Innovator’s Perspective on Follow-on Biologics

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Outline

- Key Messages
- Definition of “Follow-on Biologics”
- Generic Products and Follow-on Biologics
- Guideline
- Case Study (Quality, Efficacy, Immunogenicity)
- Conclusion

Key Messages

- Patient Safety First
- Respect for Innovator’s Intellectual Properties
- Consideration of Biologics Character

Definition of “Follow-on Biologics”

- Name

  Follow-on Biologics, Biosimilar, Biogenerics,,,,,,,,

- Follow-on Biologics

  “a drug to be developed by a different marketing approval holder as a drug that is bio-equivalent/quality-equivalent to biotechnology-derived drug already approved domestically”

  “recombinant protein, polypeptide and derivatives”

  “highly purified non-recombinant protein and polypeptide from microorganisms or cultured cells”

- Not Applicable

  “Synthesized (poly)peptide, metabolic product of cell, allergen extract, conventional vaccine based on antigen,,,,,,

Source: Final Draft of “Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics”

English Translation by PhRMA

Generic Products and Follow-on Biologics

		Generic Products	Follow-on Biologics
Regulatory Framework		Well Codified	Newly Established
Substance		Identical to Original Products	Similar to Original Products
Risk	Difference of Efficacy from Original Products	Lower (Injection)	Higher
	Toxicity	Caused by Impurities	Caused by Impurities and Immunogenicitiy

EU Guideline

User guide

Guideline on Similar Biological Medical Products
CHMP/437/04

General

Quality

Guideline on Similar Biological Medical Products Containing Biotechnology-derived Protein as a Active Substance: Quality Issues
CHMP/BWP/49348/2005

Non-clinical & Clinical

Guideline on Similar Biological Medical Products Containing Biotechnology-derived Protein as a Active Substance: Non-clinical and Clinical Issues
CHMP/BMWP/42832/2005

Specific

Non-clinical & Clinical

Insulin	Somatropin	Epoetin	G-CSF	Others
CHMP/BMWP /32775/2005	CHMP/BMWP /94528/2005	CHMP/BMWP /94526/2005	CHMP/BMWP /31329/2005	

Draft of JPN Guideline

1.Introduction

- Definition of Follow-on Biologics,
- Purpose of the guideline

2.Scope of Application

- Recombinant protein drugs, polypeptide and derivatives

3.General Principles for the Development

- Establish an independent manufacturing process
- Demonstrate high similarity with the quality attributes of the comparator biodrug
- Based on the concept of ICH Q5E

Draft of JPN Guideline (cont')

4.Manufacturing Process and Quality Characterization

4.1 Development of the Manufacturing Process

- Based on the latest knowledge at that time
- Search for the optimum strategy through non-clinical and clinical studies in case of follow-on biologics with significant glycan heterogeneity
- Assess safety from an independently established manufacturing process and the characterization results rather than simply to compare the impurities

4.2 Characterization (structure analysis, physicochemical properties, bioactivity)

- Consider the appropriate non-clinical and clinical studies because the difference of the impurity profile will be concerns over the occurrence of immunogenicity

4.3 Drug Product Design

4.4 Stability Testing

- Conduct stress and acceleration testing

Draft of JPN Guideline (cont')

5.Evaluation Studies of the Bio-equivalence/quality-equivalence of Quality Attributes

- Consider the impact on efficacy and safety of any variations from bio-equivalence /quality-equivalence study results and conduct the non-clinical and clinical studies on the basis of the results
- Can not use an official reference product for the comparator biodrug

1) Comparative Studies of the Structural Analysis and Physicochemical Properties

- Evaluate the impact of variations in heterogeneity from higher-order structures or posttranslational modifications in conjunction with the results of the analysis of bioactivity, in vivo kinetics and immunologic properties

2) Comparative Studies of Bioactivity

- Compare the bioactivity of comparator biodrugs and follow-on biologics with using several methods as much as possible in consideration of safety and efficacy
- Conduct in vivo bioactivity studies instead of in vitro studies where glycan structures etc. impact significantly on in vivo kinetics

3) Comparative studies of immunologic responses

Draft of JPN Guideline (cont')

6.Specifications and Test Procedures

- Set supplementary specifications and test procedures with reference to the results of the characterization or clinical use etc. where the required specifications are not fully stipulated in official compendia such as the Japanese Pharmacopia

7.Non-clinical Studies

7.1 Toxicity Studies

- Clarify whether the produced antibodies are neutralizing activity or whether they affect the pharmacokinetics where evaluating the production of antibodies
- Require the studies focused on impurity profile differences where the product-related impurity profile differs significantly from that of the comparator biodurg

7.2 Pharmacological Studies

Draft of JPN Guideline (cont')

8.Clinical Studies

- Require clinical studies for follow-on biologics since it is difficult to verify their bio-equivalence/quality-equivalence from the quality attributes and the results of non-clinical studies alone
- May omit further clinical studies where sufficient data to assure bio-equivalence/ quality-equivalence has been obtained through the pharmacokinetic (PK), pharmacodynamic (PD) or PK/PD studies
- Design for the next study according to the obtained data, and conduct step wise to evaluate bio-equivalence/quality-equivalence in clinical studies

8.1 Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD Studies

- Verify the pharmacokinetic bio-equivalence/quality-equivalence through appropriately designed cross-over study
- Investigate the design with reference to properties of the follow-on biologic if a cross-over study is not appropriate for medications with a long elimination half-life (antibodies, PEG-binding proteins etc.) or drugs that produce antibodies
- Study individually where multiple routes of administration exists

Draft of JPN Guideline (cont')

8.2 Comparison of Clinical Efficacy

- Conduct clinical studies to verify that the efficacy of the follow-on biologic and comparator biodrug is bio-equivalence/quality-equivalence where high similarity in terms of quality has been demonstrated, but the conduct of PK, PD or PK/PD studies is difficult, or where even a combination of the PK, PD or PK/PD study results shows inconclusive bio-equivalence/quality-equivalence of clinical efficacy
- Fully explain their validity on the basis of corroborative data or literature where appropriate surrogate endpoints are adopted in stead of true endpoints
- Possible to extrapolate to the follow-on biologics the other indications approved for a comparator biodrug where it can be explained that efficacy is equivalent in respect of certain indications and that a similar pharmacological action can be expected in other indications too
- Demonstrate bio-equivalence/quality-equivalence of efficacy for each indication where the respective indications have a different mechanism of action or this mechanism of action is not clear

