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Revising the Guidance Document for Biosimilar Agents

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Abstract

Health Canada, the national department responsible for regulating food, health and consumer products to keep Canadians safe, published the *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs* on 14 November 2016 to update its framework for the market authorization of biosimilars in Canada. Biosimilars are the off-patent copies of biologics, a class of therapeutic agents derived from complex organic processing. Biosimilars are only "similar and not identical" to their reference biologic because biologics cannot be perfectly duplicated. As a result, biosimilars may not have the same safety profile as their reference biologic. As a number of biologics will be coming off patent in the coming years, Health Canada's goal was to prepare by updating and clarifying the process surrounding market authorization.

Santé Canada, le ministère en charge de la réglementation des produits de consommation et des produits de santé au Canada, a publié le 14 novembre 2016 la Ligne directrice: exigences en matière de renseignements et de présentation relatives aux médicaments biologiques biosimilaires*, pour actualiser le cadre législatif des autorisations de mise sur le marché de biosimilaires au Canada. Les biosimilaires sont des copies de médicaments biologiques (une classe d'agents thérapeutiques issus de procédés organiques complexes) dont le brevet a expiré. Les biosimilaires sont "similaires mais non identiques" à leur médicament biologique de référence, parce que des médicaments biologiques ne peuvent être parfaitement dupliqués. Il en résulte que les biosimilaires ne peuvent offrir tout à fait les mêmes garanties d'emploi que leur médicament de référence. Compte tenu du fait qu'un grand nombre de brevets de médicaments biologiques vont expirer dans les années à venir, le but de Santé Canada était de se préparer en actualisant et clarifiant son processus de mise sur le marché.*

Key Messages

- On 14 November 2016 Health Canada revised its guidance document for biosimilars and clarified its position to manufacturers.
- Biosimilars are not the generics of biologics. Policy must, therefore, reflect their "similar but not identical" relationship.
- Biosimilars will continue to have an increasing impact on the Canadian health care system. Policymakers must be aware of their benefits and the potential challenges associated with their adoption.

Messages-clé

- *Le 14 novembre 2016, Santé Canada a modifié le document régulant les biosimilaires et a clarifié sa position vis-à-vis des producteurs.*
- *Les biosimilaires ne sont pas des génériques de produits biologiques. La régulation doit, en conséquence, tenir compte de leur caractère "similaire mais non identique."*
- *L'impact des biosimilaires sur le système de santé canadien va continuer à croître. Les politiques doivent connaître leurs avantages, mais aussi les défis potentiels posés par leur mise sur le marché.*

1 BRIEF DESCRIPTION OF THE HEALTH POLICY REFORM

Biologics, also known as biopharmaceuticals, are often described as drug products derived from living organisms. Biologics are important therapeutic agents and play an important role in treating diseases such as diabetes (Lantus/insulin glargine), neutropenia (Neupogen/filgrastim) and Crohn's (Remicade/infliximab).[1] Although many have great clinical efficacy, policymakers and clinicians must also consider their high cost. Last year, biologics accounted for the greatest share of public drug plan spending in every province and are cited as a major spending cost driver (CIHI 2016).[2] As these drugs come off patent, drug manufacturers have begun to create lower cost copies known as biosimilars. As their biological origin makes them different from conventional generic medications, Health Canada has created a special framework and evaluation process for biosimilars market authorization in Canada.

On 14 November 2016 Health Canada released the first reform of this evaluation process. Entitled *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs*, this reform builds on the 2010 original guidance document and addresses a number of concerns which had arisen over the intervening six years (Health Canada 2016a). The 2016 reform updates the old guidance document by: changing the name "subsequent entry biologics" to "biosimilars," clarifying several terms and policies, continuing a stepwise pathway to regulatory approval process for life science manufacturers, and bringing Canadian regulatory processes into closer alignment with those of other regulatory agencies.

