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Clinical programs in the development of similar biotherapeutic products: Rationale and general principles

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A B S T R A C T

Similar biotherapeutic products (SBPs) or biosimilars are biologics developed by pharmaceutical manufacturers to match originator biologics that have been on the market for a long time and lost their exclusivity (patent and market protection). The recently issued WHO guidelines on evaluation of SBPs provide clear guidance for manufacturers and regulators on how to develop and gain approval for these products.

The present contribution illustrates the rationale for and general principles of the clinical programs used in the development of SBPs, taking the example of the three biosimilar products developed and marketed in Europe by Sandoz, namely growth hormone (Omnitrope®, the first ever EU biosimilar approval), erythropoietin α (Binocrit®), and filgrastim (Zarzio®).

1. Introduction

Following the patent expiries of the first biotechnology-derived therapeutic proteins, off-patent biopharmaceuticals in general are becoming an increasingly attractive target for pharmaceutical companies. In contrast to "standard" small-molecule chemical drugs, biopharmaceuticals are considerably larger and more complex molecules, more difficult to characterize and produced from living organisms. Due to this complexity and to the inherent variability of biologics manufacturing, the generic pathway for regulatory approval cannot be used for these so-called Similar Biotherapeutic Products (SBPs) or biosimilars. In Europe, a regulatory pathway for the approval of biosimilar products has been developed and effectively implemented in recent years. Clear guidance has also been given with regard to the data needed to demonstrate the similar nature of the similar biological medicinal product to the reference product in terms of quality, safety, and efficacy [1–7]. Other countries including Canada, Japan, and the USA have now also adopted abbreviated regulatory pathways for approval of biosimilar products, relying on information in the public domain regarding the off-patent reference biologics (safety, dosing, efficacy, mechanism of action, etc.). In October 2009, the WHO Expert Committee on Biological Standardization issued guidelines on the evaluation of SBPs to promote globally accepted norms and standards for the evaluation of these products by regulatory agencies [8]. In a recent workshop which was jointly held by Korea FDA and WHO in Seoul 2010, first experience on the implementation of these guidelines was reviewed. The present contribution describes the general principles and rationale used in clinical programs for the development of SBPs with special reference to the three biosimilar products developed and marketed in Europe by Sandoz, i.e., growth hormone (Omnitrope®, the first ever biosimilar EU approval), erythropoietin α (Binocrit®), and filgrastim (Zarzio®).

2. General principles of clinical development of similar biotherapeutic products

Prior to proceeding to clinical studies, SBPs will have been extensively characterized in an iterative process to closely match the reference biotherapeutic product (RBP) (Fig. 1). The comparability exercises follow the same principles as those used for establishing comparability of originator biologics after changes in manufacturing. Manufacturers of biologics frequently make changes to the manufacturing processes of their products both during development and after approval [9]. Ample guidance exists regarding comparability exercises both for biotechnology-derived therapeutic proteins and for development of biosimilars [2,9]. Often non-inferiority designs have been used in the clinical comparability studies of originator molecules.

In general, the clinical program for SBP development will consist of studies to demonstrate a comparable pharmacokinetic (PK) and

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pharmacodynamic (PD) profile in a sensitive population. These will often be in healthy volunteers, and are typically in crossover designs, which are useful and highly sensitive designs to detect any differences between the RBP and SBPs [10]. Once PK/PD comparability has been established comparative safety and efficacy studies will follow to ultimately confirm therapeutic similarity. The confirmation of a comparable profile in the PK/PD studies will justify the same posology of SBP and RBP. No additional dose finding studies are needed. Comparative efficacy and safety is best demonstrated in head-to-head studies in a study population that is sufficiently sensitive to detect differences between the products, if such differences exist. In the WHO guidelines, equivalence study designs (requiring lower and upper comparability margins) are preferably recommended for the comparison of efficacy and safety of SBP with RBP. However, non-inferiority designs may also be used to demonstrate clinically relevant comparability. It is not to be expected that the SBP will be inferior or superior to the RBP if physicochemical, biological, non-clinical, and PK/PD comparability has been proven. While the non-inferiority margin is negotiated with the regulatory authority, the basis for the non-inferiority assessment will be the lower 1-sided 95% confidence interval (95% CI) for the difference between treatments, which represents a lower boundary for the difference.

Finally, conclusion of biosimilarity will be provided by the totality of evidence (e.g., quality, non-clinical, and clinical data).

3. Examples of approved biosimilars developed by Sandoz

During the workshop in Seoul 2010, the general principles and rationale for the clinical development programs of SBPs were illustrated by the examples of the development programs for Omnitrope®, Binocrit®, and Zarzio®. The total number of clinical studies and subjects involved in the clinical programs for confirmation of comparability with the reference originator product are summarized in Table 1.