Draft of JPN Guideline (cont')

8.3 Verification of Clinical Safety

- Consider conducting clinical safety studies including a study of immunogenicity even where bio-equivalence/quality-equivalence has been demonstrated through PK, PD or PK/PD studies
- Set the target number of subjects so as to ensure adequate investigation where the results of the impurity profile give rise to particular concern over safety
- Consider conducting repeat dose studies for drugs administered long-term
- Consider identifying any reduction of efficacy or impact on safety from the occurrence of antibodies

9.Post-marketing Surveillance

- Assure the traceability of adverse events during the respective surveillance period, and avoid the combined application of the comparator biodrug or drug with similar indications with the follow-on biologic through the treatment period notwithstanding any switch

10.Name

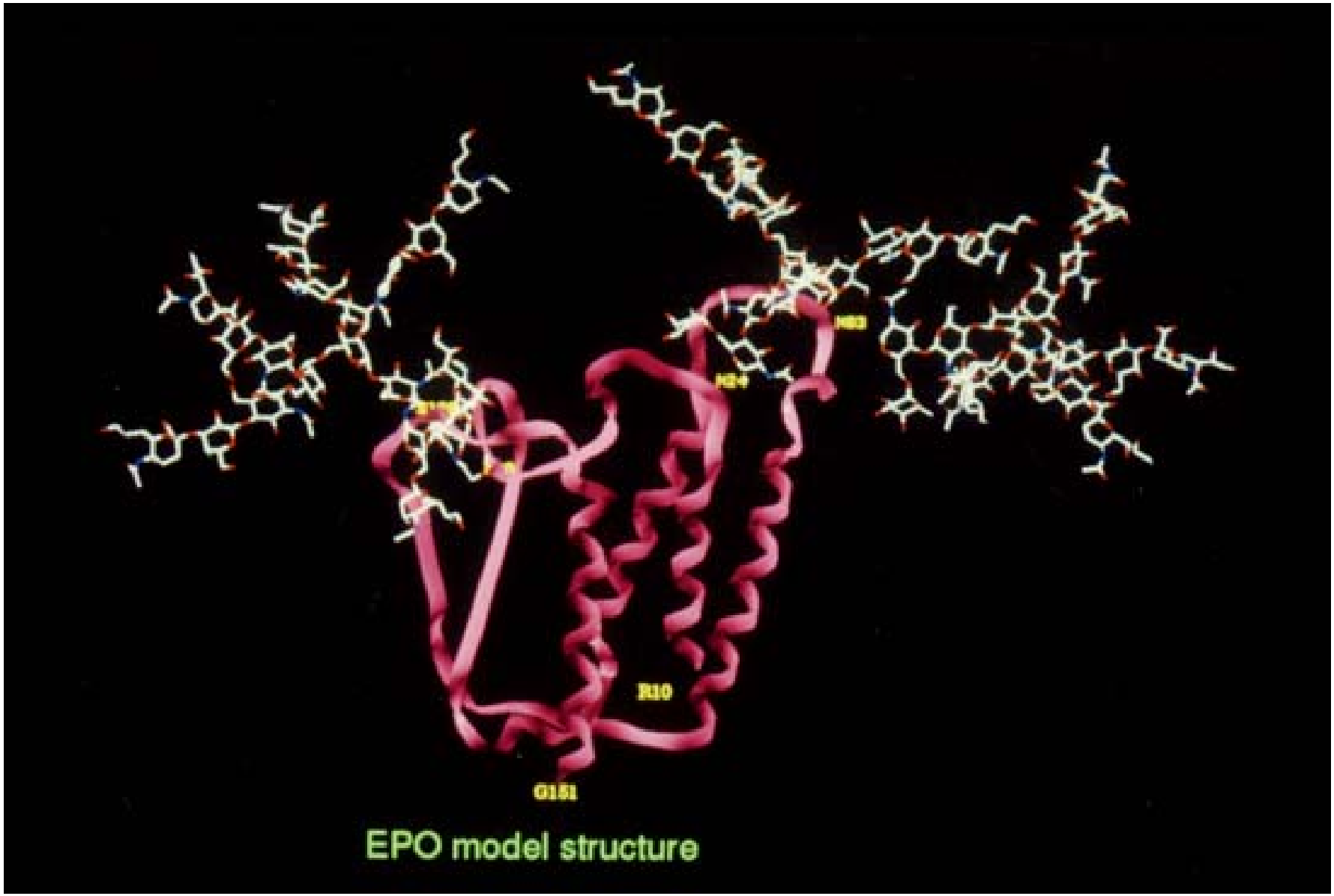
- Example; Nonproprietary Name: XXXXX (Recombinant) Follow-on 1
  Brand Name: XXXXX BS Injectable Content Company Name

Case Study
- Quality Characterization of Copy Products of Epoetin Alfa in Asian Countries -

