovator, the innovator may have stopped selling the drug (and monitoring safety or updating labels) at the same time as or years before a generic manufacturer decides to enter the marketplace.

A generic manufacturer is required (just as the innovator is required) to submit, among other things, mock-ups of every label to be used in connection with the generic drug and a statement of all the representations to be made respecting contra-indications and side effects of the generic drug. Food and Drug Regulations at C.08.002.1(2). All manufacturers, including generic manufacturers, may conduct clinical trials on their drug (be it for the initial safety and efficacy assessment on the innovator drug, or for bio-equivalency assessment of a generic drug), and both are required to report any serious unexpected adverse drug reactions that occurred

during the course of their own clinical trials for their own drug. Food and Drug Regulations at C.05.014(1).

Post-approval, the *Food and Drugs Act* and the Food and Drug Regulations do not differentiate between an innovator and a generic manufacturer with respect to their duties and obligations. Accordingly, generic manufacturers are subject to exactly the same post-market requirements for their generic drugs as innovator manufacturers are for their brand name drugs, including obligations to monitor safety and update product labeling.

Both an innovator and generic manufacturer are required to submit to the Minister all serious adverse reaction reports in respect of *their own* drug (not those of other manufacturers):

> **C.01.017** The manufacturer shall submit to the Minister a report of all information relating to the following serious adverse drug reactions within 15 days after receiving or becoming aware of the information, whichever occurs first:
>
> (a) any serious adverse drug reaction that has occurred in Canada with respect to the drug; and
>
> (b) any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug.

C.01.018 of the Food and Drug Regulations also requires manufacturers, including generic manufacturers, to prepare an annual summary report of all information relating to adverse drug reactions with their respective drugs (not those of other manufacturers), and an analysis as to whether there has been a significant change in the known risks and benefits of their respective drugs.

If a generic manufacturer chooses to change its label from that submitted in its ANDS or if the representations with respect to the contra-indications or side effects of the generic drug change, the generic manufacturer must file a supplement to the ANDS to enable the Minister to

assess the safety and effectiveness of the generic drug in relation to those changes. Food and Drug Regulations at C.08.003(1) and (2).

Unlike in the U.S., Canadian regulations do not require "sameness" of brand and generic labeling, although Health Canada will in practice require a good explanation if there are differences. *See* Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format at s. 1.3.1 available at http://www.hc-sc.gc.ca. There is no law like *Mensing* in Canada that prevents users of generic drugs from suing the generic manufacturer of that drug for an alleged failure to warn. *Pliva, Inc. et al. v Mensing*, 131 S. Ct. 2367 (2011). On the contrary, a failure to warn claim was allowed to proceed against generic manufacturers in *Ledyit v Bristol-Myers Squibb Canada Inc.* 2007 CarswellOnt 9243 (Ont. Sup. Ct), aff'd on appeal 2008 ONCA 372. There, the plaintiffs commenced a class action in negligence (including failure to warn) against both the innovator and the generic manufacturers of the drug nefazodone hydrochoide. The court granted the plaintiffs' motion to add a representative plaintiff who consumed the generic drug manufactured by Apotex, and dismissed Apotex's motion to strike the claims for lack of a plaintiff with a cause of action against it.

Under this regulatory scheme, the innovator defendants argued in *Brown* that they had no legal control over the generic manufacturer's bio-equivalency testing, or its communications and regulatory filings with Health Canada necessary for the approvals of the generic versions of risperidone. They had no legal control over the text of the generic drugs' product monographs (including what the generic manufacturer chooses to include or omit), and exerted no legal control over the generic manufacturer's conduct in monitoring adverse event and safety data, updating the product label where appropriate, and complying with its regulatory filings. In short,

the innovator defendants argued that they could not exert any legal control over whether their product was produced in a generic version in Canada, by whom or in what way, nor could they legally control the distribution or warnings provided with those generic drugs.

The plaintiffs in *Brown* relied on a case from the British Columbia Supreme Court, *Player v Janssen-Ortho Inc*., 2014 BCSC 1122, where the court summarized affidavit evidence before it from employees of the generic manufacturer, including evidence that "for generic drugs, Health Canada requires that the consumer information portion of the monograph match the form and content of the monograph for the innovator drug." However, the court in *Player* did not review the relevant regulations, and more importantly, did not make any finding or base its ultimate decision on whether the generic label had to be the same as the brand label.

