The first subsequent entry biologic authorized for market in Canada: The story of Omnitrope, a recombinant human growth hormone

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Abstract

Omnitrope is the first Subsequent Entry Biologic (SEB)/Similar Biotherapeutic Product (SBP) filed with Health Canada, for purposes of marketing. Health Canada is the home organization of the Regulatory Authority in Canada. As the first SEB to be filed for actual review, it presented unique challenges. While the principles for the review and approval of a SEB were laid out in a “fact sheet” there remained still a guidance to be drafted. The review of the submissions proceeded in parallel with the development of the guideline. This article will provide the details of how the final decision was arrived at and how that decision validated the principles underlying the guidance document, in the absence of direct regulations specifically addressing SEBs in Canada.

1. Introduction

With the expiry of patents for biologic therapeutic products that are expensive, there is an increased demand, on the part of health care systems and the public, for more affordable medicines. Canada is no exception to the need for developing and marketing more affordable products. As a result, Health Canada (HC) started to receive enquiries about the possibility of filing Subsequent Entry Biologic products (called SEBs in Canada), also called SBP (according to the WHO nomenclature), biosimilars or follow-on protein products. The variety of names is due to the fact that the nomenclature is region and jurisdiction-specific at this time, but the challenges faced by regulators are similar, if not virtually identical, in all jurisdictions. In developing an overall guideline that applies to SEBs-SBPs principles, which were already in existence at the time of drafting of a “fact sheet”, were further developed in the guidance document. At the same time, the submission of an SEB application served to illustrate and validate the principles that Health Canada had intended to follow.

The principles utilized in the development of the guidelines are partly based on current regulations and partly based on the science underlying the development of biologic therapeutic products. These principles exist within the regulatory frameworks for biologics, pharmaceuticals and generic pharmaceuticals drugs. SEBs are considered to be “New Drugs” in Canada. As with any other product, the onus is on the sponsor to provide the necessary evidence to support all aspects of an application for market authorization. Furthermore, the approach applies only to those SEBs that can be considered to be well-characterized biologics, such as human growth hormone, erythropoietins, granulocyte colony stimulating factor (G-CSF) etc.

Part C, Division 8 of the Food and Drugs Regulations, define the requirements for New Drug Submissions. The regulations do not define precisely what information ought to be contained in the submission, only that substantial evidence of safety and efficacy is required. This allows flexibility for the regulator to adapt the requirements, to the needed circumstance and situation, based on reasonable science. For the specific case of SEBS/SBPs, this means that a reduced data package, consisting of information on the quality and comparability of the product to a suitable Reference Biologic Product (RBP) could be defined, based on the extent of the knowledge on the RBP chosen. The Directions for Use, the Product Monograph in Canada, for the SEB/SBP would have to describe the basis on which the market authorization had been granted.

Other provisions considered included the following: SEBs will be authorized based only on a submission that makes a direct comparison to an innovator product, previously authorized for sale in Canada. All the laws, patents and intellectual property principles outlined in the applicable regulations apply. The applicable regulations include, in addition to the Food and Drug Regulations as noted above, Data Protection provision and Patented Medicine Regulations. These provisions contain a prohibition to the use of an innovator product as a comparator for 8 years after market authorization has been given to the innovator drug. In addition, no submission can be filed for 6 years following market approval that compares a product, directly or indirectly, to the innovative drug.
Once an SEB is authorized for sale, it is considered to be a stand-alone product and is subject to the same life-cycle approach to regulations, as all other products. Authorization of an SEB is not considered a declaration of pharmaceutical and/or therapeutic equivalence. The SEB will not automatically be granted all of the indications of the comparator.

In conducting the review of the first SEB, the following elements were considered in decision-making [1]:

- Acceptability of the reference product and bio-similarity.
- Clinical data package and indications intended to be claimed.
- Endpoints and analysis of outcomes.
- Product Monograph/Package Insert/Labelling.
- Interchangeability? Substitutability?

Other matters that required consideration were:

- the fears of the innovator industry: their concerns were deferred initially, but allayed during consultations that took place during both the drafting and the completion of the guidance document, and
- the concerns expressed by the health care system, as these products and the approach taken to their review and market authorization were new to Canadian Provinces. Ultimately, several of them decided to use the case of the first SEB authorized for market in Canada as a pilot project in their deliberations to add SEBs to Provincial Formularies.