As a guidance document, the 2016 reform is not considered to have force of law. Instead, it is considered to be an administrative instrument which highlights the process by which biosimilar manufacturers can best ensure that they meet statutory and regulatory requirements (Health Canada 2016a). This approach allows for some flexibility by both Health Canada and manufacturers during the review process of a new biosimilar submission. This reform is timely, given the demand for cost-effective drug therapies in Canada.

2 HISTORY AND CONTEXT

2.1 General context

One of the roles of Health Canada is to oversee the market authorization process for new and generic medications in Canada. Generics are medications which are chemically equivalent to their reference product and have the same quantity of active ingredient as their reference drug (CADTH 2015). The evaluation of generics by Health Canada focuses on chemical and bioequivalence trials. The emergence of biosimilars has introduced a new element

[1] Brand name/non-proprietary name

[2] Information for Québec not included

to the market authorization process. Biosimilars are medications which are "similar but not identical" to their reference biologic medication. Unlike conventional pharmaceuticals, biologics are therapeutic products derived from living organisms (Health Canada 2016b). Although these products have often proven to be effective therapeutic options, biologics are expensive interventions. By 2020, approximately 20% of all pharmaceutical spending in Canada will be on biologics (CADTH 2014). Another view is more telling, biologics represented 2.6% of the total claims, but 19% of the total eligible drugs for one private plan provider in 2015 (Telus Health 2016). Biosimilars, which in the EU cost 20% to 30% less than their reference biologics, are seen as important tools to control spending in the long term (CADTH 2014). So far, the following savings have been seen in the Canadian context:

Table 1: Approximate Biosimilar Savings for Select Medications

Brand reference	Biosimilar	Biosimilar discount vs. reference
Genotropin (hGH)	Omnitrope	26%
Remicade (infliximab)	Inflectra	47%
Lantus (insulin)	Basaglar	15%
Neupogen (filgrastim)	Grastofil	17%

Adapted from Biosimilars Market Update (Telus Health 2016).

2.2 Manufacturing context

Biologics are often manufactured using biotechnology such as genetic engineering.[3] By contrast, conventional pharmaceuticals such acetaminophen or ibuprofen are derived synthetically through chemical processes. This difference has major implications from a policy standpoint. Where biologics are concerned, it is often said, "the process is the product" (Health Canada 2009). This means that unlike chemical manufacturing for drugs such as ibuprofen, biotech manufacturing is highly complex and even slight changes in the process of creating biologics may have major effects on the end product. In the case of biosimilars, this explains why biosimilar manufacturers can produce end products which are "similar but not identical" to their reference biologic.[4] The importance of this concept can be seen in the case of Eprex, a biosimilar of the biologic Epoetin-alfa (Schellekens 2009). A small manufacturing change in the formulation process for Eprex led to an important increase in the number of patients who developed pure red blood cell aplasia (Casadevall 2009). In addition, there is concern that switching a patient currently on a reference biologic to

[3]For example, DNA recombination

[4]The quotations are kept to show that this phrase captures a concept. This concept has important policy implications as it impacts how the medication is perceived by the medical community. By contrast generic medications must, by definition, be identical to their reference product.

its biosimilar may provoke an immune response in some individuals.[5] This is known as "immunogenicity" and can be life-threatening in some cases.

2.3 Political history

The original 2010 guidance document, *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics*, served as a general policy framework which outlined the position of Health Canada regarding "subsequent entry biologics"[6] and the regulatory approval process of these products. It, along with its supporting documents,[7] also served to address the concerns of two of Health Canada's major stakeholders: health care professionals and provincial health authorities. The 2010 guidance document clearly highlighted for these two stakeholders that biosimilars should not be considered generics or "biogenerics" (Health Canada 2010a). Moreover, according to Health Canada, as "[biosimilars] are new drugs that are not declared to be pharmaceutically or therapeutically equivalent with their reference products, this should inform decisions regarding interchangeability and substitutability" (Health Canada 2010b).[8]

To manufacturers, Health Canada emphasized that biosimilars were not automatically eligible for usage in the same clinical indications as their reference biologic (Health Canada 2010a). Comparative and/or clinical studies were necessary to determine the indications of a biosimilar (CADTH 2014).[9] This policy was an important safety precaution due to the potential differences between biosimilars and their reference biologics.

