Subsequent Entry Biologics in Canada: Competition vs. Exclusivities

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Introduction

Canada has approved the subsequent entry biologic (SEB), Omnitrope (somatropin), following in the footsteps of the U.S. and European approvals. More Canadian approvals are expected because many well known biologics are facing patent expiry in the coming years.

This short article will provide an overview of biologics, highlight the ongoing developments in the approval pathway of SEB's, and explain the patent and regulatory exclusivities available to innovator biologic manufacturers.

Subsequent Entry Biologics: How are they different from generics?

In recent times, the term biologic has been used to define a new class of protein-based therapeutics that are produced using living organisms, including plants, animals and microorganism such as yeast and bacteria. Compared to conventional small molecule drugs such as Aspirin, biologics are a newer class of protein-based pharmaceuticals that are significantly larger, inherently more complex, heterogeneous and thus much more difficult to characterize. It comes as no surprise then that the manufacturing of these glycoprotein molecules such as monoclonal antibodies (mAbs) is intricate in nature. The most common manufacturing process can be summarized in 7 carefully controlled stages: host cell development, master cell bank establishment, protein productions, purification, analysis, formulation and storage and handling. It has been demonstrated that even slight alterations in any stage can lead to significant changes in protein structure and lead to clinically relevant implications for safety, immunogenicity and potency. Governmental regulatory bodies agree that the current approval process of generic versions of small molecular drugs are not suitable for SEB approval and have taken steps to develop a separate pathway for SEBs to safeguard patent safety. To aid in decision-making regarding SEB submissions, on March 5th 2010 Health Canada published its finalized guidance document titled "Information and Submissions Requirements for Subsequent Entry Biologics and related documents". The Omnitrope SEB was approved in Canada on April 22, 2009.

Regulatory approval: Ongoing developments and controversies

Generic drugs receive marketing approval under the abbreviated new drug submission (ANDS) pathway. Through this pathway the generic manufacture need only demonstrate pharmaceutical equivalence and bioequivalence between the generic and innovator products. Since generic drugs are considered therapeutically equivalent to the reference product they are often substituted for economic reasons. This differs with SEB's. Health Canada emphasizes that SEBs are not generic biologics, and the authorization of a SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug. To this end, the SEB manufacture needs to invest in additional clinical trials as a part of the submission. According to the recently published guidance document, the SEB manufacturer is required to provide a reduced nonclinical and clinical package including comparability data (analytical comparison with reference product) and stringent post-marketing pharmacovigilance plans demonstrating similar safety and efficacy in larger populations.

On a global scale, Health Canada and the Food and Drug Administration (FDA) are moving in the right direction with ongoing developments that will provide more certainty in the legal and regulatory framework for SEBs. The European Medicines Agency (EMEA) a leader in biosimilar regulation. In 2005, the EMEA released its first guidelines on similar biological medicinal products (in Europe referred to as biosimilars) and since then the agency has granted marketing approval for more than 12 different biosimilars competing with 4 innovator biologics: somatropin (Genotropin, Humatrope), epoetin (Eprex) and filgrastim (Neupogen).

Biologic Patents

A biologic that meets Health Canada's safety and efficacy standards is eligible to receive a marketing authorization called an NOC. Canada created specialized rules to proactively prevent patent infringement during the Health Canada approval process. This unique system, informally called the NOC Regulations, requires biosimilar companies to establish patent freedom-to-operate as a

precondition to issuance of the NOC. This is in sharp contrast to conventional patent enforcement that begins only after issuance of an NOC.

Under the NOC Regulations, the pioneering company that first develops a biologic drug has the opportunity to list its relevant patents on the Health Canada Patent Register. The patents may cover the biologic compound, formulations, dosage forms or uses. There are strict time limits for listing patents and the patents must be directly pertinent to the approved Canadian product. If a biosimilar company files a drug submission that references the pioneer's data, the biosimilar company must also address freedom to operate with respect to patents on the Health Canada Patent Register. The biosimilar company must ultimately justify that all the patents are invalid, non-infringed or expired. If this is not done, then the biosimilar will not receive an NOC until the patents expire.

If the patent owner and biosimilar manufacturer disagree about freedom to operate, a court case known as an NOC Proceeding will assess evidence about patent infringement and validity. The court will then decide whether to prohibit Health Canada from issuing the biosimilar a NOC because of the risk of patent infringement. No NOC can be issued while the court is considering the issues, which can take up to 24 months. If the biosimilar company wins, it gets its marketing authorization. If the biosimilar company loses, it has to wait until patent expiry to get its NOC. The biosimilar litigation landscape is complex because a conventional patent infringement or invalidity lawsuit may be initiated concurrently with, or after, a NOC Proceeding.

The NOC Regulations have been extensively litigated in the context of conventional, small molecule pharmaceuticals. No NOC Proceeding has been completed for a biosimilar yet. However, the NOC Regulations will be an important biosimilar patent protection tool once biosimilar development increases.

Europe does not have patent regulations linked as a precondition to a marketing authorization. Biosimilar manufacturers can get their marketing approval without addressing patents. In the US, a complex patent clearance system has been implemented as a precondition to biosimilar approval. The biosimilar manufacturer must disclose its regulatory submission to the reference product sponsor. The reference product sponsor then provides a list of patents it believes could be infringed. There are opportunities during the process for settlement negotiations and a patent infringement lawsuit.

Regulatory Exclusivities

Canada, the US and Europe all have data exclusivity. During the exclusivity period, the pioneer biologic data cannot be relied on by a biosimilar company seeking approval of its own drug. In Canada, innovative biologic drugs may be eligible to receive an 8 year period of data exclusivity. Slightly modified versions of previously-approved biologics will not be eligible. An additional six months of data exclusivity is available for biologics that have been the subject of pediatric studies. The intent is to allow the brand name company a period of exclusivity to recoup its R&D investments in the biologic. A biosimilar manufacturer cannot even have Health Canada review its drug submission during the first six years of the data exclusivity period.

Conclusions

SEBs are undoubtedly here to stay. Health Canada has created guidance documents to facilitate approval of SEBs, which will increase competition in the biologic marketplace. The extent to which a SEB will be allowed to rely on the pioneer biologic data will vary considerably depending on the nature of the product. Awareness of patent and regulatory exclusivity strategy will become increasingly important for both pioneer companies and SEB manufacturers. Lastly, it is important to ensure that all stakeholders are educated to make well-informed decisions with the goal of patient safety as the top priority.

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