The Biosimilar Landscape in Canada

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Biologics are drugs which contain an active medicinal ingredient that is derived from living organisms or their cells. They are generally larger and more complex than chemically produced small molecule pharmaceuticals. Biosimilars are approved by the short-cut of showing to regulators they are sufficiently similar to a biologic reference drug that is already approved for sale. The biosimilar manufacturer may have to wait out a data exclusivity period. There may also be patent litigation through conventional patent infringement litigation, or through the specialized *Patented Medicines Notice of Compliance Regulations* (PMNOC) that allow patentees to try to block biosimilar products from receiving their marketing authorization. In the PMNOC process, if there are patents listed at Health Canada, biosimilar manufacturers may enter the market only after patent expiry, or after justifying their allegations of invalidity or non-infringement of the reference drug patents.

Monoclonal Antibodies

Monoclonal antibodies are a class of biologics used to treat autoimmune diseases, inflammation and cancers. A number of monoclonal antibody biologic reference drugs, and biosimilars, have been approved for marketing in Canada. There has been much litigation over the entry of certain biosimilars into the Canadian marketplace.

Litigation involving approved biosimilars

Infliximab

Infiximab is a biologic drug used in the treatment of autoimmune diseases including Crohn's disease and psoriasis, as well as inflammation caused by ulcerative colitis and arthritis. Janssen's Remicade was the first infliximab drug approved for marketing in Canada in 2001. Remicade was the reference drug for the development and subsequent approval of three infliximab biosimilars: Remsima (Celltrion), Inflectra (Hospira/Pfizer) and Renflexis (Samsung Bioepis/Merck).

Inflectra and Remicade were the subject of a recent impeachment/infringement patent proceeding.[1] Hospira challenged that the Remicade patent[2] was invalid. Janssen/Kennedy Trust counterclaimed that Hospira's biosimilar, Inflectra, infringed the patent. The Federal Court determined that the patent was valid[3] and infringed.[4] The Court further found that, in addition to direct infringement, Hospira induced infringement of the Remicade patent because its product monograph for Inflectra amounted to instructions for infringement.[5] Pending Hospira's right to appeal, this decision closes the door to future sales of that version of Inflectra in Canada until expiry of the Remicade patent.

Adalimumab

Adalimumab is a monoclonal antibody used to treat arthritis and autoimmune diseases. Abbvie Corp's Humira was the first adalimumab biologic approved for marketing in Canada and the United States. In 2018, Samsung Bioepis' biosimilar Hadlima was granted approval in Canada. It appeared that Abbvie and Samsung were gearing up for a patent lawsuit with Abbvie filing 6 PMNOC applications to deny approval to market Hadlima[6] and Samsung commencing an action to impeach the Humira patent in response.[7] These proceedings have all been discontinued as of 2018. The terms of any settlement are unknown and Hadlima has yet to be marketed in Canada.

Bevacizumab

Hoffman-La Roche's Avastin was the first Bevacizumab biologic approved for marketing in Canada and the United States to

treat a number of cancers as well as eye disease. Recently, Amgen's biosimilar MVASI was granted approval in Canada. A series of patent proceedings have begun over the Bevacizumab biologics. Hoffman/Genentech brought a PMNOC prohibition application against MVASI.[8] Pfizer has also brought an action against Hoffman to invalidate the Avastin patent and obtain a declaration of non-infringement.[9]

Litigation involving biosimilars pending approval

Rituximab

Rituximab is used in the treatment of certain cancers and autoimmune diseases. Hoffman-La Roche's Rituxan was the first rituximab biologic to gain approval in Canada. Celltrion has applied for approval of its rituximab biosimilar (marketed as "Truxima" in Europe) citing Rituxan as the reference drug. In response, Hoffman launched four PNMOC applications seeking to prohibit Celltrion's biosimilar.[10] Hearings for those applications are scheduled for June 2019.

Trastuzumab

Trastuzumab is a treatment for breast cancer. Herceptin manufactured by Hoffman/Genentech is the only trastuzumab biologic approved in Canada. Amgen's biosimilar ABP 980, citing Herceptin as the reference drug, is pending approval. ABP 980 has been endorsed for approval in Europe, but was at least initially denied approval in the United States.

Hoffman/Genentech, appear determined to maintain their monopoly over trastuzumab biologics in Canada and have initiated a number of infringement proceedings against the proposed trastuzumab biosimilars of Amgen[11], Celltrion[12] and Pfizer[13]. Pfizer has countered with impeachment actions to invalidate certain patents for Herceptin.[14]

Summary Chart

Medicinal ingredient	Reference Drug / manufacturer	Biosimilar / manufacturer	Canada marketing approval	Foreign Approval
Infliximab	Remicade / Janssen	Remsima / Celltrion	2014	EU, 2013 US, 2016
		Inflectra / Hospira	2014	EU, 2013 US, 2016
		Renflexis / Samsung Bioepis	2017	US, 2017 EU, 2016 ("Flixabi")
Adalimumab	Humira / Abbvie	Hadlima / Samsung Bioepis	2018	EU – NA US – NA
Bevacizumab	Avastin / Hoffman-La Roche	MVASI / Amgen	2018	EU, 2018 US, 2017
Rituximab	Rituxan / Hoffman-La Roche	Proposed biosimilar / Celltrion	Pending	EU, 2017 ("Truxima") US – pending