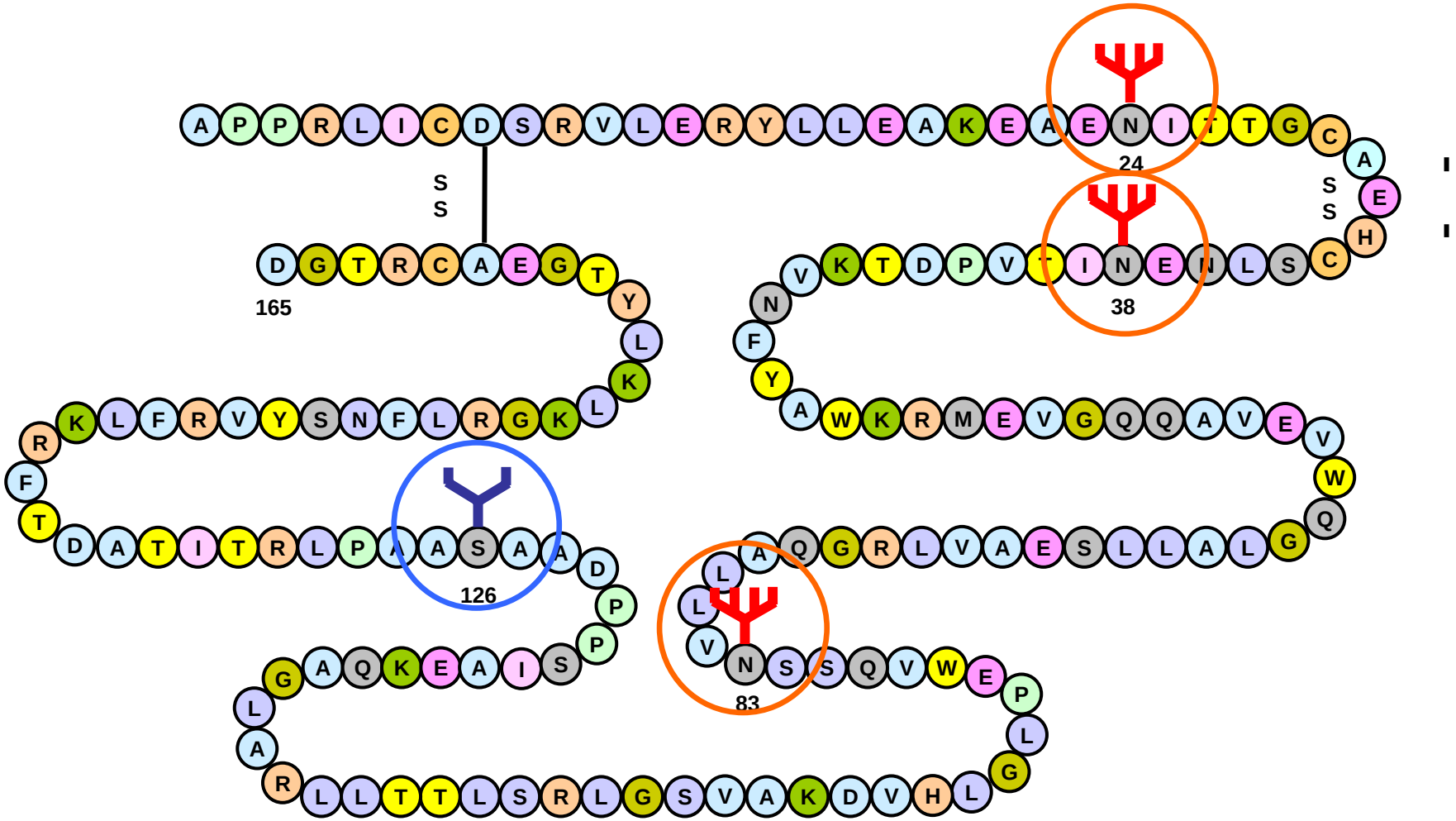
Epoetin Alfa

- Erythropoiesis Stimulating Agent (ESA)
- Glycoprotein which stimulates red blood cell
- 165 amino acid glycorotein which manufactured by recombinant DNA technology
- Molecular weight; 30,400 daltons
- Same biological effects as endogenous erythropoietin

Structure of Epoetin alfa



Structure of Epoetin alfa (cont')



: *N*-Glycoside : *O*-Glycoside SS : Disulfide Bond

Biochemical Assessment of Erythropoietin Products From Asia Versus US Epoetin alfa Manufactured by Amgen

SUNGAE S. PARK,[1] JIHEA PARK,[1] JASON KO,[2] LOUISE CHEN,[1] DAVID MERIAGE,[1] JILL CROUSE-ZEINEDDINI,[3] WENDY WONG,[4] BRUCE A. KERWIN[2]

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

Table 1. Recombinant Human Erythropoietin (rHuEPO) Sample List from Asia

Marketed Country	Trade Name	Company	Exp. Date	HSA	CHO Cell	Label Conc. (IU)	Lot #	Container Type
USA	Epogen®	Amgen	August 5, 2007	Yes, 0.25%	Yes	2000	P029954	Vial
USA	Epogen®	Amgen	February 2, 2007	Yes, 0.25%	Yes	3000	P008951	Vial
USA	Epogen®	Amgen	January 8, 2007	Yes, 0.25%	Yes	10000	P028155	Vial
Korea	Eporon	Dong-A	February 2007	Yes[a]	Yes	4000	ED50398	Vial
Korea	Eporon	Dong-A	March 2007	Yes[a]	Yes	4000 IU/0.4 mL	PD50908	PFS
Korea	Espogen	LG	November 2007	Yes, 2.5 mg/mL	NA	2000 IU/0.5 mL	EPO05017	PFS
Korea	Epokine	CJ	March 2007	Yes[a]	Yes	4000 IU/0.4 mL	5530	PFS
China	Epiao	SS-Pharm	November 2007	Yes, 0.25%	NA	2000	20051101	Vial
China	Jia Lin Hao	Shandong E- Hua	December 2007	Yes[a]	Yes	3000	20051203	Vial
China	Ji Mai Xin	Hua-Bae Pharm	August 2007	Yes[a]	NA	3000	Y20050931	PFS
China	Ji Mai Xin	Hua-Bae Pharm	September 2007	Yes[a]	NA	3000	Y20051031	PFS
China	Huan Er Bo	Beijing Four Rings	March 2008	Yes[a]	NA	3000 IU/0.6 mL	20060305	PFS
China	Huan Er Bo	Beijing Four Rings	February 2009	Yes[a]	NA	3000 IU/0.6 mL	20060203	PFS
China	SEPO	China-SPG	August 2007	Yes	Yes	4000	20050905	Vial
India	Zyrop	Imported from Argentina (Bio Sidus)	March 2008	Yes, 0.25%	Mammalian cell	10000	H10-4031H01	Lyophilized In vial
India	Wepox	Wockhardt	August 2008	NA	Mammalian cell	40000	XF10336	PFS
India	Shanpoietin	Shantha Biotech	April 2008	NA	Yes	4000	EPO2206	PFS
India	Shanpoietin	Shantha Biotech	July 2008	NA	Yes	4000	EPO2806	PFS
India	Epotin	Imported from China (NCPCGB)	April 2008	Yes	Yes	4000	Y20060541	PFS

NA, not available; PFS, prefilled syringe.
[a]Not listed as an excipient, but listed in precautions.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