The innovator defendants in *Brown* argued that *Goodridge* and other cases had already refused to impose a duty of care on a manufacturer for products manufactured by others, and that even if the court wished to reconsider the question of innovator liability, no such duty of care should be recognized because (1) regardless of foreseeability, there is not a sufficiently proximate relationship between the brand manufacturer and users of the generic medicine to create a prima facie duty of care; and (2) there are public policy reasons to negate a duty even if a prima facie duty were found to exist. In addition to those policy reasons recognized in *Goodridge* (imposing strict liability for defective products and discouraging innovation), imposing such a duty would create the prospect of indeterminate liability. The defendants argued that allowing such liability would make innovator manufacturers *de facto* insurers for the whole industry, and that this involved policy choices more appropriately within the legislative domain.

The court in *Brown* ultimately struck all allegations of innovator liability in the plaintiffs' amended claim on the grounds that the plaintiffs' claims relating to generic risperidone had no

reasonable chance of success. Also see *Brousseau v Laboratoires Abbott Ltée,* 2016 QCCS 083, where a Quebec court held, following a trial, that individuals who consumed generic versions of a drug had no claim against the manufacturer of the innovator drug. The court stated:

> In my view, this court's decision in *Goodridge v Pfizer* is directly on point and was correctly decided. I agree with Perell J.'s reasons and his conclusion that the innovator drug manufacturer has no duty of care to the consumers of the generic version manufactured and sold by the generic competitors. Indeed, no Canadian court has ever held that a brand name drug manufacturer owes a duty of care to users of the generic version manufactured by a competitor. I can usefully add nothing further to the reasoning in *Goodridge v Pfizer*.

Reference Biologics and Biosimilars

In the context of reference biologics and biosimilars, it can be argued that, based on *Brown, Goodridge,* and *Brousseau,* it is settled law in Canada that an innovator manufacturer owes no duty of care to consumers of products manufactured by another. Moreover, even if a court was inclined to reconsider the duty question from first principles using the two-part analysis discussed above, under the regulatory regime governing biosimilars and reference biologics, the proximity between the manufacturer of the reference biologic and consumers of the biosimilar is even more remote than in the brand/generic drug context. See *Anns* and *Cooper, supra* at note 2. The Food and Drug Regulations regarding biosimilars support all the same comments above regarding the obligations on the generic drug manufacturers, but go even further. Under the biosimilar regime, a biosimilar is not "bioequivalent" or "interchangeable" with the reference biologic; the manufacturing process for the reference biologic and biosimilar is not the same, and the manufacturing process is recognized as having a direct and significant impact on the safety and efficacy of biologic drugs; and, further, the labeling of the reference biologic and biosimilar

is not the same. Accordingly, there is even greater justification not to impose innovator liability on the reference biologic manufacturer.

Biologic drugs are "derived through the metabolic activity of living organisms and tend to be significantly more variable and structurally complex than chemically synthesized drugs." *Biosimilar Guidance, infra* note 26 at 1.5. Biosimilars are drugs that enter the market subsequent to a reference biologic previously authorized in Canada. They have "demonstrated similarity" to a previously approved biologic drug and rely, in part, on prior information regarding that biologic drug to obtain approval for sale from Heath Canada. This reliance enables biosimilars to submit a reduced clinical and non-clinical package for their submission.

Reference biologics and biosimilars are both subject to the provisions of the *Food and Drugs Act* for new drugs, including the requirements referenced above governing submissions for approval of brand drugs. While Health Canada previously stated that it intended to amend the *Food and Drugs Act* to provide a comprehensive legal basis for the approval of biosimilars, it ultimately opted to deal with biosimilars using the existing regulatory framework and guidance documents, including *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs.* (2016) Available from http://www.hc-sc.gc.ca [*Biosimilar Guidance*]. This 2016 *Biosimilar Guidance* updates and replaces the 2010 *SEB Guidance, supra* note 1. Conformance with this guidance document is said to enable a manufacturer to comply with the relevant sections of the *Food and Drugs Act* and its regulations (although guidance documents are administrative instruments not having force of law). *See Biosimilar Guidance, supra.* Biosimilars are also subject to the laws, and patent and intellectual property principles outlined within the *Food and Drug Regulations (Data Protection),* the *Patent Act,* and the *Patented Medicines (Notice of Compliance) Regulations*. *Biosimilar Guidance* at 1.3.6.

