Comments Re: Consultation: Handbook for healthcare professionals on biosimilar biologic drugs

Submitted electronically April 29, 2022 via email to: brddopic-bpcidmbr@hc-sc.gc.ca.

To Whom it May Concern;

Please accept these comments on the draft "Handbook for healthcare professionals on biosimilar biologic drugs" from the Alliance for Safe Biologic Medicines (ASBM). ASBM is a multinational patient advocacy coalition with more than 140 member organizations worldwide, including more than a dozen patient advocacy organizations based in Canada.

I. Equivalence, Interchangeability and Switching

As written, the *Handbook for healthcare professionals on biosimilar biologic drugs* sends mixed signals throughout the document about the "equivalence" of reference and biosimilar products, switching and interchangeability. E.g.;

- "In contrast to generic drugs, Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug.**"**

This statement would suggest the importance of having multiple products and a strong biosimilars market, which is inconsistent with policies in some Canadian provinces of forces switching:

- "The availability of biosimilar versions of important biologic medications provides:
  - the benefit of less reliance on single, global supply chains
  - additional options for patient treatment plans (Figure 3)"

This case study certainly suggests the caution that should be taken in assuming equivalency and switching:

- "As differences in ADCC were observed between Inflectra® and Remicade®, and because ADCC may be an active mechanism of action for infliximab in IBD, but not rheumatic disease, authorization of the IBD indications was not acceptable without further evidence to demonstrate biosimilarity in ADCC. "

Other parts of the Handbook suggest reference products and biosimilars can be considered interchangeable. E.g.,

- "Health Canada has not observed any differences in post-authorization safety signals for biosimilars compared to their reference biologic drugs since the first biosimilar was authorized in 2009 in Canada. Health Canada receives drug safety information from other jurisdictions including the US and the EU. Biosimilars have been used for over 10 years in the EU and over 5 years in the US and no unexpected safety signals have been identified."

While the handbook acknowledges that substitution policies are decided at the provincial level, the above language suggests that Health Canada attitudes toward equivalence, substitution and interchangeability are consistent with regulators in Europe and the United States, as does this section:

- "The key principles Canada uses to evaluate biosimilars align with those of other regulators and international organizations, such as:
    - the World Health Organization (WHO)
    - the European Medicines Agency (EMA)
    - the United States Food and Drug Administration (FDA)

In fact, many of the automatic- and forced-substitution policies increasingly being implemented in Canada stand in stark contrast to the substitution practices in Europe and the United States.

In nearly every European county, for example, automatic substitution of biologic medicines at the pharmacy level is banned. Forced substitution is also extremely rare, and in nearly every country, physicians are free to choose between multiple reimbursed products. While use of the lowest-price drug is encouraged for new patients, European physicians are largely free to keep stable patients on the product which is working for them, rather than being forced to prescribe the government-chosen product. With few exceptions, savings to the health system are achieved by competition between multiple reimbursed products, not by restricting physician and patient choice. A 2017 survey of 403 Canadian physicians, all of whom prescribe biologics, revealed that 64% are not comfortable with a third-party switching a patient to a biosimilar for non-medical (i.e. cost) reasons.

In the United States, automatic substitution is permitted only for biosimilars which have provided additional data to FDA demonstrating no loss of efficacy or additional risks following repeated switching between the biosimilar and reference product. (In the U.S. this is referred to as an "interchangeable" biosimilar.) 82% of the 403 Canadian physicians surveyed believe such studies should be conducted that measure the effects of switching on patient safety and product efficacy, prior to automatic substitution being permitted.

We suggest softening or clarifying language in the Handbook that implies interchangeability of reference products, emphasizing the importance of prescriber responsibility for determining the choice of a biologic for their particular patient, and acknowledging more accurately the regulations in other countries, particularly the EU and USA.

II. Pharmacovigilance and Adverse Event Reporting

The handbook text correctly and appropriately emphasizes the importance of pharmacovigilance programs and clear product identification when dealing with multiple similar biologic products all sharing a non-proprietary name. Repeated references to this need appear in the draft handbook language:

- "A biosimilar's RMP should include:
    - a discussion about methods to distinguish adverse event reports for the biosimilar from those for other licensed products, including the reference biologic drug."
- "**Adverse reaction reports** require specific elements in order to be assessed for a causal association with a health product:
    - name of the health product, including brand name and lot number if available"
- "To facilitate product-level identification of biologic drugs, including biosimilars, Health Canada recommends that throughout the medication use process, health professionals use:
    - unique brand names
    - non-proprietary name
    - other product-specific identifiers, such as the DIN and the lot number"
- "The specific brand should be specified by the prescriber on the prescription before dispensing in a pharmacy."
- "Product-specific identifiers should be included in ADR reports to facilitate the traceability of an adverse reaction to a specific suspect drug product."
- "Healthcare professionals can help improve pharmacovigilance for biosimilars by ensuring that key pieces of information are:
    - tracked in the prescribing and dispensing of biosimilar drugs

- provided in any ADR reports
- In particular, healthcare professionals should:
    - record the medicine's brand name at all levels, from prescription to dispensing and patient administration
    - record the lot number whenever possible
    - report the brand name and lot number in case of suspected adverse drug reactions"
- "It is important to record the brand name and lot number for both medicines if a patient switches from:
    - one biosimilar to another
    - one biological medicine to a biosimilar"