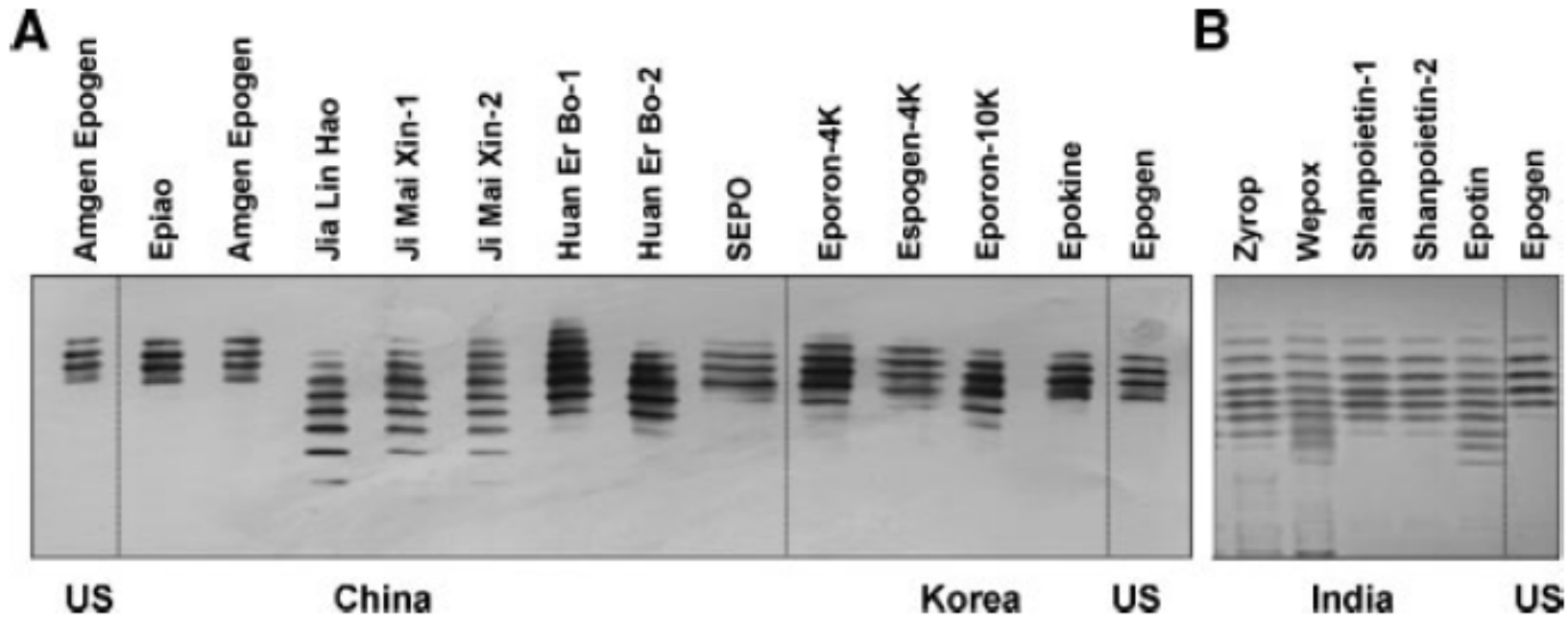


Figure 1. Iso-electro-focus (IEF) Gel with Western blots for isoform detection: (A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

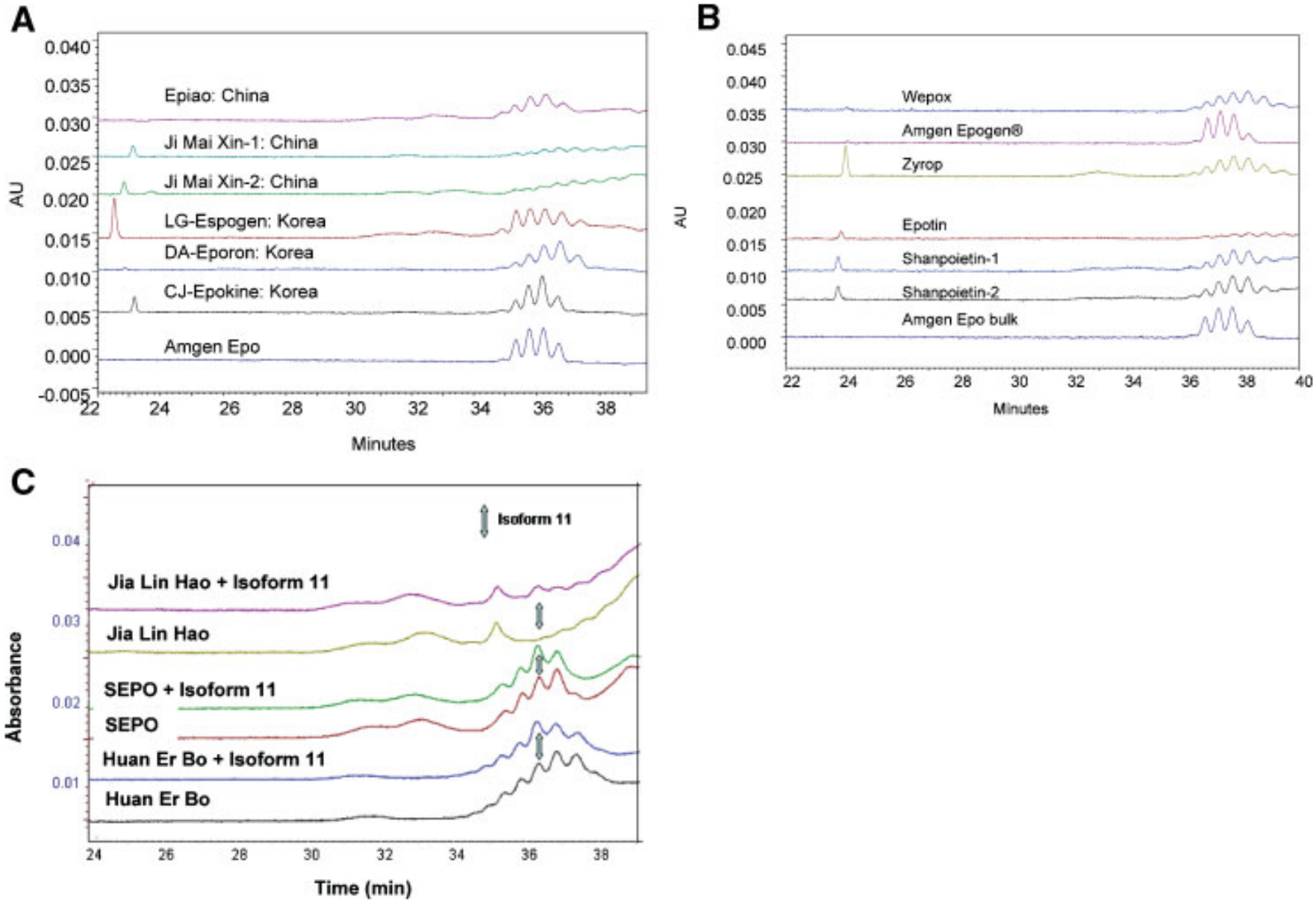


Figure 2. Capillary zone electrophoresis of rHuEPO: (A) from China and Korea, (B) India, and (C) Chinese EPO samples with isoform 11 spiked to confirm isoform 11 position.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