Trastuzumab	Herceptin / Hoffman-La Roche	Proposed biosimilar (ABP 980) / Amgen	Pending	EU, 2018 US – denied

Protein/Peptide Drugs

Filgrastim/Pegfilgrastim

Filgrastim/Pegfilgrastim is a recombinant glycoprotein used as a treatment for low white blood cell count. Amgen's Neupogen was the first filgrastim biologic approved for sale in Canada, and was the reference drug for Apotex's biosimilar Grastofil which was subsequently approved. Neulasta developed by Amgen is a pegfilgrastim biologic, and was the reference drug for Apotex's Lapelga.

Amgen and Apotex are currently engaged in a patent dance over their competing filgrastim and pegfilgrastim products. Amgen brought a PMNOC application to block the marketing of Apotex's biosimilars[15] and separately brought an action for patent infringement[16]. The Federal Court dismissed Amgen's application to block Apotex's Grastofil biosimilar, and further found that the allegation of invalidity for obviousness appeared justified.[17] In turn, Apotex sued Amgen for damages claiming unjust enrichment under PMNOC section 8[18]

Somatropin

Somatropin (human growth hormone) is used as a treatment for growth deficiencies. Pfizer's Genotropin, a recombinant form of somatropin, was the first biologic approved in Canada. In 2009, Omnitrope manufactured by Sandoz became the first biosimilar approved in Canada. Genotropin and Omnitrope are both marketed in Canada.

Insulin glargine

Insulin glargine is an insulin analog for treatment of diabetes. Sanofi's Lantus was the first insulin biologic approved in Canada. Since then, Eli Lilly's Basaglar has been approved as a biosimilar. Lantus and Basaglar are both marketed in Canada.

Etanercept

Etanercept is a fusion protein used to treat arthritis and autoimmune diseases. The first etanercept biologic approved for marketing in Canada was Amgen's Enbrel. Subsequently, two biosimilars citing Enbrel as the reference drug were approved: Brenzys (Samsung Bioepis) and Erelzi (Sandoz). Brenzys and Erelzi entered the market after expiry of the first Enbrel patent.

Summary Chart

Medicinal ingredient	Reference Drug / manufacturer	Biosimilar / manufacturer	Canada marketing approval	Foreign Approval
Somatropin (HGH)	Genotropin / Pfizer	Omnitrope / Sandoz	2009	US, 2006 EU, 2006
Insulin glargine	Lantus / Sanofi-Aventis	Basaglar / Eli Lilly	2015	EU, 2014 US, 2015
Filgrastim	Neupogen / Amgen	Grastofil / Apotex	2015	EU, 2013 US - NA

Pegfilgrastim	Neulasta / Amgen	Lapelga / Apotex	2018	EU – NA US – NA
Etanercept	Enbrel / Amgen	Brenzys / Samsung Bioepis	2016	EU, 2016 ("Benepali") US – NA
		Erelzi / Sandoz	2017	EU, 2017 US, 2016

Conclusion

The trend in recent years is that biosimilars are gaining approval at a faster rate; pre-2017, six biosimilars were approved, compared to five biosimilars approved post-2017. It should be noted with caution however, that marketing approval does not shield biosimilar manufacturers from potential liability for patent infringement of the reference drug. While there have been few decisions on the merits involving biosimilars, the patent dances between manufactures of reference drugs and biosimilars shows no sign of abating. As such, manufacturers of biosimilars must weigh the benefits of obtaining approval for early entry into the marketplace against the potential losses if patent litigation ensues.

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[1] *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2018 FC 259

[2] CA2261630

[3] Supra note 1 at para 265.

[4] *Ibid* at paras 319-323.

[5] *Ibid* at paras 326-335.

[6] Federal Court Files T-598-17, T-599-17, T-600-17, T-601-17, T-602-17, T-603-17, T-604-17, T-605-17.

[7] Federal Court File T 1355-17.

[8] Federal Court File T-1678-17.

[9] Federal Court File T-1471-17.

[10] Federal Court Files T-1486-17, T-1487-17, T-1488-17, T-1489-17.

[11] Federal Court File T-1921-17.

[12] Federal Court Files T-1969-17, T-1970-17, T-1971-17.

[13] Federal Court Files T-401-18, T-402-18.

[14] Federal Court Files T-876-17, T-1239-17, T-869-17, T-1269-17, T-1270-17.

[15] Federal Court files T-2072-12, T-1710-15.

[16] Federal Court file T-633-16.

[17] *Amgen Canada v Apotex Inc*, 2015 FC 1261, aff'd 2015 FCA 196.

[18] Federal Court file T-934-16.

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