

Maximising potential

Smart & Biggar/Fetherstonhaugh's **Daphne Lainson** explains how to exploit patent protection for biologics

The global biosimilars market is expected to reach almost \$20bn by 2018, a staggering increase from the estimated market of \$2bn in 2012.¹ This sea change is likely to have a marked influence on patenting strategies for biologic drugs.

Biosimilars v generic pharmaceuticals

A biologic drug is usually produced by or extracted from a biological source, unlike most pharmaceuticals, which are chemically synthesised.

Generic pharmaceuticals are typically approved based upon an abbreviated drug submission, which relies upon a previous approval of a reference pharmaceutical product, to satisfy health authorities that the generic drug is as safe and effective as the reference product. No clinical testing is required, only comparative laboratory studies need be performed, because the drugs are effectively the same.

Biosimilars are not the same drug as the reference product. Differences in biological source material and methods of manufacturing invariably provide a biologic drug that is only similar but not identical to the previously approved biologic reference product. For biosimilars, there is therefore a general consensus that some clinical testing is required to show that the biosimilar is sufficiently similar to the reference biologic, to permit approval based on a reduced regulatory data package.

Europe has been a leader in biosimilar approvals, establishing its first directive in 2003, and the European Medicines Agency

has authorised 12 biosimilar products. Other countries, such as Canada and the US, have only more recently developed a regulatory framework for biosimilar approval.

The patenting landscape

Top filing countries for many pharmaceutical and biologic patentees remain the US, Europe, Japan and Canada, which have very different patenting landscapes for biologics (see below, left, table).

Patent linkage permits patentees and generic or biosimilar manufacturers to address issues of patent infringement and validity before the follow-on product enters the market, and it is patent linkage (coupled with the other factors) that may drive patenting strategies for biologic drugs.

Patent linkage overview

Canada

A publicly available Patent Register is maintained by Health Canada under the 'Patented Medicines (Notice of Compliance) Regulations' (PMNOC Regulations). The Register identifies those patents that a "subsequent entry biologic" (SEB) sponsor will need to address (eg, alleging non-infringement or invalidity), in order to obtain marketing approval pre-patent expiry.

There are a number of factors within the framework of the PMNOC Regulations that may drive patenting strategies:

1. **Listing on the Patent Register.** A patent must have a Canadian (Patent Cooperation Treaty) filing date that precedes the filing date of the related regulatory submission to be listable. This will drive when patent

applications are filed in Canada. In addition, a patent list must be submitted to Health Canada with the related regulatory submission, or within 30 days of grant, if patents have not granted at the time the submission is filed.

2. **Eligible patents.** A patent must claim the medicinal ingredient (eg, a biologic for use in humans), formulation, dosage form or use of the medicinal ingredient, which has been approved through issuance of a Notice of Compliance (NOC). Claims should therefore be pursued during patent prosecution that will meet this matching requirement. Patents claiming only non-approved variations of medicinal ingredients, and non-approved uses, formulations or dosage forms are not eligible for listing. Since the SEB is not identical to the reference biologic and an SEB sponsor may seek new indications that have not been approved for the reference biologic,⁸ patents that are relevant to the SEB might not be listed on the Patent Register. In addition, patents claiming only a process of manufacture are not eligible for listing, which may be key to protecting the biologic drug.
3. **Licensed patents.** Patents can be listed if they are owned, or exclusively licensed, by the reference product sponsor, or have the patentee's consent to list (eg, a non-exclusive licensee). A patent that is licensed after the listing deadlines noted above cannot be listed.
4. **Patents to be addressed.** A SEB sponsor only needs to address those patents that are listed at the time the SEB submission is filed. Patents therefore need to be granted before the earliest expected date that a SEB submission can be filed, which will be following grant of the NOC to the reference product sponsor, or within six-years of NOC grant if data protection provisions apply.
5. **Other litigation.** Litigation under the PMNOC Regulations only decides whether an SEB sponsor's allegations are justified or unjustified. If an SEB enters the market, the

Country/region	Patent linkage legislation	Patent term extension/restoration	Data protection for biologics	Drug pricing: patented medicines
US	✓	✓	✓ (4/4.5, 12/2.5) * ³	✗
Europe	✗	✓	✓ (8 + 2 + 1) * ⁴	✗
Canada	✓	✗	✓ (6 + 2/2.5) * ⁵	✓ * ²
Japan* ⁶	✗	✓	✓ (8) * ⁷	✗

same patents asserted under the PMNOC Regulations can therefore be asserted again by the patentee or its licensee in an infringement action, together with any other patents that were not eligible for listing. In addition, the manufacturer of a subsequent entry product could file a stand-alone new drug submission and avoid triggering the PMNOC Regulations and data protection provisions, and the patentee or licensee would then need to seek relief in an infringement action. It is therefore important to build a patent portfolio that will not only be useful in litigation under the PMNOC Regulations, but that also includes patent properties that could be asserted outside of the Regulations.

Canada has approved one SEB, Sandoz's Omnitrope (somatropin), and the first SEB litigation under the PMNOC Regulations was commenced in May 2012, with Teva seeking approval for filgrastim based on Amgen's Neuopogen approval. Both biosimilar products have already been approved in Europe and in the US.