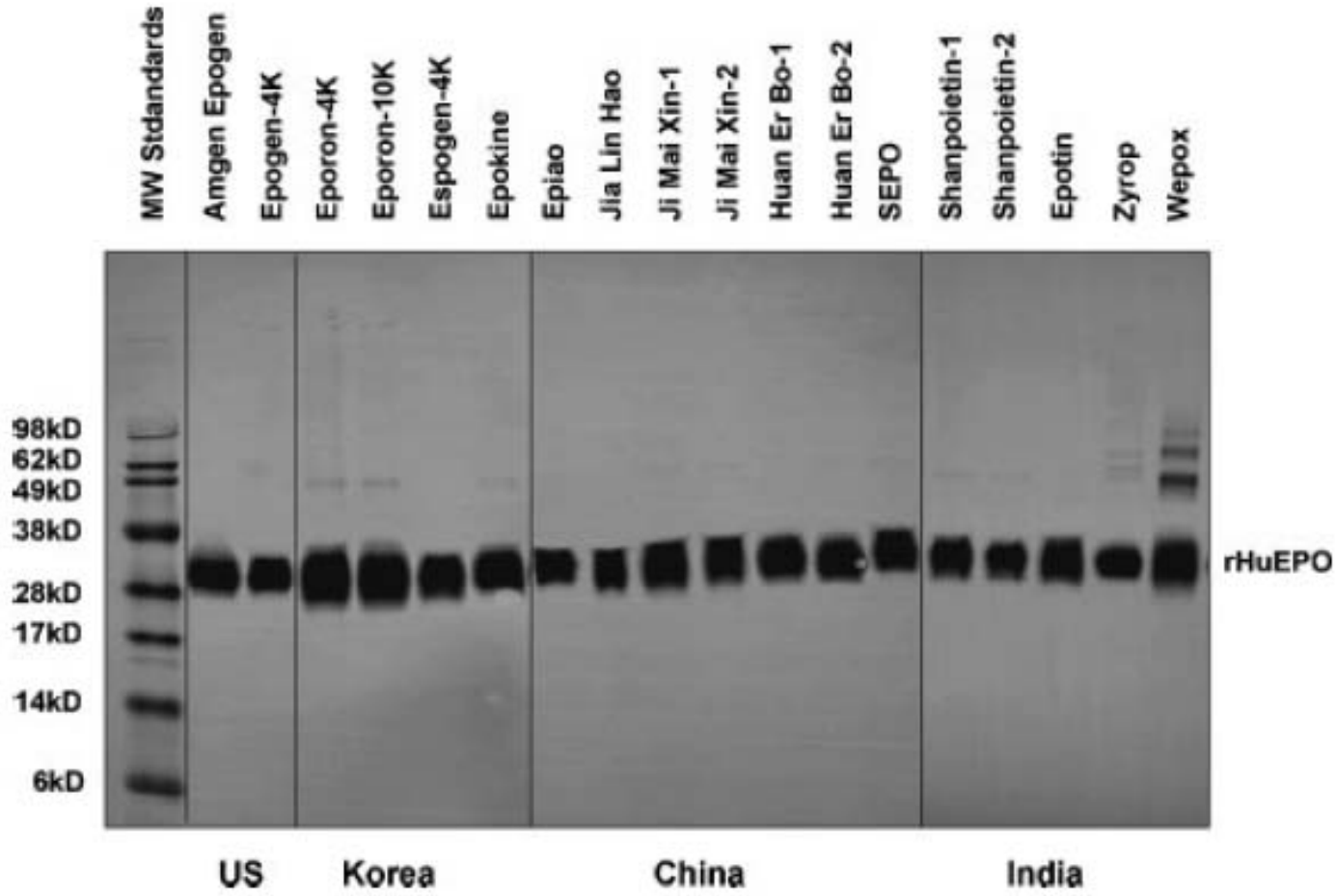


Figure 3. SDS–PAGE with Western blot analysis for detection of aggregation.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

