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The Barriers to Marketing and Selling Biosimilar Drugs in Canada

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Below we provide a general summary of the barriers, such as patents and regulatory requirements, to marketing and selling biosimilar drugs in Canada.

Biologics and Biosimilars

A biologic drug is based upon a bioactive compound that is generated by a living organism and then used as a pharmaceutical. In contrast to the more traditional small molecule drugs that are produced by chemical reactions, a biologic drug often includes a large molecule, bioactive-compound that is produced by complex processes in animals or microorganisms. A biosimilar drug is a biologic drug that is similar to but not equivalent to a prior biologic drug that has already received regulatory approval for use in humans. The prior biologic drug is often called a reference biologic. A biosimilar drug is often compared with the concept of a generic version of a brand-name small molecule drug. However, as discussed below, different regulatory regimes apply for biosimilar drugs and generic drugs.

Part of the burgeoning interest in biosimilar drugs is that the patents for many reference biologics are expiring and this may reduce some of the barriers to other parties bringing related biosimilar-drugs into the market.

Patents

A patent typically provides the owner a 20-year monopoly to make, use, and sell an invention. This monopoly is enforceable by the owner through the courts. In exchange for this monopoly, the patent document must sufficiently disclose the invention so that a person skilled in the art can practice the invention.

There have been many biologic drug patents issued in Canada and some for biologic drugs that have generated very high revenues for the owners. These patents typically provide protection for the biologic compound itself, pharmaceutical compositions that include the biologic compound, and for methods to make the biologic compound. However, many of these biologic patents have reached or are

approaching the end of the 20-year patent term. The implication of which is that there is expected to be an increase in the introduction of new biosimilar drugs into the market in the future. The producers of biosimliar drugs can often sell their products at a discount to the innovator's biologic drug and make substantial profits. At least one reason for this discounting is that the biosimilar drug producer has the benefit of the teaching of the expired, or soon to be expired, biologic drug patent. This teaching likely allows the biosimilar drug producer to produce a biosimilar drug while reducing or avoiding the costly research and development that the innovator owners of the biologic drug patents were forced to incur.

Another potential implication of the end of the biologic-patent monopolies is that patent filings for improvements on biologic drug patents may increase. One reason for this potential increase is that improvement patents can be filed by any entity that has developed an improvement that is new and not obvious over an underlying technology. It should be noted that an improvement patent does not provide any rights in the underlying technology. However, if the patent for the underlying technology is expired, then this may open the door for a biologic producer to acquire an improvement patent and with it a competitive advantage without infringing an underlying patent.

With or without patent protection, the producer of any new biosimilar drug must satisfy specific regulatory requirements before any biosimilar drug can be marketed or sold for use in humans in Canada.

Regulatory Requirements

Biologic drugs must obtain a Notice of Compliance (NOC) from Health Canada after meeting the requirements of the Canadian *Food and Drugs Act* and the associated regulations.[1] Biosimilar drugs are regulated by Health Canada's Biologics and Genetic Therapies Directorate, which is the same entity that regulates biologic drugs. A biosimilar drug can receive regulatory approval if it can be demonstrated that the biosimilar drug is similar to an earlier approved, reference biologic. Health Canada has published a guidance document entitled *Information and Submission Requirements for Biosimilar Biologic Drugs* and the latest version was published in November 14, 2016.[2] Briefly, like the reference biologic, a New Drug Submission (NDS) must be submitted to Health Canada for the new biosimilar drug to receive regulatory approval in the form of an NOC. Note, a biosimilar must establish similarity with a reference biologic that has already received a NOC and not another biosimilar drug.

The NDS for a biosimilar drug must provide sufficient information to allow Health Canada to determine that the characteristics of the biosimilar drug are so similar to the reference biologic that any differences between the characteristics of the two drugs should have no detrimental impact on the safety or efficacy of the biosimilar drug. Furthermore, the characteristics of the two drugs must also be so similar that the reference drug data, both clinical and non-clinical, is relevant to the biosimilar drug.

The nature and amount of information that is required in order to allow Health Canada to make this determination of similarity is assessed on a case-by-case basis. Some of the types of required information include scientific evidence as to the quality attributes (including physiochemical properties, biological activity, immunological activity and others) of the reference biologic drug and the biosimilar

[1] *Food and Drugs Act*, RSC 195, C F-27.

[2] Available online at: < http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/biosimilars-biosimilaires-eng.php>.

drug and further clinical data (such as pharmacokinetic and pharmacodynamics data) and non-clinical data (such as *in vivo* studies). Should Health Canada determine that the biosimilar drug is highly similar to a suitable reference biologic drug, then a Notice of Compliance may be granted.

In addition to obtaining regulatory approval from Health Canada, biosimilar drugs are subject to other statutes or regulations that significantly affect how these types of drugs get to market in Canada. One example of such regulations is the *Food and Drug Regulations* that provides data protection measures for "innovative drugs".[3]

Data Protection Measures in Canada

If a reference biologic drug falls within definition of an "innovative drug", then the producer of the biosimilar drug cannot submit an NDS to Health Canada until six years after the date of the first NOC for the innovative drug. An innovative drug is a drug that contains a medicinal ingredient that has not previously been approved by Health Canada and that is not a variation of a previously approved medicinal ingredient.

The data protection measures prevent the filing of an NDS for any drug that includes a reference to the secret data of an innovative drug for a period of eight years after the date of the first Notice of Compliance for the innovative drug. The secret data is provided as part of the innovative drug's regulatory submissions. An additional six-month exclusivity period may be provided if the originator of the innovative drug conducts appropriate pediatric trials on the innovative drug.

In the result, the regulatory data-protection measures can pose a significant time barrier upon the producer of a biosimilar drug. As discussed above, the regulatory approval for a biosimilar drug is based upon establishing similarity between the reference drug and the biosimilar drug. This is likely a difficult task to accomplish without referring to any data of the reference biologic if the reference biologic meets the definition of an innovative drug.

Even after receiving an NOC, a biosimilar drug must be placed on a provincial or federal formulary in order to be purchased in Canada.

Market Access Issues

In Canada, provincial and federal public drug programs can be very large purchasers of drugs. The manner in which biosimilar drugs are treated by these public drug programs is different than for generic versions of small molecule brand-name drugs. If a generic small molecule drug receives a NOC, then Health Canada can issue a declaration of equivalence. The declaration of equivalence means that Health Canada has determined that the generic drug is a bioequivalent to the brand name reference drug. This declaration of equivalence is important because provincial laws can allow for the substitution of a generic product in place of a prescription written for a brand-name product.

Biosimilar drugs, on the other hand, are approved on the basis of similarity with a reference biologic-drug, not bioequivalence. As such, Health Canada will not issue a declaration of equivalence.

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[3] *Food and Drug Regulations*, CRC, C. 870.

This means that a biosimilar drug cannot be substituted when a prescription is written for the reference biologic-drug. As such, in spite of likely being able to offer a cheaper drug to the public formularies, the producer of a biosimilar drug may still face barriers to bring a new biosimilar drug to market in Canada.

Conclusion

Some of the barriers to entry of new participants in the biosimilar drug market will continue to decrease while the opportunity for acquiring new patent protection may be increasing. However, obtaining regulatory approval to market a biosimilar drug involves negotiating various sets of regulations and guidance documents. Consultation with knowledgeable regulatory or legal professionals is crucial for companies seeking to provide a biosimilar drug in Canada.

*This article provides information only and does not provide any legal advice.