In the years following the release of the 2010 guidance document, Health Canada adjusted its regulation process by introducing a 3-year pilot program in 2015. This program was based on feedback from biosimilar manufacturers and involved a stepwise approach to the approval process for new biosimilars (Health Canada 2015). The stepwise process was intended to provide important feedback to manufacturers sooner in the market authorization process regarding their submissions and to help with streamlining evaluation.

[5] Under Health Canada's framework, Eprex would not have been considered a subsequent entry biologic, however many researchers and papers classify it as such.

[6] "Subsequent entry biologics" was the name used for biosimilars before the 2016 guidance document (Health Canada 2016a)

[7] The major supporting documents are: the Q & A posted to support the guidance document, the letter addressed to the Provincial and Territorial Drug Plan Directors, and the 2015 Scientific Review document (Health Canada 2010a; Health Canada 2010b; Health Canada 2015).

[8] Interchangeability refers to the requirement to interchange a lower cost generic version of a name brand drug (cost-driven decision). Substitutability refers to substituting an altogether different drug as functionally equivalent to a prescribed drug for treating the same medical condition (a medical decision) (Klein and Wang 2013).

[9] Indications are the approved uses of a medication.

3 GOALS OF THE REFORM

With a number of biologics coming off patent within the next ten years, many biosimilars may by entering the approval pipeline. The 2016 guidance document was created in anticipation of this potential influx of biosimilars into the market authorization process. The goal of this reform is to clarify Health Canada's position and update the 2010 guidance document.[10] These clarifications include:

- changing the term "subsequent entry biologic" to the more internationally recognized term "biosimilar,"
- clarifying the scientific basis for biosimilar authorization by clearly explaining how "similarity" between a biosimilar and its reference biologic is determined,
- including a new subsection on immunogenicity,
- clarifying the terminology regarding authorization of indications to biosimilars, and
- permitting the inclusion of safety and efficacy data from reference biologics authorized in Canada to the product monograph of biosimilars.

In addition, the 2015 stepwise consultation pilot will be continued until 2018 as planned. As yet, no changes have been made to Health Canada's position on substitutability and interchangeability. These changes and clarifications have had the effect of aligning or "harmonizing" Health Canada's regulatory approval processes for biosimilars with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Biosimilars Canada 2017).

4 INFLUENCING FACTORS

4.1 Problem

The original guidance document was created in anticipation of the first biosimilars being brought through the drug market authorization process. In the subsequent years, Health Canada began to determine the points of confusion and issues with its 2010 guidance. In addition, through consultation with biosimilar manufacturers in the subsequent years, Health Canada also determined that a number of them would be developing biosimilars.[11] With biosimilar products destined for multiple markets there was concern that a lack of clarity in the guidance document could prove costly and unproductive for both Health Canada and biosimilar manufacturers, and indirectly impact other stakeholders. Furthermore, Health Canada needed to reassure health care professionals and provincial authorities that its po-

[10] According to the guidance document, biosimilars may hold all the indications of the reference biologic if similarity between the two is demonstrated. This is particularly important as indications determine reimbursement for many insurers and many reference biologics have multiple indications (e.g., Remicade [infliximab] may be used for rheumatoid arthritis psoriasis, Crohn's disease, etc.) This means that it is possible for a biosimilar to be approved with fewer indications than its reference biologic.

[11] Telephone interview by author with Dr. Agnes Klein on 19 November 2015

sition on the interchangeability and substitutability of biosimilars for reference biologics had not changed.