The US

The 'Biologics Price Competition and Innovation Act' of 2009 (BPCIA), establishes the framework for approval of biosimilars, and a process for patent litigation prior to biosimilar marketing approval. No biosimilar has yet been approved under the BPCIA.

The US framework under the BPCIA is very different from Canada's framework under the PMNOC Regulations, which is far more in line with ANDA litigation under the 'Hatch-Waxman Act'. Some key differences include:

1. **No public register.** Instead, a biosimilar applicant must notify the manufacturer of the reference biologic of its biosimilar application, and provide a confidential disclosure of information. This disclosure forms the basis for identifying patents that might be infringed by the biosimilar.
2. **Eligible patents.** There are no limits on the types of patents that can be asserted under the BPCIA.
3. **Licensed patents.** The patents to be asserted under the BPCIA are either owned or exclusively licensed to the reference biologic sponsor.
4. **Patents to be addressed.** This will depend upon the round of litigation – (a) immediate infringement litigation following the filing of a biosimilar application will be based on an agreed upon list of patents that may be infringed by the biosimilar; and (b) a reference product sponsor may seek a preliminary injunction following receipt of the at least 180 days advance notice of commercial marketing by the

biosimilar applicant. This later litigation will be based upon any patents identified by the reference product sponsor and that were not on the agreed upon list, as well as any later granted or licensed patents that were identified within 30 days of acquisition of the right. The initial list needs to be complete, and any updates to the list timely made, to ensure the patents can be litigated. From a prosecution stand-point, there must therefore be coordination between patent grant and the expected date of a biosimilar application under the BPCIA.

5. **Other litigation.** There are transitional provisions under the BPCIA that may permit a subsequent entry manufacturer to file biologic licence applications under the 'Food, Drug and Cosmetics Act' for certain products, and a subsequent entry manufacturer may avoid triggering litigation under the BPCIA and data protection terms by submitting a stand-alone submission. Litigation relating to biosimilar products may therefore occur outside of the framework of the BPCIA.

Other factors in the patent landscape

Appropriate patent drafting and prosecution strategies may differ in order to address country-specific issues. For instance, evolving law on what is patent-eligible subject matter may drive patenting strategies, particularly in the US.⁹ The ability of innovators to protect diagnostics in particular, and develop a comprehensive personalised medicines patent portfolio, may be restricted in the US, which could impact on biosimilar market entry.

The fact of price control over patented medicines in Canada should be considered within the context of the patent portfolio as a whole.

Unlike in the US where a biosimilar may be entitled to its own data protection term, a SEB in Canada is not so entitled.¹⁰ This, coupled with the relatively simple framework for litigation under the PMNOC Regulations, and shorter data protection terms for innovative biologics, may result in biosimilar litigation in Canada far ahead of any related US litigation.

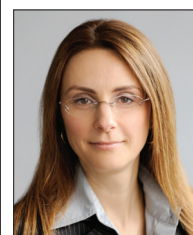
Patenting strategies

For the US, Canada and elsewhere, a robust patent portfolio for litigation under linkage schemes and outside of linkage schemes is critical for protecting the market for a biologic product. However, decisions regarding patenting strategies, including claims to be pursued and the timing of patent grant, may be materially different as between these jurisdictions. Regional distinctions must be kept in mind when developing a global strategy.

Footnotes

1. *Research and Markets*, 15 March 2013 news release for its report "Global Biosimilars Market - Products, Applications and Regulations".
2. The price of patented medicines is governed by the Patented Medicine Prices Review Board.
3. A biosimilar application cannot be filed for four years and the biosimilar cannot be approved for a total of 12 years after the date on which the protected reference product is approved. Each term can be extended by six months if the paediatric extension applies.
4. A biosimilar application cannot be filed for eight years from approval of the protected reference product, and the biosimilar cannot be approved for a further two years. The term can be extended by one year if further indications are approved.
5. A subsequent entry biologic (SEB) submission cannot be filed for six years from approval of the protected reference biologic, and the SEB cannot be approved for a further two years, which can be extended by a six months if the paediatric extension applies. These terms may be increased if the Comprehensive Economic and Trade Agreement (CETA) negotiations between Canada and the EU are successful. CETA could also result in Canada adopting patent term restoration.
6. In general, generic or biosimilar products will not be approved in Japan if there is a patented reference product.
7. The data protection term is eight years.
8. See Health Canada's "Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)", 5 March 2010.
9. *Mayo Collaborative Services v Prometheus Laboratories, Inc.*, 10-1150 (SCt 20 Mar 2012); *Association for Molecular Pathology v Myriad Genetics* 12-398 (S Ct 13 June 2013).
10. Guidance Document: Data Protection under C080041 of the Food and Drug Regulations, 11 October 2011.

Author



Daphne Lainson is a partner in the Ottawa office of Smart & Biggar/Fetherstonhaugh. She specialises in securing patent protection for chemical, pharmaceutical and biotechnology related inventions. With over a decade of experience, she is sought after to provide advice and guidance to many of the top global innovators.