2. Case study

Human Growth Hormone (HGH) is one of the early biologics marketed in Canada. While originally it was extracted from human pituitaries, it soon began to be produced as a recombinant product in E. coli. At the time of submission of SEB application for HGH by Sandoz, 7, or more, different brands of growth hormone were authorized for market (although not all were marketed) and a guideline for SEBs was in the initial phases of its drafting. Therefore, the submission for Omnitrope was used, not only to authorize the first similar biological product, but also to gain the experience needed to validate the concepts and principles behind SEBs.

Omnitrope was filed to be marketed as a powder for solution in the following strengths: 5.8 mg/vial; 5 mg/1.5 mL and 10 mg/1.5 mL and intended for administration by the subcutaneous route. The submission was filed under the current New Drug Submission Regulations for a multiplicity of indications authorized for the entire group of marketed human growth hormones, including those for which the RBP, Genotropin was also authorized:

- For the long-term treatment of children with GH failure; no other causes of short stature
- Long-term replacement of HGH, in adults with GH deficiency who were growth deficient in childhood

Initially, the submission was rejected with a Notice of Deficiency, because it was not reviewable for several reasons. The most prominent reason was that the comparator or the Reference Biologic Product (RBP), Genotropin, had never been marketed in Canada. However, the sponsor re-filed after three months with an acceptable dossier. The number of indications and uses for Omnitrope was still beyond the ones authorized for the comparator. The sponsor was requested to withdraw the indications that were beyond those of those authorized for Genotropin. Following withdrawal of the excess indications, the review proceeded.

The use of an authorized, but never marketed RBP, led to much discussion and controversy. A number of issues needed to be resolved so that any approach that would be ultimately taken in accepting an authorized, but never marketed product, would not result in inconsistencies in the requirements between those for a biological versus those for a pharmaceutical agent, and that unwarranted legal precedents would not be generated. Following internal consultations, it was finally decided that Genotropin would be acceptable as an RBP and that Omnitrope would be reviewed because it was in line with the principles and provisions of the Canadian SEB Guidance document, for the following reasons:

- The use of Genotropin was in line (certainly not contrary) to the principles set out for comparators for SEBs.
- The size of the Canadian market which required that some flexibility be exercised, thus ensuring that an SEB would reach the Canadian market.
- The need to use this first submission as a learning situation, in the absence of safe haven provisions in the regulations, similar to those used in the USA. (Safe haven provisions allow sponsors to file submissions with the regulator who, in turn, would review the file, without penalty to the sponsor or without the need to arrive at a regulatory decision, either positive or negative).
- The package was extensive and was determined to be complete on screening.
- The submission was a solid package and contained complete and solid data on the quality attributes of the proposed product.
- There was a very extensive set of comparability studies between the RBP and Omnitrope that demonstrated similarity between the two products.

2.1. Preclinical information: non-human data

- There were full Pharmacodynamic studies in the submission, carried out in the rat. These studies confirmed (by rat weight-gain bioassay the pharmacodynamic properties of Omnitrope) and by the rat tibia-width assay, the comparability of the potency between Omnitrope and the RBP, Genotropin.
- While pharmacokinetic studies were not conducted, this was considered acceptable at that time, as the need was eventually balanced against the rest of the pre-clinical and clinical information.
- The submission contained a reduced toxicology package: a 14 day toxicity study, no Genotoxicity studies, reproductive or developmental toxicity study. This approach was considered acceptable based on the ICH Guideline S6, applicable to biological drugs.
- Local tolerance to the sc injection was carried out in the rabbit; there were no remarkable differences found between Omnitrope and the RBP chosen. However, based on some local reactions to the injection, rotation of injection sites is being recommended.

2.2. Clinical information: human data

2.2.1. Clinical basis for decision

There were four comparative Pharmacokinetic (PK) and Pharmacodynamic (PD) studies [2]. These demonstrated bioequivalence based on the approach and according to the requirements of the Canadian Bioequivalence Guidelines. The parameters measured in these studies were: ILGD-1 (Same as IGF-1 Insulin-like growth
factor 1 also known as somatomedin C); IGFBP-3 (Insulin-like growth factor-binding protein 3) and NEFA (Non-esterified fatty acids in serum), and were all highly comparable between products and formulations.

