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# China's perspective on similar biotherapeutic products

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A B S T R A C T

In order to ensure most Chinese patients, particularly in the population with relatively low incomes, have access to safe, low cost, effective and quality-assured medicines, a number of "stand-alone" biological products, which have good quality, safety and efficacy have been marketed in China. Many countries and regions' regulatory agencies are actively engaging in the development of bio-similar guidance and documents, which is being coordinated by WHO. As a major developing country of new drug development, China is now working hard to promote the process of new similar biotherapeutic products (SBPs) approval and also actively involved in developing and updating technical documents.


## 1. Introduction

China is the most populous and largest developing country in the world. Hundreds of millions of people with low incomes who need abundant, available and affordable medicines are a huge potential market for similar biotherapeutic products (SBPs). For decades, Chinese drug regulatory agencies have been working hard to establish and improve the approval documents and technical guidelines for biological products consistent with national conditions and scientific principles. China's efforts have been not only to assure the quality and efficacy of licensed products, but also to prompt bio-industry development. In the Chinese market, the available biological products have played an extremely important role in clinical treatment. Over the past ten years, there have been no serious adverse events related to the quality of these biological products reported in China. In recent years, China has actively participated in WHO's conferences focusing on guidance development for SBPs. From the authors' personal views, below is a summary of the current situation in China concerning SBP regulation and future perspectives.

## 2. Overview of the current regulatory situation in China

### 2.1. Regulations and guidelines

As of now, there are no specified regulations for SBPs in China. None of the marketed biological products have been approved using the term "SBP". But some of the regulations included in appendix 3 of "Provisions for Drug Registration (SFDA Order 28)" are related to 'non-innovator products'. Part one of the Appendix 3 is the "Registration Categories and document requirement for Biotherapeutic Products" which includes fifteen categories. Three of which are related to 'non-innovator product' as follows:

- Category 7: Biological products already marketed overseas but not marketed locally.
- Category 10: Products with a manufacturing process different from the already marketed one (such as use of different expression system, host cells etc).
- Category 15: Biological products with National Standards.

### 2.2. Requirements for the registration of 'non-innovator products'

#### 2.2.1. Quality

- Full characterization is required for all biological products. Key quality attributes include physicochemical properties such as structure, biological activity and purity, including identification of impurities.
- For 'non-innovator products', comprehensive dossiers describing quality comparability should be submitted. The gene and amino acid sequence, the production process, the biological activity, the final product formulation and the specification of quality control of the SBPs should be basically consistent with the marketed products.

#### 2.2.2. Non-clinical evaluation

Generally, only one relevant animal is needed for toxicology testing. Normally only one month of study is required for the

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long term toxicity test. Only 1–2 animals are needed for the pharmacodynamic studies. If similarity with the marketed product has been thoroughly verified, non-clinical studies can be reduced.

Although the requirements permit smaller non-clinical studies for SBPs, most 'non-innovator products' having been marketed or approved for clinical trial have actually been subjected to complete non-clinical evaluation.

*2.2.3. Clinical trials*

Complete clinical trials, as are required for new drugs are necessary for the products included in categories 7 and 10. Only phase III clinical trials are needed for the products included in category 15. If relevant differences are found in the quality, a complete clinical trial is also required.

*2.3. Examples of domestic 'non-innovator products' marketed in China*

- Cytokines: Such as interleukins (IL), interferons (IFN), erythropoietin (EPO), granulocyte colony stimulating factor (GCSF), granulocyte/macrophage colony stimulating factor (GM-CSF), etc.
- Hormones: Such as recombinant human insulin (rh-Insulin) and its analogues, recombinant human growth hormone (rh-GH), recombinant human parathormone1-34 (rh-PTH1-34), recombinant human follicle stimulating hormone (rh-FSH), etc.
- Enzymes: Such as streptokinase (SK), staphylokinase (SAK), recombinant urate oxidase (r-UOX), etc.
- Antibodies: Such as recombinant humanized CD25 monoclonal antibody, recombinant humanized CD11a monoclonal antibody and TNFR-Ig fusion protein.

*2.4. The current situation with 'non-innovator products' in China*

- Although comparative evaluation is required for licensure of 'non-innovator product', few applicants in China can offer a complete data package for head-to-head comparison. Therefore, most marketed 'non-innovator products' are "Stand-alone", whose registration information required is the same as for new products without thorough comparability studies.

