Intellectual Asset Management

Life Sciences 2016

Key issues for senior life sciences executives

Biosimilars in Canada: at a tipping point

J Bradley White and Nathaniel Lipkus
Osler, Hoskin & Harcourt LLP

Biosimilars in Canada: at a tipping point

By J Bradley White and **Nathaniel Lipkus**, Osler, Hoskin & Harcourt LLP

Biosimilars, or highly similar versions of innovative biologic medicines, have now been approved and marketed in developed countries for several years. As with the advent of generic small-molecule drugs decades ago, some physicians and patients are sceptical of biosimilars because they are not exact copies of a branded drug. Yet the potential cost savings to patients and government-funded drug plans from the use of safe and effective biosimilar medicines are undeniable.

Canada has slowly begun to adapt existing drug policies to permit approval and use of biosimilars. To date, the Canadian approach has been more cautious than that of the European Union, where the European Medicines Agency (EMA) pioneered an analytical framework for biosimilar review that has led to several market approvals and significant cost savings. No Canadian laws have yet been amended to accommodate unique aspects of biosimilars. This stasis may provide some comfort to sophisticated companies familiar with the Canadian regulatory, patent and market access regimes. However, biosimilars present unique challenges, and and significant uncertainty remains about how Canada's existing policy infrastructure will be adapted to the unique aspects of biosimilars.

In Canada, biosimilars are called 'subsequent entry biologics' (SEBs), although Health Canada recently acknowledged in a draft guidance document that the term 'SEB' is synonymous with the term 'biosimilar'. Regulatory approval and patent issues associated with biosimilars are managed by the federal government, while provincial governments set policy on market access to these medicines (in part because they are collectively the medicines' most significant buyers).

The first biosimilar in Canada, Omnitrope, was approved in 2009 and Health Canada approved Celltrion's Remsima/Inflectra in 2014. Health Canada recently issued updated draft SEB guidance, which will likely be finalised in 2016. There are now multiple pending patent cases involving biosimilar products on the Federal Court of Canada's docket, with many novel issues at stake. Canada's provinces are finally figuring out how to capitalise on biosimilar competition within their formularies. This chapter provides an overview of how stakeholders in the Canadian market have grappled with key issues arising from the recent introduction of biosimilars in the marketplace.

Regulatory approval

Biosimilars in Canada are approved in the same manner as other biologic drugs. Applicants file a new drug submission (NDS) with Health Canada, and Health Canada's Biologics and Genetic Therapies Directorate (BGTD) reviews the submission. The BGTD is the same department that reviews innovative biologic drug submissions. However, BGTD is separate from the department that reviews small-molecule generic drug submissions, meaning that there is no historical infrastructure for handling abbreviated biologic submissions.

In 2009, alongside its approval of Omnitrope, Health Canada issued draft guidance for the approval of SEBs, which was finalised in early 2010. The 2010 SEB guidance was general in nature. It confirmed the following positions on issues deemed important at the time:

- SEBs are not 'generic biologics' and authorisation of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug.

"Health Canada has also announced that it is undertaking a three-year pilot programme in which it will offer scientific advice on companies' comparability packages at an early stage in the process"

- In appropriate circumstances, SEB applicants may compare their products to foreign reference products.
- It may be possible to extrapolate from approval of a studied indication for which clinical data is provided to an indication for which no clinical data has been generated.

The SEB guidance states an intention to harmonise Health Canada's approach with that of other competent regulators and international organisations, such as the World Health Organisation. Specifically, the SEB guidance directs sponsors to the product class-specific guidance documents developed within the EMA, as the EMA's scientific principles are stated to be consistent with those of Health Canada.

The first true test of the SEB guidance was Health Canada's review of Inflectra, a biosimilar version of Janssen's Remicade (infliximab), submitted by Celltrion to be marketed in Canada by Hospira. Celltrion sought approval for six indications: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease. Health Canada courted controversy with its decision in January 2014 to approve Inflectra for only four of the six indications, denying approval for ulcerative colitis and Crohn's disease – the two indications that drive most of Remicade's revenues.

