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Experience of reviewing the follow-on biologics including Somatropin and erythropoietin in Japan

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ABSTRACT

To share the experience of reviewing clinical data required for the licensing of follow-on biologic products (biosimilar products and similar biotherapeutical products as EU and WHO terminology, respectively) in Japan, the data packages of two follow-on biologics, "Somatropin BS s.c. [Sandoz] (Omnitrope®)" and "Epoetin alfa BS [JCR]", which have been recently approved in Japan according to the "Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics" published on March 4th 2009, are described. The clinical data package and indication of Somatropin BS/Omnitrope® were different in each country. In case of Epoetin alfa BS [JCR], non-clinical and clinical data-package was different from those of erythropoietin biosimilar products approved in EU. Submission of post-marketing surveillance plans for both products was required.

Even though there seem to be differences in data requirements by each national regulatory authority, the accumulation of experience will provide the rationale and consensus on how to design the clinical trials for follow-on biologics.

1. Introduction

Recently, the expiration of patents and/or data protection for the first major group of originator's biotechnology-derived products has promoted the development of biotechnology-derived products that are designed to be 'highly similar' to a licensed innovator product [1–4]. These highly similar biotechnology-derived products (namely follow-on biologics) rely for their licensing on accumulated information regarding safety and efficacy obtained from the reference products. The clinical experience and established safety profile of the reference products should contribute to the development of follow-on biologics. Therefore, the sponsor could develop the products through the abbreviated approach of non-clinical and clinical studies by using the experiences of the reference products. In fact, the amount and extent of data required for the licensing of follow-on biologics is likely to be less than is normally required for the innovator products.

Japanese regulatory authority, Ministry Health Labor and Welfare (MHLW), has been confronted with the new challenge of regulating follow-on biologics. To ensure the quality, safety and efficacy of follow-on biologic products, MHLW have published the "Guideline for Quality, Safety and Efficacy Assurance of Follow-on Biologics" on March 4th 2009 [5]. In EU, more than ten products already have been marketed as biosimilar products following their biosimilar guidelines [6,7]. WHO, Canada and Korea also published the guidelines of biosimilar [8–10]. These products have been differently named as follow-on biologics (Japan), similar biological medical products (biosimilar products in EU and Korea), subsequent entry biologics (Canada) and similar biotherapeutic products (WHO). However, the basic concept of these products is quite similar judging from each guideline. For the development of follow-on biologics, the manufacturing process should be independently well-established as for innovator products, and the quality attributes of follow-on biologics should be well-characterized, as required for the development of new recombinant protein products (innovator products). In addition, a high degree of similarity in quality attributes with the reference product should be demonstrated. For the approval of follow-on biologics, comparability with the reference products should be demonstrated from both non-clinical and clinical studies. Clinical studies should be designed based not only on the comparability data in quality and non-clinical studies but also on the relevant information about reference products.

Generally, the clinical studies to evaluate efficacy and safety are the main element in the development process of biotechnology-

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Table 1
Data-packages of Follow-on Biologics approved in Japan.

		Guideline	Somatropin BS	EPO BS
Quality	Manufacturing Process	○	○	○
	Characterization (Quality Attribute)	○	○	○
	Specification	○	○	○
Stability	Long-term test	○	○	○
	Stress test	Δ	–	○
	Accelerated test	Δ	○	○
Pharmacology	Primary PD	○	○	○
	Safety Pharmacology	–	–	○
	Others	–	–	–
PK	ADME (non-clinical)	Δ	–	○
	BE (human)	–	–	–
	Others	Δ	–	–
Toxicology	Single-Dose Toxicity	Δ	Δ	○
	Repeat-Dose Toxicity	○	○	○
	Genotoxicity	–	–	○
	Carcinogenicity	–	–	–
	Reproductive & Developmental	–	–	○
	Local Tolerance	Δ	○	○
	Others	Δ	–	–
Clinical	Clinical Studies	○	○	○

derived products. Furthermore, clinical studies extend over a long period of time. Therefore, the abbreviation of some clinical studies will help rapid development of follow-on biologics. The design of clinical studies to evaluate the comparability of follow-on biologics with the reference products is very important. In this review, experiences of reviewing the follow-on biologics approved in Japan are described, and then compared with other countries. We also address the post-marketing surveillance of follow-on biologics in Japan.

2. Clinical data required in the guideline

Japanese guideline basically requires the comparative pharmacokinetics (PK) studies as is the case with other regions/countries. Where available, it is important to select appropriate pharmacodynamic (PD) markers to see clinical effect and to assess these in comparability studies. Moreover, it is suggested that, based on the analysis of the PK/PD studies, the clinical comparability between the follow-on biologics and reference products will be evaluated.