4.2 Politics

The focus of this reform was updating the 2010 guidance document with input from the past six years. Health Canada received comments from over 20 stakeholders ranging from patient groups, law firms, and biosimilar manufacturers to provincial ministries of health (Health Canada 2016b). Discussions with biosimilar manufacturers and patient groups were especially important in this process.[12] While information regarding these talks is not readily available, it is known that a number of patient groups such as The Arthritis Society and the Canadian Skin Patient Alliance have adopted a cautious tone in regard to biosimilars (Siu and Wyatt 2016). Most support mandated post-market surveillance and are against automatic substitution between biosimilars and their reference biologic (Siu and Wyatt 2016). These concerns focus on patient safety and the relative novelty of biosimilars. Manufacturer concerns centred on the cost of making unsuccessful submissions to Health Canada and the cost of meeting the idiosyncrasies of each regulatory authority (e.g., FDA, EMA, Health Canada, etc.).

4.3 Policy

Health Canada's goal was to create a document which would guide biosimilar manufacturers through the Canadian market authorization process while providing transparency to all stakeholders. Health Canada considered the various concerns of stakeholders while crafting its policy. The goal was to create a framework that would be fair and flexible to all parties involved. Under the structure of the 2016 guidance document, Health Canada can make requests for information not specified in the document. On the other hand, biosimilar manufacturers are not locked into a rigid submission process. They are able to work with Health Canada to present submissions which may be adapted from other applications to other regulatory authorities. As such, the new guidance document is harmonized with other national regulatory jurisdictions while ensuring that the process reflects the Canadian context.

In the preparation for the 2010 original document, stakeholders (provincial governments, health care practitioners) asked Health Canada to review data that supported therapeutic interchangeability between biologics and biosimilars, and to make recommendations as to whether this could be done safely and effectively by physicians. Health Canada's response by letter to the directors of the provincial health plans highlighted that while "specialized clinical studies can be used to support therapeutic interchangeability," manufacturers of could subsequently make changes to their production process which would impact the validity of such studies. As such, "Health Canada does not support automatic substitution

[12] Telephone interview by author with Dr. Agnes Klein on 19 November 2015

of a [biosimilar] for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange" (Health Canada 2010b, 1). This approach carried important political undertones as it provided strong guidance while leaving the door open for the provinces to design their own policies. This context is important as in the 2016 guidance document interchangeability and substitutability are not directly addressed.

5 IMPLEMENTATION

The implementation of the guidance document was relatively straightforward. Health Canada follows a framework known as Good Guidance Practices which outlines the process for the development, revision, and approval of guidance documents. A draft revision was published on 7 December 2015 and two and a half months were given for comment (Health Canada 2016c). These comments were evaluated by the Biologics and Genetic Therapies Directorate Management Committee and used to finalize the current guidance document (Health Canada 2017). Health Canada has noted that it will continue to review this document on an ongoing basis through the Biologics and Genetic Therapies Directorate (Health Canada 2016a).[13]

6 EVALUATION

6.1 Impact evaluation

This guidance document is a communication tool intended to allow Health Canada to widely and clearly establish its position on biosimilars in Canada. Manufacturers, provincial governments, patient groups, and health care professionals can look to this document to understand the approach intended by Health Canada. The document was positively received by most stakeholders. For example, Biosimilars Canada, which represents biosimilar manufacturers, praised the changes stating, "[w]ith the release of this revised Guidance Document, Health Canada has significantly improved its approach and requirements, and is now much more aligned with leading regulatory partners" (Biosimilars Canada 2017).

By combining this document with the 3-year stepwise consultation pilot, Health Canada aims to decrease the number of inappropriate submissions and ensure that biosimilar manufacturers have a strong understanding of the regulatory pathway their drugs will follow. Further revisions will also serve to further clarify the submission process for manufacturers and to better protect Canadians.

Overall, the effect of this document is a clarified process for the evaluation of new biosimilars. The result should be an increased number or proportion of successful submissions. This will have important downstream effects.

[13]Response by Health Canada on 22 March 2017 to email inquiry from author.

6.2 Future and areas of consideration

The 2016 guidance document focused primarily on changes which impacted biosimilar manufacturers. However, future revisions and stakeholder consultations should consider: provincial governments, health care professionals and nomenclature.