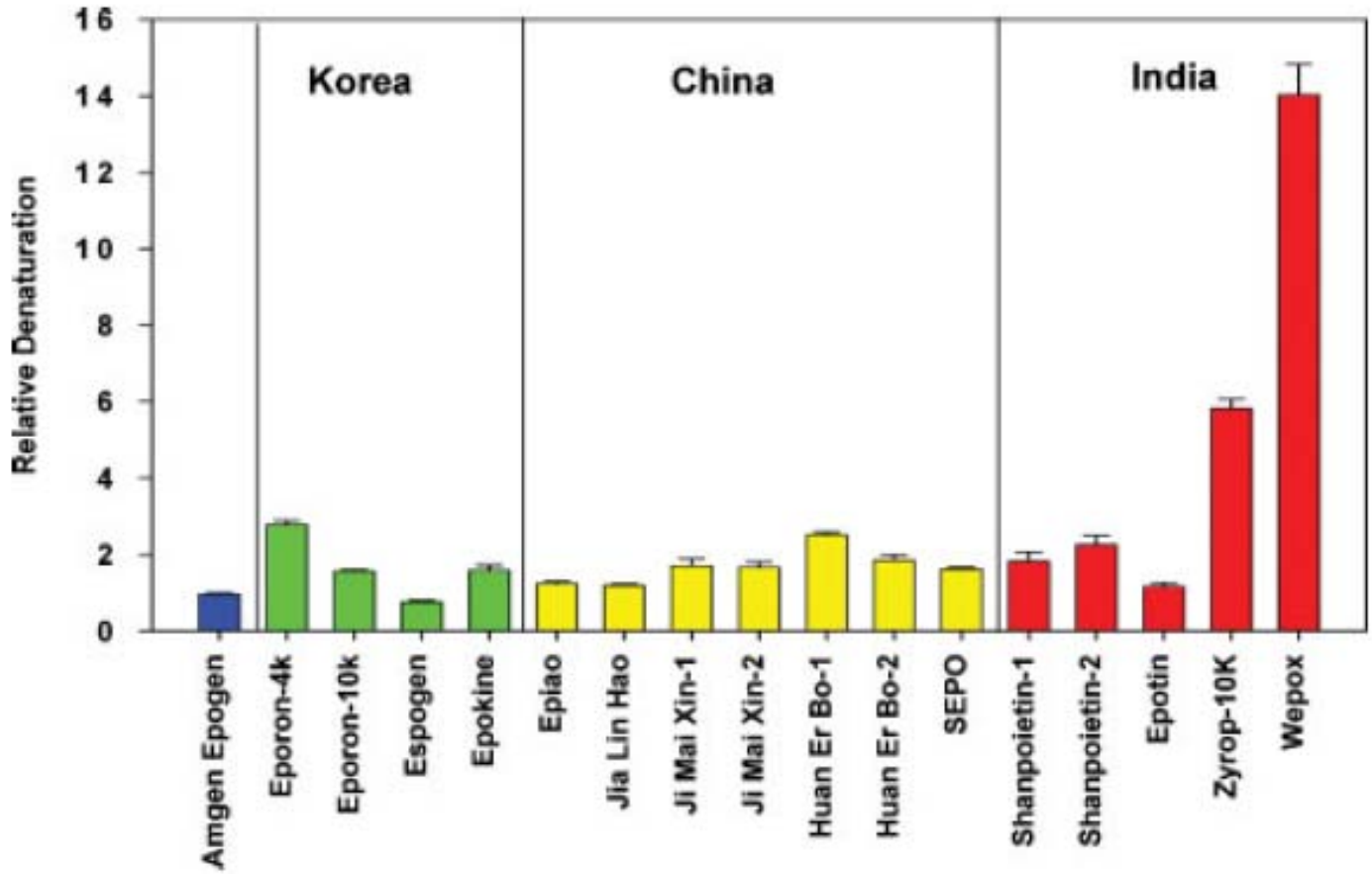


Figure 4. Relative denaturation by 9G8A antibody assay to detect unfolding structure: Samples from China, Korea and India were compared to Amgen Epogen. A value of 1 indicates no difference in folding between the sample and the EPO standard.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

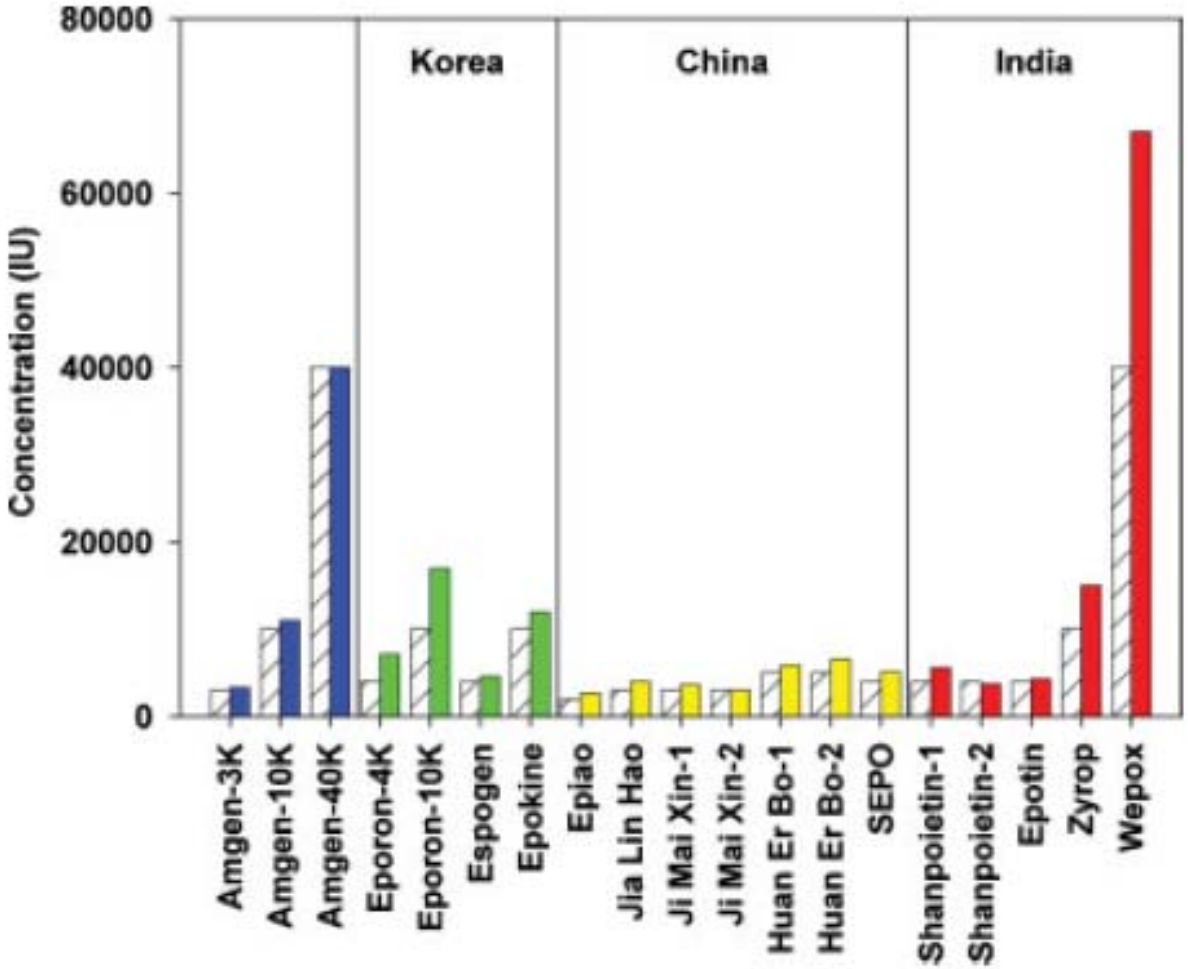


Figure 5. Concentration determination by enzyme-linked immunosorbent assay (ELISA). Striped bars represent the labeled concentration and solid bars represent the concentration measured by ELISA.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

Table 2. Measured Values of pH, Osmolarity, *InVitro* Potency, and Concentration of rHuEPO Samples from Asian Market