In Japan, the comparability of follow-on biologics should be evaluated through the clinical studies, as similar to the other region. In case that PK/PD studies are sufficient to assure comparability of clinical efficacy, additional clinical studies might be omitted in Japan as well as in the EU, Korea (except Canada) as per the WHO guideline.

In certain case, the safety profile of follow-on biologics may differ from that of the reference products due to the difference of several factors, such as post-translational modifications, product- and process-related impurities, and these may affect the immunogenicity. In Japan, therefore, studies should be conducted to evaluate antibody formation and other immunogenicity at an appropriate stage of the clinical development, like the other region.

If reference products have more than one indication, the important issue is whether follow-on biologics could be approved for other indications where clinical studies have not been conducted. Japanese guideline describes that it may be possible to extrapolate from one indication to other indications of the innovator product used as the reference product if the mechanism of action is the same, like the other region.

3. Data-package of follow-on biologics approved in Japan

Two follow-on biologics, "Somatropin BS s.c. [Sandoz] (Omnitrope®)" and "Epoetin alfa BS [JCR]", have been approved in Japan according to the Japanese guidelines. Omnitrope® has been also approved in EU, Canada and USA. Several follow-on biologics for erythropoietin have been approved in EU; Abseamed® *et. al.* and Retacrit® *et. al.* In order to clarify the concept of regulatory pathway to approval of follow-on biologics in other regulatory authorities, the data-packages of follow-on biologics in Japan (Table 1) were compared with those in other countries [11,12].

3.1. Data-package of Somatropin BS in Japan

The data-package of Somatropin BS [Sandoz] is comprised of manufacturing process, characterization of quality attribute, specification, long-term and accelerated stability tests, pharmacology, repeat-dose toxicity study, local tolerance and clinical study. Non-clinical data-package of Somatropin BS [Sandoz] in Japan was the same as that of Omnitrope® in EU, Canada and USA (data not shown).

Clinical data-package of Somatropin BS/Omnitrope® approved in each country was summarized in Tables 2a and 2b [11,13–15]. A three-period cross-over study in 54 Japanese healthy volunteers comparing PK profiles of Somatropin BS 5 mg, Somatropin BS 10 mg with Genotropin® after a single s.c. dose was conducted for the submission. In addition to this evaluation data, 5 PK studies and Phase III trials in growth hormone deficiency (GHD) in pediatric populations conducted in foreign countries were included as supportive data in the clinical data-package for Japan. These supportive data may be very useful to evaluate the comparability of Somatropin BS [Sandoz]. Even though the PK studies comparing

Table 2a
Clinical Data-package of Somatropin BS s.c."Sandoz"(Omnitrope).

[PK/PD studies]						
Study Number	Study Design	Subjects	Japan	EU	Canada	USA
EP00-106	A 3-arm cross-over trial to compare Omnitrope solution (5 mg/1.5 mL), Omnitrope solution (10 mg/1.5 mL) vs Genotropin powder	54 Healthy volunteers (Japanese, Male)	○			
EP00-104	A 3-arm cross-over trial to compare Omnitrope powder (5.8 mg/vial), Omnitrope solution (5 mg/1.5 mL) vs Genotropin powder	36 Healthy volunteers	Δ		○	
EP00-105	A 3-arm cross-over trial to compare Omnitrope powder (5.8 mg/vial), Omnitrope solution (10 mg/1.5 mL) vs Genotropin powder	36 Healthy volunteers	Δ		○	
EP2K-99-PhISUSA	A placebo-controlled 2-arm cross-over trial of Omnitrope powder (5.8 mg/vial)	12 Healthy volunteers	Δ	○	○	○
EP2K-99-PhIUSA	A 2-arm cross-over trial to compare Omnitrope powder (5.8 mg/vial) vs Genotropin powder	24 Healthy volunteers	Δ			○
EP2K-00-PhIAQ	A 2-arm cross-over trial to compare Omnitrope powder (5.8 mg/vial) vs Omnitrope solution (5 mg/1.5 mL)	24 Healthy volunteers	Δ	○	○	○

○: Evaluation Data, Δ: Reference Data.

Table 2b
Clinical Data-package of Somatropin BS s.c."Sandoz"(Omnitrope).