3.1. Recombinant human growth hormone - Omnitrope®

In 2006, Sandoz received the first centralized biosimilar market authorization in the EU for its recombinant human growth hormone (rhGH), Omnitrope® [11]. Omnitrope® (somatropin) is also approved in other countries and regions including the US, Canada, Japan, Australia, Mexico, and Argentina. The reference product was Genotropin®, the recombinant human growth hormone of Pfizer (formerly Pharmacia) originally authorized in Europe in 1988. A similar pharmacokinetic and pharmacodynamic profile of Omnitrope® and Genotropin® was demonstrated in randomized, double-blind, single-dose, crossover PK/PD studies in healthy volunteers. In these studies, endogenous GH secretion was equally suppressed with a 25 h continuous i.v. infusion of octreotide (40 mg/h) starting 1 h before rhGH administration [12,13]. Comparable therapeutic efficacy between Omnitrope® and the reference product Genotropin® was demonstrated in a head-to-head study of rhGH treatment in 89 short children due to growth hormone deficiency [14,15]. Growth hormone treatment will result in a rapid and marked increase of longitudinal growth velocity in GH-deficient children (so-called catch-up growth) [14]. After nine months, the baseline-adjusted difference between Omnitrope® and Genotropin® in mean height velocity (HV) was −0.19 cm/yr (95% confidence interval (CI) [−1.34; 0.95]) and in mean height velocity standard deviation score (HVSDS) was 0.79 (95%CI [−0.56; 2.15]). There were no clinically relevant differences between treatments at any time point, thus showing comparable efficacy across all treatment groups. Clinical comparability in terms of safety and immunogenicity between Omnitrope® and Genotropin® was also confirmed [11,14,15]. Switching rhGH preparations (Genotropin® lyophilizate to Omnitrope® liquid and Omnitrope® lyophilizate to Omnitrope® liquid) was well tolerated and safe. Long-term efficacy and safety of Omnitrope® treatment has been demonstrated [11,15].

Table 1
Number of clinical studies and total number of subjects in the clinical development programs of Sandoz SBPs.

Product	PK/PD studies		Pre-marketing efficacy/ safety studies	
	No. subjects	No. studies	No. subjects	No. studies
Omnitrope®	133	5	210	5
Binocrit®	234	5	593	2
Zarzio®	146	4[a]	170	1

[a] Two studies with a total of 80 subjects have been designed to demonstrate comparable efficacy using ANC as primary surrogate parameter of efficacy.

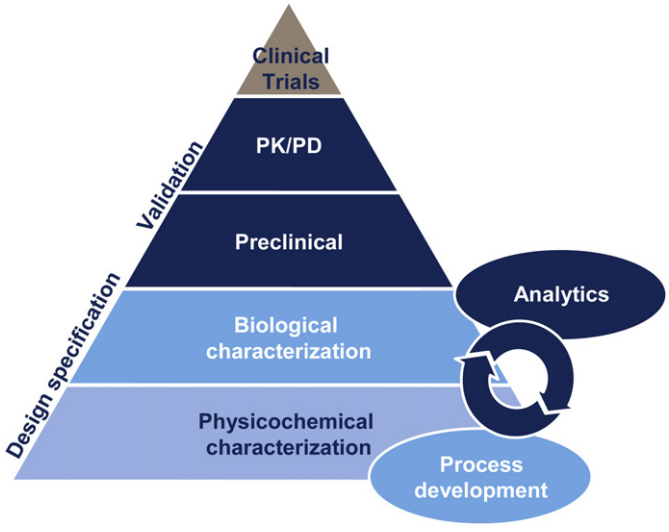

Fig. 1. Biosimilars are systematically engineered to match the reference product.

3.2. Recombinant erythropoietin α – Binocrit®

Binocrit® was developed using the reference product, Eprex®/Erypo®, the Janssen–Cilag recombinant erythropoietin α authorized in the EU in 1994 [16]. A similar pharmacokinetic and pharmacodynamic profile of Binocrit® and the reference product was demonstrated in comparative PK/PD studies in healthy volunteers for i.v. and s.c. routes of administration [16–19]. Comparable efficacy was confirmed in treatment of anemia by administration of i.v. erythropoietin α in 478 chronic renal failure patients receiving hemodialysis [20]. Patients with hemoglobin (Hb) levels of 10.0–13.0 g/dl were randomized to either continue their current i.v. erythropoietin α treatment or switch to Binocrit®. During treatment, erythropoietin α dosages were titrated to maintain Hb values. The primary endpoint was the difference between treatment groups in the mean absolute change of Hb levels between baseline and evaluation period (weeks 25–28). Mean changes in Hb levels were 0.15 ± 0.09 g/dl in the Binocrit® and 0.06 ± 0.12 g/dl in the comparator group. The difference between groups in the per protocol population of 325 patients was 0.08 g/dl Hb (95% CI [−0.17; 0.34]), well within the predefined equivalence margin of ±0.5 g/dl Hb for demonstration of comparable efficacy. Comparability was also demonstrated in the intention-to-treat (ITT) population of 465 patients with a difference in Hb change between groups of 0.19 g/dl