6.2.1 Provincial governments

Given the impact of biosimilars on patient safety and cost, Health Canada should continue to work with provincial partners to help implement evidence-based policies. Provincial governments designate interchangeability and substitutability rules in Canada. Since the 2010 guidance document was created, only four provinces (Alberta, British Columbia, Ontario, and Québec) have issued major statements on interchangeability. The current guidance document does not directly address this issue and future revisions would be an opportunity for Health Canada to capture the result of its consultations with the provinces in this regard.

It is important to note that considerable variation exists between the provinces in terms of pricing, discounting, reimbursement and even covered indications for biosimilars. For example, in mid-2016 the price of the biosimilar Inflectra was approximately 25% greater in Saskatchewan compared with Alberta (Siu and Wyatt 2016). These differences are an important consideration for Health Canada's stakeholders.

6.2.2 Health care professionals

The issue of interchangeability and substitutability of biosimilars is a salient one for health care professionals. The relative novelty of biosimilars means knowledge of these agents in relation to their reference biologic is not widespread. In the case of physicians, a 2014 survey of 427 specialists reported that 31% had "heard of [biosimilars] but could not define them" and 10% "had never heard of them" (Reilley 2014, 15). Given that Health Canada recommends that therapeutic interchange be at the discretion of the physician, efforts will need to be made to increase the information available to physicians regarding biosimilars.[14] The FDA, for example, provides some continuing education for interested health care professionals. Furthermore, the FDA produces a compendium of biologics and interchangeable biological products known as the "Purple Book" (FDA 2017). A similar resource would be of tremendous value for Canadian health care professionals.

[14]Other health care providers face similar challenges. In the case of pharmacists, for example, provincial interchange and substitution laws remain to be defined. In France, pharmacists were recently given the authority to substitute biologics for biosimilars under specific conditions (Legifrance 2013). In the United States, eight states have passed biologic substitution bills (Thimmaraju et al. 2015).

6.2.3 Nomenclature

The nomenclature or the naming of biosimilars is of particular importance. Each biosimilar is currently given an international non-proprietary name (INN) which is the same as that of its reference biologic. However, as noted previously, biosimilars and biologics are "similar but not identical." This is important considering that in the aforementioned poll of specialists, 64% thought that if two medicines have the same INN, they are structurally similar and 76% believed that they could be used for the same indications (Reilley 2014). This issue is also important in regards to the traceability of adverse drug events in patients. If biosimilars and biologics share the same INN and are not structurally similar, there could be a negative impact on adverse event traceability and patient safety.

For the time being, Health Canada will use brand name and drug identification number (DIN) tracking for post-market surveillance. This, however, is expected to change in the near future (Health Canada 2016c). In 2014, the WHO sent a proposal regarding a standard separate nomenclature for biosimilars to member countries for comment. Health Canada has acknowledged that if this proposal is accepted internationally, it will implement the proposal's recommendations.[15]

7 STRENGTHS, WEAKNESSES, OPPORTUNITIES AND THREATS

Table 2: SWOT Analysis

Strengths	Weaknesses
• Establishes an internationally harmonized policy for biosimilar approval • Creates clear policy that can be rapidly adapted • Guidance document is not legally binding, allowing for flexibility in policy	• Biosimilars are not widely known • INN is currently shared by biologics and biosimilars • Little support for health care professionals in terms of biosimilar education

[15]Telephone interview by author with Dr. Agnes Klein on 19 November 2015

Opportunities	Threats
• Reform of biosimilar nomenclature • Potential to leverage policies from other drug regulatory jurisdictions • Creation of education initiatives on biosimilars geared to health care providers • Work with the provinces to ensure that there are policies in each province for substitutability and interchangeability • A Canadian "Purple Book"	• Biasing information sources currently available to healthcare professionals • Variations in interprovincial policies on interchangeability and substitutability • Challenges in adverse event reporting as new biosimilars are improved and nomenclature practices remain the same

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