Months earlier, the EMA Working Party on Biosimilar Medicinal Products (BMWP) had issued a detailed scientific justification for recommending approval of Celltrion's product despite slight differences in antibody-dependent cell-mediated cytotoxicity (ADCC), which has been suggested to play a role in inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. The BMWP reviewed the totality of the evidence and found that small observed differences between Remicade and the Celltrion product did not detract from the products' comparability. Soon after, the EMA approved the product for all indications.

Whereas the EMA focused on structural and biological data to determine that the products were comparable, Health Canada concluded that it could not complete a risk/benefit analysis in respect of the inflammatory bowel indications due to differences that could have an impact on safety and efficacy. The EMA had emphasised the importance of non-clinical data, while Health Canada's approach suggests that only clinical data will support extrapolation where minor differences have been observed. Most recently, in February 2016 the US Food and Drug Administration (FDA) Arthritis Advisory Committee reached the same conclusion as the EMA, after hearing submissions from FDA reviewers, Celltrion and Johnson & Johnson. It remains to be seen whether the recent consistent approach taken by the FDA and EMA will persuade Health Canada to abandon its comparatively cautious approach.

In December 2015 Health Canada issued revised draft SEB guidance to reflect its experience with biosimilar applications over the last few years. The document contains revised information on:

- the interplay between the degree of analytical and biological similarity and the scope and breadth of clinical and non-clinical data, as well as preferred clinical study approaches, noting that study populations and endpoints should be the most sensitive to potential differences;
- additional detail on issues to address in justifying extrapolation, the possible effect of comparability and mechanisms of action, and encouragement to contact Health Canada whenever considering extrapolation;
- circumstances under which it may be possible to extrapolate to new indications for already approved biosimilars; and
- restrictions on the types of representation that a company can make regarding relative performance of the biosimilar in comparison with the reference product.

Health Canada has also announced that it is undertaking a three-year pilot programme in

which it will offer scientific advice on companies' comparability packages at an early stage in the process. Parties are encouraged to seek meetings of this nature at least six months before filing their submissions.

Patent pathway

Rather than creating a new regulatory pathway for pre-approval patent notification and clearance for biosimilars, Health Canada has issued guidance that biosimilar patents will be addressed under the existing pathway for small-molecule drugs.

Canada's patent linkage system applicable to biosimilars resembles the Orange Book linkage system created in the United States under the Hatch-Waxman Act. Innovators list patents on Health Canada's Patent Register that are relevant to the medicinal ingredient, formulation, dosage form or use of the innovator biologic. Follow-on entrants are required to address the listed patents in association with their biosimilar NDS by serving a notice of allegation (similar to a Paragraph IV notice letter) on the innovator. The innovator may then commence an application under the Patented Medicines (Notice of Compliance) Regulations in the Federal Court of Canada for an order to prohibit approval of the biosimilar NDS until expiry of the listed patents. Commencement of the proceeding triggers an automatic stay of approval for up to 24 months while litigation is pending.

The government made no changes to the Patented Medicines (Notice of Compliance) Regulations to adapt the existing linkage system to biosimilars. Rather, Health Canada simply amended its guidance document pertaining to the regulations to clarify that they do apply to SEBs. This approach provides some predictability to stakeholders, which now have over 20 years' experience with the current system. However, since Canada's linkage system was not designed for biosimilars, companies may soon expose inadequacies of the current system that do not address unique aspects of biosimilar products. For example, in an appropriate case, a biosimilar entrant may challenge the applicability of the regulations to its product submission if it has not relied on the innovator's clinical data. Innovators are likely to seek to expand the scope of patent linkage litigation to include additional patent types, such as manufacturing process patents. There may be an opportunity for stakeholders to have input on reforming the system when the Canadian government amends the Patented Medicines (Notice of Compliance) Regulations in its implementation of the Canada-European Union Comprehensive Economic and Trade Agreement.