Marketed Country	rHuEPO Samples	pH	Osmolarity (mOsm/kg)	Potency[a] by Bioassay (IU/mL)	Concentration Based on Label (IU/mL)	Concentration by ELISA (IU/mL)	Measured[b] Concentration as % of Label Value
Korea	Eporon-4K	6.91	274	6200	4000	7100	180
	Espogen-4K	6.97	348	4100	4000	4600	120
	Eporon-10K	6.94	274	14000	10000	17000	170
	Epokine-10K	6.89	239	10000	10000	12000	120
China	Epiao-2K	6.80	241	2600	2000	2700	140
	Jia Lin Hao-3K	6.80	279	4100	3000	4000	130
	Ji Mai Xin3K-1	6.79	245	3300	3000	3600	120
	Ji Mai Xin3K-2	6.83	245	3000	3000	3000	100
	Huan Er Bo5K-1	6.75	291	5300	5000	5900	120
	Huan Er Bo5K-2	6.70	244	6200	5000	6600	130
	SEPO-4K	6.87	251	4400	4000	5100	130
India	Zyrop10K	7.19	291	15000	10000	15000	150
	Wepox40K	6.73	334	52000	40000	67000	170
	Shanpoietin4K-1	6.91	220	7000	4000	5600	140
	Shanpoietin4K-2	7.25	27	4500	4000	3700	93
	Epotin4K	6.88	240	4700	4000	4300	110
USA	Epogen®	6.88	246	3000	3000	2900	97

[a]Relative potency determined as compared to Amgen Reference Standard.
[b]100 × concentration by ELISA/concentration based on label.

Source: J Pharm Sci 2008 Sep 9 [Epub ahead of print]

Result & Discussion of Case Study
- Quality Characterization of Copy Products of Epoetin Alfa in Asian Countries -

- Copy products of Epoetin alfa showed the variety and discrepancy in quality characterization
- In a test method some copy products described differences from the original product, which demonstrated well similarity with it in another test method
- Most of copy products had a higher concentration of active substance than what was stated on the label

Various test methods should be adopted to investigate the quality of the product and to demonstrated the similarity.

It should be noted that copy products have a higher content of active substance.

Case Study
- Efficacy of Approved Follow-on Biologic of Epoetin Alfa in EU -

SCIENTIFIC DISCUSSION

1. Introduction

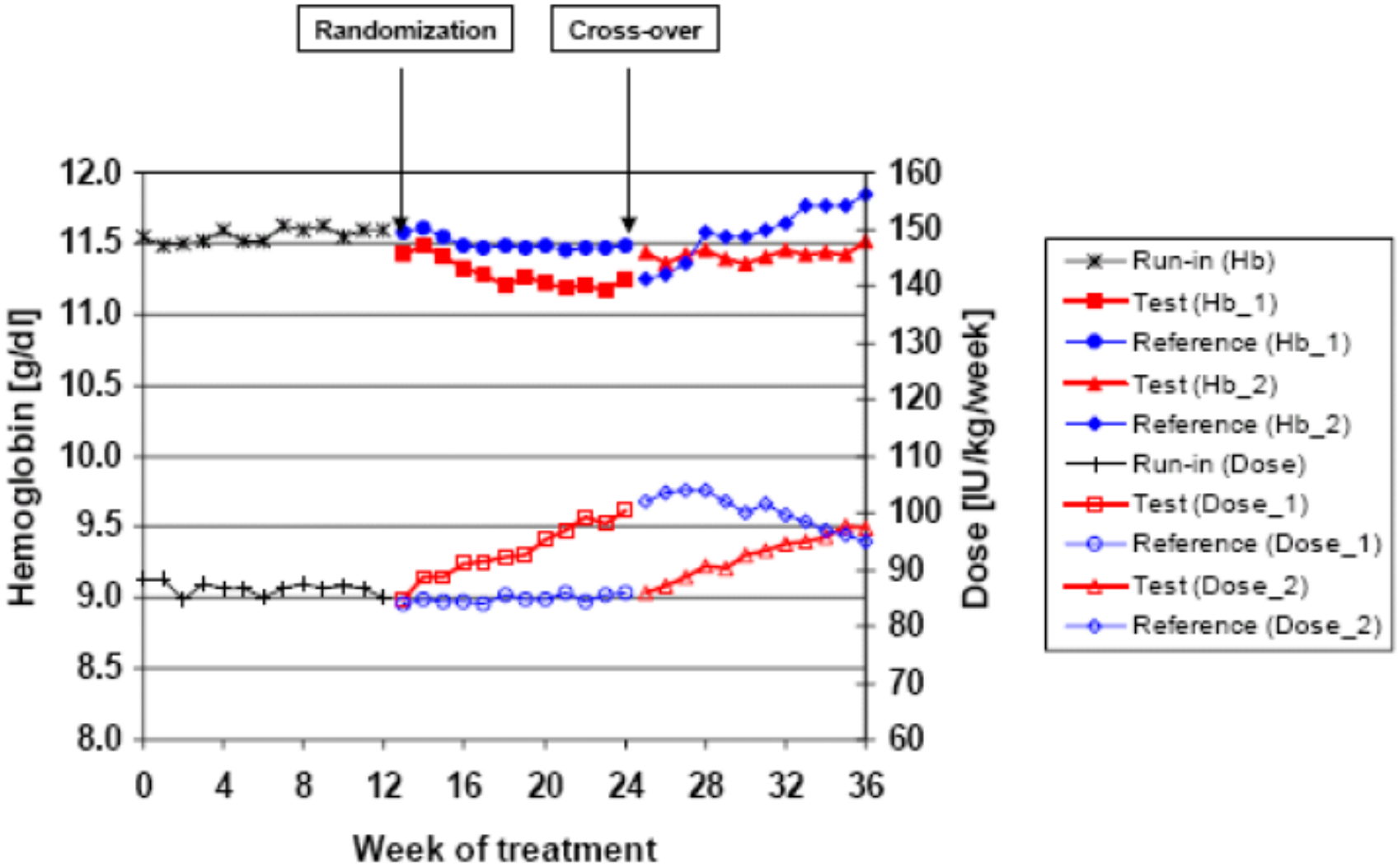
Patients with chronic renal failure (CRF) develop uraemic anaemia as one of the most obvious signs of the disease. This symptom is caused by impeded renal production of erythropoietin (EPO). EPO is produced primarily in the kidneys and stimulates red blood cell counts (RBC) production by promoting survival, proliferation and differentiation of erythroid progenitors in the bone marrow. Epoetin-containing medicinal products are currently indicated for several conditions besides anaemia in patients with chronic renal failure, namely, chemotherapy induced anaemia in cancer patients, for increasing the yield of autologous blood from patients in a pre-donation programme, and for reducing exposure to allogenic blood transfusions in adult non-iron-deficient patients prior to major elective orthopaedic surgery.