A Biosimilar Is Not "Bioequivalent" to the Reference Biologic

The *Biosimilar Guidance* specifies that Part C, Division 8 of the *Food and Drug Regulations* governs the sale of all new drugs in Canada, including biosimilars. *Biosimilar Guidance* at para 2.1.1. Accordingly, the manufacturer of a biosimilar must submit an NDS, and not an ANDS, to receive approval for sale, containing structural, functional, non-clinical, and clinical studies that provide extensive data on the demonstration of similarity with the reference biologic. *Biosimilar Guidance* at para 2.3.2.4. Health Canada specifies that the demonstration of similarity does not signify that the quality attributes of the two products being compared are identical, but that they are highly similar with two consequences: 1) that the existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no adverse impact upon safety or efficacy of the biosimilar, and (2) that non-clinical and clinical data previously generated with the reference biologic drug is relevant to the biosimilar. *Biosimilar Guidance* at para 2.3.2.4. While manufacturers of the biosimilar can rely in part on prior information submitted by the reference biologic manufacturer, clinical trials must still be conducted in support of a biosimilar's safety and efficacy, including comparative pharmacokinetic, pharmacodynamics, safety, and immunogenicity studies. *Biosimilar Guidance* at para 2.3.3.3. These clinical trials are regulated in the same manner as trials for reference biologics. This differs from the approval process for generic drugs, as generic drug manufacturers are permitted to submit an ANDS, which requires evidence primarily of bioequivalence.

According to Health Canada's *Biosimilar Guidance*, a biosimilar must establish "demonstrated similarity" to a previously approved biologic drug, which depends upon "detailed and comprehensive product characterization." *Biosimilar Guidance* at para 1.2. The active substance (medicinal ingredient) of the reference biologic and that of the biosimilar must be

shown to be similar, and the dosage form, strength, and route of administration of the biosimilar should be the same as that of the selected reference biologic. *Biosimilar Guidance* at para 2.1.3. The goal of the comparability exercise is to ascertain whether the biosimilar and the chosen reference biologic can be judged highly similar in terms of quality attributes, and thus provide support for a possible conclusion of similarity for safety and efficacy. Health Canada makes clear that biosimilars are not "generic biologics" and authorization of a biosimilar "is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug." *Biosimilar Guidance* at para 1.3.5. Unlike the U.S. regime, the Canadian regime does not contemplate a subset of biosimilars that are considered "interchangeable" or which have "clinical equivalence" to the reference biologic.

No information is provided in the guidance documents on interchangeability, but in a question and answer document that accompanied the release of the *Biosimilar Guidance*, Health Canada stated that it "does not support automatic substitution of a biosimilar for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange." (2010) "Questions & Answers to accompany the final *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (Biosimilars)"* available at http://www.hc-sc.gc.ca. Health Canada has also stated that it will ultimately leave decisions regarding interchangeability up to the provinces. To date, the majority of provinces have not made formal decisions as to whether they will allow post-approval declarations of interchangeability. At least one province (Alberta) has decided that biosimilars will not be eligible for review as interchangeable products.

Given that there is no requirement for the biosimilar to be "bioequivalent" or clinically equivalent to the reference biologic, the manufacturer of the reference biologic could not and

should not be liable for any "negligent design" claims associated with the biosimilar (whether specific to the benefit risk decision, or reasonableness of testing and analysis of test results). In the common law provinces of Canada, there are essentially three relevant types of product liability in negligence: negligent design, negligent manufacture, and failure to warn.