Patents listed on the Patent Register are particularly valuable due to the automatic 24-month stay and potential to prohibit approval of a biosimilar competitor until expiry of the listed patent. Some companies facing rejection of potentially listable patents have persisted in the face of Patent Office rejection and succeeded in obtaining late issuance of patents filed many years ago, further increasing the barrier to early market entry for biosimilar applicants. For example, AbbVie had been pursuing a dosage regimen patent filed in 2002 for its top-grossing product, Humira. The patent application had been rejected by the commissioner of patents as being directed toward an unpatentable method of medical treatment. In *AbbVie Biotechnology Ltd v Canada (Attorney General)* (2014 FC 1251) Justice Kane of the Federal Court distinguished AbbVie's patent claims from the method of medical treatment doctrine, ruling that the claims do not interfere with a physician's skill and judgement. AbbVie listed the patent on the Patent Register soon afterwards.

To date, only one biosimilar case has been litigated through to hearing under the Patented Medicines (Notice of Compliance) Regulations. In *Amgen v Apotex* (2015 FC 1261) Justice Hughes of the Federal Court considered whether a composition of matter claim to filgrastim (a polypeptide defined by its amino acid sequence) was obvious in view of prior art teaching the purification of the naturally occurring protein from which filgrastim is adapted. Hughes ruled that the filgrastim claim was obvious, despite the skilled effort required to discover the naturally occurring protein's sequence. The ruling was appealed, but is moot under the regulations now that Apotex's filgrastim product has received Health Canada approval. Amgen has asked the Federal Court of Appeal to exercise its discretion to hear the appeal despite its mootness.

Celltrion/Hospira obtained regulatory approval in Canada for a subset of indications for Inflectra, a biosimilar version of Remicade. At the time Celltrion filed its NDS, no patents were listed on the Patent Register in respect of Remicade. However, while the Inflectra submission was pending, a patent issued to the Kennedy Institute of Rheumatology. Hospira commenced an action under the Patent Act to invalidate this late-listed patent, which relates to the use of infliximab in conjunction with methotrexate in rheumatoid arthritis.

The Inflectra case is scheduled for trial in Autumn 2016, more than three years after it commenced. In the meantime, Celltrion filed a supplemental new drug submission (SNDS) and was required to address the patent separately under the Patented Medicines (Notice of Compliance) Regulations. Janssen commenced a proceeding to prohibit approval of the SNDS. Given that Inflectra is already approved to treat rheumatoid arthritis without a restriction on use with methotrexate, and the patent issues are poised to be addressed in the impeachment proceeding, this proceeding under the regulations appears redundant. Hospira has moved to strike the application as an abuse of process.

Other biosimilar cases that have been commenced under the regulations include litigation between Sanofi and Eli Lilly regarding insulin glargine and litigation between Amgen and Samsung Bioepis regarding etanercept. Both of these cases have been discontinued.

Market access

Even after a biosimilar product receives regulatory approval and has cleared the Patent Register, there remain several regulatory and market hurdles on the road to market success. Companies must go to the Canadian Agency for Drugs and Technology in Health (CADTH) to obtain a recommendation that provinces list the product on their formularies

J Bradley White
Partner
bwhite@osler.com

J Bradley White, partner and chair of the national IP department, practises IP law with an emphasis on complex patent litigation and patent prosecution. He provides strategic advice on the enforcement of patent rights, including the coordination and management of litigation strategies throughout multiple jurisdictions. He has appeared as lead counsel before the Federal Court of Appeal, the Federal Court and the Ontario Superior Court. A registered patent agent, he specialises in Canadian and foreign patent and industrial design prosecution, strategic reviews of IP portfolios, patentability and advising on worldwide patent portfolio management and enforcement. Mr White is also registered to practise before the US Patent and Trademark Office and is recognised internationally as a leading patent litigator and practitioner.