[PhIII studies]						
Study Number		Subjects	Japan	EU	Canada	USA
EP2K-99-PhII/EP2K-00-PhIIIFo	Sequential randomized open-label parallel study to compare Omnitrope powder (5.8 mg/vial) vs Genotropin powder	89 GHD children	Δ	○	○	○
EP2K-00-PhIIIAQ (Part A)	Sequential randomized open-label parallel study to compare Omnitrope powder (5.8 mg/vial) vs Omnitrope solution (5 mg/1.5 mL)	86 GHD children	Δ	○	○	○
EP2K-00-PhIIIAQ(Part B)	Sequential study to confirm the safety and efficacy of Omnitrope solution (5 mg/1.5 mL)	86 GHD children	Δ	○	○	○
EP2K-00-PhIIIb-E	A single-arm study to confirm long-term safety and efficacy of Omnitrope solution (5 mg/1.5 mL)	70 GHD children	Δ		○	
EP2K-02-PhIIILyo	A single-arm study to confirm long-term safety and efficacy of Omnitrope powder (5.8 mg/vial)	51 GHD children	Δ	○	○	

○: Evaluation Data, Δ: Reference Data.

Omnitrope® and Genotropin® were not included in the data-package for EU, the efficacy between these products were compared in Phase III trials in GHD pediatric group.

Indication of Somatropin BS/Omnitrope® in each country is summarized in Table 3. Phase III trials were conducted in GHD pediatric group only, but it was possible to extrapolate from one indication GHD in pediatric population to the other indications such as Turner Syndrome and chronic renal insufficiency in Japan since the mechanism of action was the same. The extrapolation only granted after the re-examination periods (exclusive periods) of indications on reference products were finished. Genotropin®, Norditropin®, Humatrope®, Saizen® and Growject® were approved as new molecular entities (NMEs) in Japan. The indications of such innovator products (NMEs) were based on clinical trial data of each product. On the other hand, it is possible to extrapolate from one indication to the other indications in follow-on biologics if the mechanism of action is the same. In EU, Omnitrope® has all indications of reference products Genotropin®. In contrast to EU, the extrapolation from the indication GHD in pediatric population was limited to the GHD in adults in Canada. In USA, the extrapolation from the indication GHD in pediatric population was limited to the GHD in adults in USA when it was originally approved. Recently Prader–Willi syndrome, small for gestational age and idiopathic short status were added to the indications of Omnitrope® by using the clinical data of other somatropin products in USA [16].

3.2. Data-package of Epoetin alfa BS in Japan

Epoetin alfa BS [JCR] was originally developed in Japan as a NME. However, during product development, Japanese guideline for follow-on biologics was published, so the licensure strategy for Epoetin alfa BS [JCR] was changed to a follow-on biologic. Therefore, non-clinical studies of Epoetin alfa BS [JCR] were conducted following the requirement of new recombinant protein products (Table 4) [12]. As for non-clinical toxicity studies, genotoxicity study, reproductive and developmental toxicity studies were conducted in addition to repeat-dose toxicity and local tolerance studies which were conducted for Abseamed® and Retacrit® which have been approved as biosimilars in EU [17,18]. The comparative repeated-dose toxicity study of Abseamed® and Retacrit® were conducted with Eprex®/Erypo® as reference, while non-comparative repeated-dose toxicity study was conducted for Epoetin alfa BS [JCR]. In case of glycoprotein, it may be useful to compare the non-clinical PK between the follow-on biologics and reference products such as the case for Epeotin alfa BS [JCR] and Abseamed®.

Table 5 shows the clinical data-package of Epoetin alfa BS [JCR]. Phase I study was an exploratory PK study assessing the PK profile of Epoetin alfa BS [JCR] in healthy volunteers. Two cross-over studies comparing the safety and PK profile of Epoetin alfa BS [JCR] and reference product ESPO® were conducted using both i.v. and s.c. injection since ESPO® (contain 750–3000 IU) has these two routes of administration. One of them was a two period cross-over study in 32 healthy volunteers after a single s.c. dose; the other was a two period cross-over study in 24 heamodialysis patients with renal anemia after a single i.v. dose. Phase II/III study was a randomized, double-blind, parallel-group, multicentre design study in 329 heamodialysis patients with renal anemia to compare the efficacy and safety between Epoetin Alfa BS [JCR] and ESPO®. 1500 IU or 3000 IU was administrated to patients 2 or 3 times/week for a total of 24 weeks. Primary endpoint was absolute change in hemoglobin (Hb) level between the baseline period and the evaluation period. The 95% confidence intervals of absolute change in Hb level was within the acceptance range of −0.5 ~ 0.5 g/dL. Long-term study was a single-arm study to confirm long-term safety and

Table 3
Indication of Somatropin BS s.c."Sandoz"(Omnitrope).

Indication	Genotropin (Japan)	Japan	EU	Canada	USA
GHD in Pediatric	○	○	○	○	○
Turner Syndrome	○	○	○		
Chronic renal insufficiency	○	○	○		
Prader–Willi syndrome	○		○		*
Small for gestational age	○		○		*
GHD in Adults	○		○	○	○
Idiopathic Short Status					*

*: new indication added 4 years after first approval.