Yet despite the acknowledgement of the importance of accurately identifying the medication on reporting adverse drug events, the pharmacovigilance tools that the Handbook suggests (e.g., DIN, Batch/Lot Number, Brand Name) are insufficient to achieve this. The 2017 Canadian physician survey revealed that brand name is not consistently used in reporting and the DIN number is not widely used by clinicians:

- Prescribers record only the non-proprietary name 20% of the time when prescribing, which lead to incomplete patient records and the potential for inadvertent or inappropriate substitution.
- Only 1% of physicians record the DIN when prescribing.
- In adverse event reporting, 26% of physicians *record only the non-proprietary name*. This can lead to pooling of adverse events, misattribution of adverse events to the wrong product, or the inability to attribute an event to the actual product prescribed.
- Only 4% of physicians record the DIN in adverse event reports.
- Only 23% consistently report Batch Number in adverse event reports. 16% rarely include it, and 20% never include it.

A breakdown of adverse event reporting among physicians in four large provinces reveal *that brand name is absent in roughly 25-50% of reports.* Similarly, only non-proprietary names are used exclusively in between 20% and 40% of adverse event reports. Physicians essentially do not record DIN. Together, this leaves enormous gaps in the Canadian biologic pharmacovigilance system which must be addressed.

Included in Adverse Event Reports?	**Total (n=403)**	**Alberta**	**B.C.**	**Ontario**	**Quebec**
Brand name	**70%**	68%	52%	74%	76%
Non-proprietary name only	**26%**	23%	43%	24%	22%
DIN number	**4%**	9%	6%	2%	3%

These data are supported by a subsequent analysis of Canadian adverse event reports that have shown reliance onbBrand name to be insufficient to identify the specific biologic product responsible for the adverse event. A

review of 2020 Canadian ADR reports for infliximab products were found to contain brand name only 63% of the time.

We suggest Health Canada make reference to the importance of distinguishable non-proprietary names and the current problems of relying solely on brand names and the DIN for documentation in medical records and adverse drug event reports.

III. International Harmonization of Biologic Nomenclature

In the draft handbook language, Health Canada appropriately emphasizes the importance of international harmonization with international counterparts:

- "Health Canada works closely on an ongoing basis with its international counterparts and participates in several initiatives aimed at:
    - harmonizing approaches to the regulation of biosimilars internationally"

In 2014, following years of studying the issue, the World Health Organization's International Nonproprietary Names (INN) Expert Group proposed a voluntary distinct naming standard for biologic medicines. Health Canada was among the early supporters of this proposal, along with the United States, Australia, Japan, and other countries. Despite this broad support, the global standard was not made available by the WHO, leading to a proliferation of country-specific naming systems, many of which rely on distinct suffixes appended to a shared INN. The U.S. FDA (which has implemented a suffix system similar to that proposed by the WHO) held several meetings with Health Canada to discuss harmonization into a "North American Approach" that would extend the benefit of distinct naming of biologics to Canadian patients. These benefits include accurate attribution of adverse events to the correct product, reduced chance of accidental or inappropriate substitutions, and increased manufacturer accountability for their products.

In an attempt to build on the harmonization discussions between these regulators, ASBM held a series of meetings with FDA, Health Canada, and the WHO in 2018 and 2019, to discuss the benefits of international harmonization around a distinct naming system. The first two meetings were held in Washington, DC, and the third was held in Ottawa. Despite their longstanding support for distinct naming and harmonization, Health Canada suddenly and inexplicably reversed course in February 2019, announcing it would rely on brand name reporting and DIN. At the Ottawa meeting however, Health Canada's representatives did express their willingness to harmonize with the WHO, should it make an international nomenclature standard available.

Reliance on brand name reporting is a problem that is not unique to Canada. A 2020 WHO report identified this issue as one of a handful of remaining regulatory challenges for biosimilars, acknowledging that "this could potentially lead to problems with identifying products and pharmacovigilance unless careful attention is paid to the issue. This situation has caused concerns, for example, prescription mix-ups, unintentional switching, and questions on traceability."

Europe has taken a similar approach to Canada in its reliance on voluntary brand name reporting, with similar results: a 2018 analysis of EudraVigilance ADR reports for infliximab products found that 35% did not contain brand name- *despite the inclusion of brand name in ADR reports being required by EU law since 2012.*

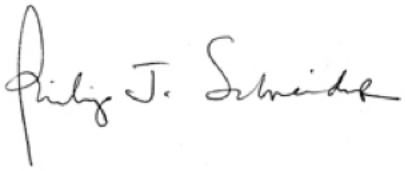
In light of the well-documented pharmacovigilance concerns with the "brand name" approach and the negligible use of DIN by physicians, we urge Health Canada to reconsider its reliance on these identifiers; and instead consider adopting (or harmonizing with) a distinct naming system similar to that of the U.S. or that proposed by the WHO.

Accordingly, we recommend the handbook language be updated to reflect that voluntary reporting of DIN and brand name, while helpful tools, are not in themselves adequate. In addition, we urge the handbook to emphasize that Health Canada is working with other major regulators to improve pharmacovigilance through international harmonization based on a system of distinct biologic nomenclature.

Thank you for the opportunity to comment on these important issues.

Sincerely,

Michael S. Reilly
Executive Director, Alliance for Safe Biologic Medicines



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