2.2.2. Efficacy

- Efficacy was supported by 5 Phase III clinical efficacy and safety studies; these were three sequential studies of Omnitrope versus the RBP, of which three were sequential studies of Omnitrope versus Genotropin involving liquid and powder formulations, twice crossed over. They were designed as open-label parallel studies, with patients being followed for over 15 months for long-term safety and efficacy. These three studies constituted, in reality, a single multiple cross-over trial that enrolled 89 children.
- A fourth trial was carried out with Omnitrope, solution only: 50 children were followed for up to 30 months.
- A fifth trial was carried out with Omnitrope powder dissolved for injection: interim analyses were carried out at 12 and 24 months of HGH therapy.

Of the above, four studies were conducted in Poland and Hungary (and the fifth study was conducted in Spain). Although the Guidelines for SEBs in Canada express a preference for equivalence trials, the same guidelines also allow for some flexibility, if there is adequate evidence for the design and/or if the sponsor justifies the design chosen. Because this was the first SEB submitted to the regulator, and because there was a need to learn by experience as the guideline was being drafted, additional flexibility was exercised in accepting a complex, non-conventional cross-over study as the pivotal trial and that compared Omnitrope to Genotropin as well as various formulations of Omnitrope, to each other (Fig. 1).

In addition to the issues noted above regarding whether the comparator could be used, the nature of the studies noted above, and most notably, due to the standards used for growth assessment which were Tanner or National growth standards, the submission was rejected and ‘A Notice of Deficiency’ issued. When the submission was re-filed, the clinical studies on growth were reanalysed according to CDC (American Centres for Disease Control) standards. In the three sequential studies, the clinical efficacy and safety profiles were found to be comparable between Omnitrope and the RBP, Genotropin, while in the other studies, Omnitrope growth patterns were consistent with results from other studies with HGH, conducted in children.

No trials were conducted in adults with Omnitrope. However, consistent with the principle that the indications for a product could be extrapolated on the basis of mechanistic and pathophysiological considerations, it was considered that the information obtained from the trials in children might be suitable for extrapolation to certain adult populations, in particular to adults with HGH deficiency due to underlying hypothalamic or pituitary disease, especially adults associated with HGH deficiency in childhood.

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**Fig. 1.** Design of the three consecutive Phase III studies EP2-K-99-PhIII/EP2K-00-PhIIIFo/EP2K-00-PhIIIaq [3].
2.2.3. Safety

- Safety considerations were based on the same studies as those carried out for efficacy purposes. The first three sequential studies were only analysed for the first 9 months of treatment. Adverse Events (AEs) seen in clinical trials were of the type and nature of those already known for the RBP and other HGHs.
- The following AEs were reported: injection site reactions, eosinophilia, headaches, increase of HgbA1c (glycosylated haemoglobin used to follow diabetic control status), etc.
- There were interventions for the following AEs: hypothyroidism and headache. Hypothyroidism is commonly seen in children with HGH deficiency, especially if due to pituitary or hypothalamic disease, and is not surprising.
- There were two cases of worsening pre-existing scoliosis, a side effect also seen with other growth hormone products.

2.3. Labelling considerations

As with all new drugs, the labels relating to Omnitrope are specific to the product. The label was considered to be both (class) and product-specific, but without any mention of interchangeability or substitutability. Interchangeability and substitutability are both under provincial jurisdiction in Canada and derive from the authority of the Provinces to deliver health care. The package insert, the Product Monograph in Canada includes specific mention of the studies that formed the basis for the decision to authorize Omnitrope for market.

2.4. Post-market considerations

There were also post-market commitments required and these included safety considerations and longer-term follow-up.

3. Conclusions

Omnitrope was the first SEB application filed in Canada and its contents constituted a good learning experience from the regulatory perspective. All the principles allowing the generation of a well-characterized subsequent entry biological product were considered in the regulatory review and the market authorization of Omnitrope. Information and general knowledge from the literature was leveraged to help decide on the acceptability of the RBP and in shortening the development of the drug. The various iterations in the review, with Notices of Deficiency and questions posed to the sponsor clearly showed the direction that can be taken in authorizing a SEB/SBP. The process also showed the flexibilities of the Canadian regulatory system and allowed for a thorough evaluation of the quality considerations (comparability analysis and determination), that were critical for the final decision.

The entire process underscored how solid science and rational consideration can lead to logical and consistent regulatory outcomes.

Conflict of interest

No potential conflicts of interest to disclose.
There is no confidential information in this article.

References