Table 4
Data-packages of Epoetin alfa BS.

		GL (JP)	EPO BS (JCR)	Abseamed *et. al*	Retacrit *et. al*
Quality	Manufacturing Process	○	○	○	○
	Characterization	○	○	○	○
	Specification	○	○	○	○
Stability	Lond-term test	○	○	○	○
	Stress test	Δ	○	?	?
	Accelerated test	Δ	○	?	?
Pharmacology	Primary PD	○	○	○	○
	Safety Pharmacology	–	○	–	–
	Others	–	–	–	–
PK	ADME (non-clinical)	Δ	○	○	–
	BE (human)	–	–	–	–
	Others	Δ	–	–	–
Toxicology	Single-Dose Toxicity	Δ	○	–	–
	Repeat-Dose Toxicity	○	○	○	○
	Genotoxicity	–	○	–	–
	Carcinogenicity	–	–	–	–
	Reproductive & Developmental	–	○	–	–
	Local Tolerance	Δ	○	○	○
	Others	Δ	–	–	–
Clinical	Clinical Studies	○	○	○	○

Table 5
Clinical Data-package of Epoetin Alfa BS "JCR".

	Study Design	Subjects	Dosage
Ph I	A placebo-controlled trial to confirm the safety & PK	24 Healthy volunteers	Single Dose; iv 300 IU, 1500 IU, 3000 IU
Clinical Pharmacology	A 2-arm cross-over trial comparing the safety & PK of Epo BS vs ESPO®	32 Healthy volunteers	Single Dose; sc 1500 IU, 3000 IU
	A 2-arm cross-over trial comparing the safety & PK of Epo BS vs ESPO®	24 Heamodialysis patients with renal anemia	Single Dose; iv 1500 IU, 3000 IU
Ph II/III	A double-blind trials comparing the safety & efficacy of Epo BS vs ESPO®	329 Heamodialysis patients with renal anemia	iv 1500 IU, 3000 IU 2～3 times/week
Long-term	A single-arm study to confirm long-term safety and efficacy of Epo BS	143 Heamodialysis patients with renal anemia	iv 750～9000 IU 1～3 times/week

efficacy of Epoetin Alfa BS [JCR] in 143 heamodialysis patients with renal anemia. There is no significant difference between Epoetin alfa BS [JCR] and ESPO® regarding adverse events and serious adverse events. Adverse events had not increased during the long-term study. No anti-EPO antibody was identified.

While Phase III study of Retacrit® was conducted in both correction phase and maintenance phase, clinical studies of Epeotin alfa BS [JCR] were only conducted in patients on heamodialysis in maintenance phase. Clinical data about patients on peritoneal dialysis and in correction phase were not collected and clinical study for anemia of prematurity has not been conducted even though reference product ESPO® has two indications, renal anemia undergoing dialysis and anemia of prematurity. It was possible to extrapolate from renal anemia undergoing hemodialysis to the two indications of reference product since the mechanism of action is the same.

4. Post-marketing surveillance in Japan

Data from pre-authorization clinical studies normally are insufficient to identify the all potential safety profiles, thus post-marketing surveillance (PMS) of the safety profile including immunogenicity is required in Japan, like the other region. The specific method and design of the PMS and risk management plan should be submitted together with the application for approval and be discussed with the regulatory authorities. The findings obtained from the PMS should be reported to the regulatory authority.

In case of Somatropin BS [Sandoz], patients' data (～300) were required to collect as PMS. Since the clinical studies on Turner syndrome and chronic renal insufficiency had not been conducted, the sponsor was required to collect clinical data for both indications during PMS. Furthermore, the sponsor should analyze the lack of efficacy and immune reactions possibly due to expression of antibodies against either somatropin or host cell protein.

In case of Epoetin Alfa BS [JCR], patients' data (≧500) should be collected for 5 years as PMS. Since the clinical studies on PD patients and anemia of prematurity had not been conducted, the sponsor was required to collect clinical data from these patients during PMS. Furthermore, the sponsor should analyze the lack of efficacy possibly due to expression of antibodies.

5. Conclusion

Even thought there are some differences of data-packages submitted for each national regulatory authority, comparative PK/PD studies and/or comparative Phase III studies were required or recommended in all countries/regions. In case that reference products has more than one indication, the extent of the possible extrapolation from one indication to other indications of the reference products were different in each country/region. Since the follow-on biologics are generally approved with the abbreviated clinical data, safety data collected during PMS period is very important. The accumulation of experiences will provide the rationale and consensus on how to design the clinical trials for follow-on biologics.

Conflict of interest

The authors have disclosed no potential conflicts of interests.

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