Nathaniel Lipkus
Partner
nlipkus@osler.com

Nathaniel Lipkus, a partner in the Toronto office, is an IP litigator. His practice focuses on contentious legal issues confronting innovation-intensive industries, with an emphasis on patent and regulatory issues facing pharmaceutical and biotechnology companies. He has represented numerous companies in the life sciences, technology, energy and gaming industries in patent proceedings across Canada and *pro hac vice* in the United States. He has also litigated trademark, copyright, trade secret and other commercial matters. Mr Lipkus has advocated on behalf of life sciences clients before numerous regulatory agencies in Canada and the United States on IP, regulatory approval, pricing and reimbursement and antitrust matters. He is a registered patent and trademark agent and also provides strategic advice on IP portfolio and risk management.

at a proposed price. Companies can begin this process shortly before Health Canada approval, but should expect a delay of at least six months following approval before receiving a recommendation.

A CADTH recommendation is the basis for approval on provincial drug formularies. Provinces currently coordinate their approaches to listing follow-on products within the Pan-Canadian Pharmaceutical Alliance (PCPA). PCPA negotiations introduce additional delay before public payers commit to reimbursing a product. The necessity of these additional layers of oversight is questionable, as it ought to be straightforward to recommend listing a demonstrably safe and effective biosimilar at a lower price than an innovator product.

One question that remains is the manner in which innovators will retaliate against biosimilar entrants in their pricing. For small-molecule products, innovators have used authorised generics, product switches, next-generation products and co-pay cards as dominant strategies. Historically, innovators have rarely lowered their list prices in response to a new entrant. However, the closer the prices of the innovator and biosimilar, the less likely physicians are to prescribe the biosimilar product. However, the effective discount of the biosimilar product will need to be significant to induce physicians to consider the follow-on product.

Canadian provinces, facing spiralling drug costs, are anxious to benefit from savings through the use of biosimilars. Upon Inflectra's approval, the Quebec government indicated that it would not reimburse any version of infliximab above the biosimilar list price. This decision was applied for all of infliximab's indications, despite Inflectra's approval for only four of Remicade's six indications. More recently, in February 2016 the Ontario government gave preferential access to Inflectra on its formulary; whereas Remicade is available only in exceptional circumstances after other drugs have been tried without success, Inflectra will be reimbursed on a 'limited use' basis with fewer restrictions and no individualised government approval necessary. Ontario's preferential access decision is highly significant, as it causes the biosimilar to be far more convenient for a physician to prescribe than the innovator product. This may indicate the frustration of provinces with the pricing of innovator biologic products.

Since biosimilars will not receive declarations of pharmaceutical equivalence from Health Canada, there is no ready pathway for substitution of an innovator prescription for a biosimilar at the pharmacy level. Therefore, market uptake will depend primarily on physicians' willingness to prescribe biosimilars specifically, which in turn will depend on their trust in biosimilar products and the companies selling them. Despite the importance of physician acceptance, no deliberate efforts have been taken by Canada's public sector to educate physicians regarding the scientific basis for approving biosimilars or their potential role in controlling drug spending.

Despite the myriad challenges, Canada will soon develop a more formalised and sophisticated regime for the review, approval and market uptake of biosimilar medicines. An influx of biosimilar submissions is anticipated over the next two to three years. Challenges of adapting the existing regime to biosimilars will become better understood, and regulatory reform to facilitate biosimilar success will likely follow. Companies exhibiting patience and persistence with their Canadian biosimilar investments are sure to benefit. *iam*

OSLER Osler, Hoskin & Harcourt LLP

Osler, Hoskin & Harcourt LLP
Suite 1900, 340 Albert Street
Ottawa ON K1R 7Y6
Canada
Tel +1 613 235 7234
Fax +1 613 235 2867
Web www.osler.com