The Manufacturing Process for Biosimilars and Reference Biologics Is Distinct

Health Canada recognizes that biologic drugs are practically impossible to replicate because "they tend to be labile and sensitive to changes in manufacturing processes." *Biosimilar Guidance* at para 1.5. In fact, Health Canada states that "changes to source materials, manufacturing processes, equipment, or facilities can result in significant unexpected changes to the intermediate and/or final product." *Id*. Over time, these changes can become so pronounced that existing versions of the drug do not resemble the original versions that were approved by regulators. Public Policy Forum, *Subsequent entry biologics in Canada*, available at https://www.ppforum.ca. This phenomenon, known as "manufacturing drift," might affect the degree of similarity between a biosimilar and its reference product. *Id*. For this reason, Health Canada has stated that once authorized for the market, a biosimilar is a new drug with all of the associated regulatory requirements. *Biosimilar Guidance* at 2.4.2.

Given that the manufacturing process alone has such a direct and significant impact on the safety and efficacy of a biologic, it would be even more unfair to impose liability on the innovator manufacturer for alleged harms associated with the manufacture of the biosimilar, or any "negligent manufacture," because the innovator exercises no control over the manufacturing process for the biosimilar. As stated in *Goodridge,* the reference biologic manufacturer "is in no position at all to control, qualify or stop the conduct" of the biosimilar manufacturer.

The Biosimilar and Reference Biologic's Labeling Are Not the Same

As with generic drugs, there is no regulatory requirement of "sameness" for the biosimilar product labeling. The 2010 guidance document provided that "the sponsor of a [biosimilar] will not be able to utilize the product monograph of the reference biologic drug in its entirety as that of its own product." *SEB Guidance, supra* note 1 at 2.3.4. While that language was removed in the most recent *Biosimilar Guidance,* there will still be differences in the labeling. The *Biosimilar Guidance* now provides that the contents of the product monograph for biosimilars should include the following information:

- A statement indicating that the product is a biosimilar and that similarity between the biosimilar and the reference biologic drug has been established based on comparative structural and functional studies, non-clinical studies, human PK/PD studies, and clinical trials, as applicable.
- A statement that indications have been granted on the basis of similarity between the biosimilar and the reference biologic drug and taking into consideration the mechanism(s) of action, disease pathophysiology, safety profile, dosage regimen, and clinical experience with the reference biologic drug.
- Comparative data generated by the biosimilar sponsor on which the decision for market authorization was made summarized in a tabular format.
- Relevant safety and efficacy information from the product monograph of the biologic drug authorized in Canada to which a reference is made, including warnings and precautions, Adverse Drug Reactions/Adverse Drug Effects and key post-market safety information for all indications that are authorized for the biosimilar.

Biosimilar Guidance at para 2.3.5.

It is important to note that the product monograph for the biosimilar is not permitted to claim bioequivalence or clinical equivalence between it and the reference biologic. *Biosimilar Guidance* at para 2.3.5 The biosimilar may be approved for some, or all of the same indications for use as the reference biologic. *Biosimilar Guidance* at para 2.3.4.

Once granted an NOC, a biosimilar becomes a new drug with all of the associated regulatory requirements. *Biosimilar Guidance* at para 2.4.2. That is, the manufacturer of a biosimilar is subject to the exact same post-approval reporting obligations, and the same obligations to ensure that its product labeling is up to date and supports safe conditions of use, as brand, generic, and reference biologic manufacturers. *Biosimilar Guidance* at para 2.4.

In light of this regulatory scheme, which contemplates greater differences between the labeling of the biosimilar and the reference biologic than in the brand/generic drug context, there are even more compelling reasons as to why the manufacturer of the reference biologic should not owe a duty to warn users of the biosimilar.

Conclusion

Given that Canadian courts have rejected the imposition of innovator liability in the brand/generic drug context, there is no reason to believe that courts will not follow suit in the reference biologic/biosimilar context. There is even less proximity between the reference biologic manufacturer and consumers of biosimilars than between brand name manufacturers and generic drug users. The same policy reasons that were recognized in *Goodridge* as negating the imposition of a duty of care on the brand name manufacturer also exist for reference biologics, including not discouraging innovation. Moreover, liability should not be imposed on the reference product manufacturer because it would impose indeterminate liability on the

reference biologic manufacturer, which cannot control how much biosimilars are sold or for how long.