The application for SB309 has been submitted as a "similar biological medicinal product" under Article 10(4) of directive 2001/83/EC (as amended), hereafter referred to as biosimilar.

SB309 has been developed as a biosimilar product referring to epoetin alfa, authorised in the EU, e.g. in the UK under the brand name Eprex (Janssen-Cilag Ltd.) and in Germany under the name Erypo (Ortho Biotech, a division of Janssen-Cilag GmbH).

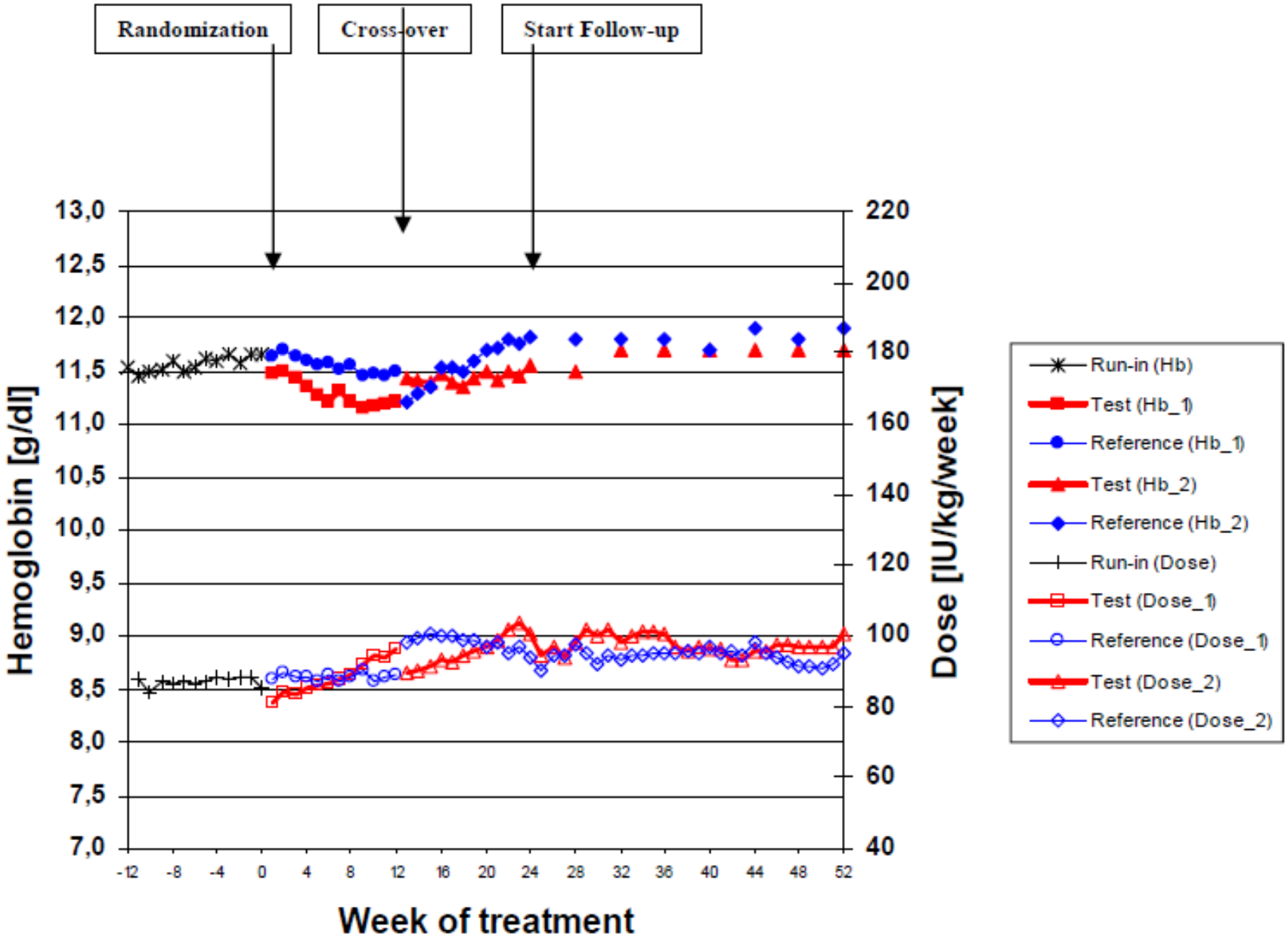
Source: EPAR for Epoetin zeta, Retacrit Revision 3 – Published 10/12/08

Figure 2 Haemoglobin levels vs nominal-based epoetin dosage



Source: EPAR for Epoetin zeta, Retacrit Revision 3 – Published 10/12/08

Figure 3:



Source: EPAR for Epoetin zeta, Retacrit Revision 3 – Published 10/12/08

Result & Discussion of Case Study

- Efficacy of Approved Follow-on Biologic of Epoetin Alfa in EU -

Since there may be a difference of the content between follow-on biologic and original innovative biopharmaceutical, administration dose should be carefully selected.

Case Study
- Immunogenicity of Recombinant Human Protein -

- Experiences

  Erythropoietin (Pure Red Cell Aplasia), Interferon,

  Thrombopoietin, Chimera Antibody

- Considerable Sources

  Conformation change (variety)

  Impurities (aggregation, degradation, process-related)

Immunogenicity of follow-on biologics should be investigated carefully not only in development stage but also in post-marketing stage

Conclusion

We, innovators, understand that some follow-on biologics will obtain the regulatory approval and be used, which can meet the criterion. However, since their collected data is limited compared with the original innovative product, much more data and information should be fully collected after launch, especially for safety.

When the original product is switched to follow-on biologic, administration dose should be carefully selected. And if immunogenicity is observed, it should be sufficiently investigated.

On the other hand, innovators should consider whether the latest technology and science can be adopted to improve their products if needed.