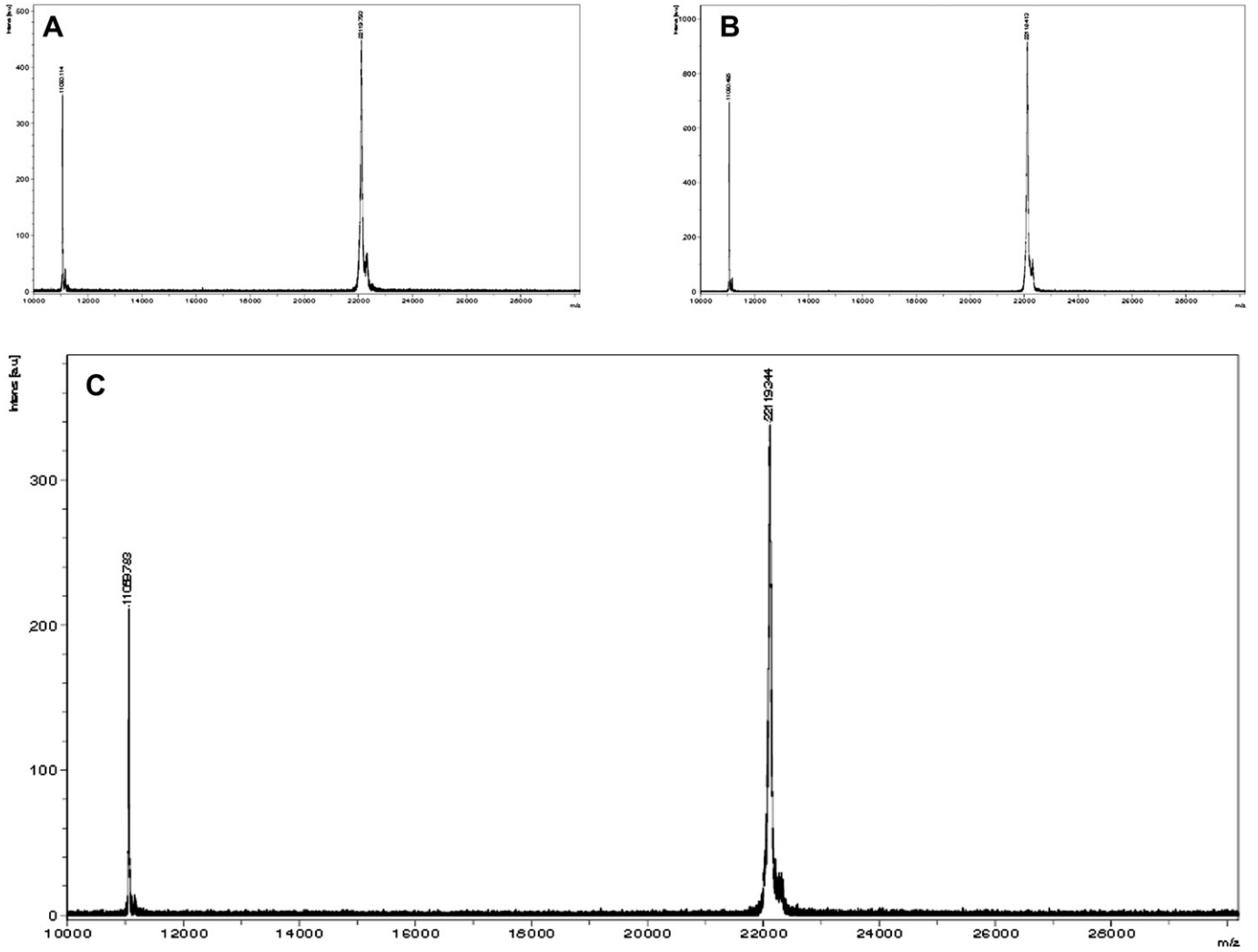


**Fig. 1.** Comparison of rh-GH determined by MALDI-TOF. A. Mass spectrum of the European rh-GH standard, the mass MW is 22119.793. B. Mass spectrum of the domestic rh-GH product, the mass MW is 22118.413. C. Mass spectrum of the mixture of the EU standard and the domestic rh-GH product, the mass MW is 22119.344.

- Some of the marketed 'non-innovator products', such as EPO and GCSF, may be produced by many different manufacturers simultaneously. Although in the past ten years, the situation of having multi suppliers for one product has had benefits for lowering the price and ensuring the availability of these 'non-innovator products', it has also reduced the profits and limited the development of 'non-innovator products' by manufacturers.
- Up to now, there have not been any detailed requirements for the reference biotherapeutic product (RBP) in China.
- In recent years, the market opportunity for developing 'non-innovator products' for the relative simple biological products has decreased. The need for the innovative complex 'non-innovator products', such as glycoproteins, therapeutic antibodies and PEG modified proteins, has gradually increased. This means that it is more difficult to carry out the comparability exercise for such products. Therefore, there is an urgent demand for guidelines on developing and evaluating such 'non-innovator products'.
- Often, experience with state-of-art technologies is limited. For example, comparative pharmacodynamic studies cannot be required as a general requirement because of the limited technical knowledge of PK/PD.

## 3. On-going efforts of Chinese NRA

### 3.1. Following WHO guidelines in practice

With the guidance on 'similar biological medicinal products' containing Somatropin, Insulin, IFN, GCSF, and EPO published by EMA, and the "Guideline on Evaluation of Similar Biotherapeutic Products (SBPs)" published by WHO in recent years, the Chinese NRA has made great efforts in establishing the science basis and evaluating principles for the licensing of SBPs in China. These include:

- Requirements for the comparability exercise for new 'non-innovator products' are being increasingly strengthened. Comprehensive comparisons of quality are extensively required especially for complex macromolecules including glycoproteins, PEG modified proteins, antibodies and some multi-subunit proteins, etc.
- Actively joining and organizing WHO seminars and academic symposia related to SBPs.
- Taking full advantages of the regulatory resources and evaluation experience to keep training the manufacturers to understand the content and rationale of the new guidelines

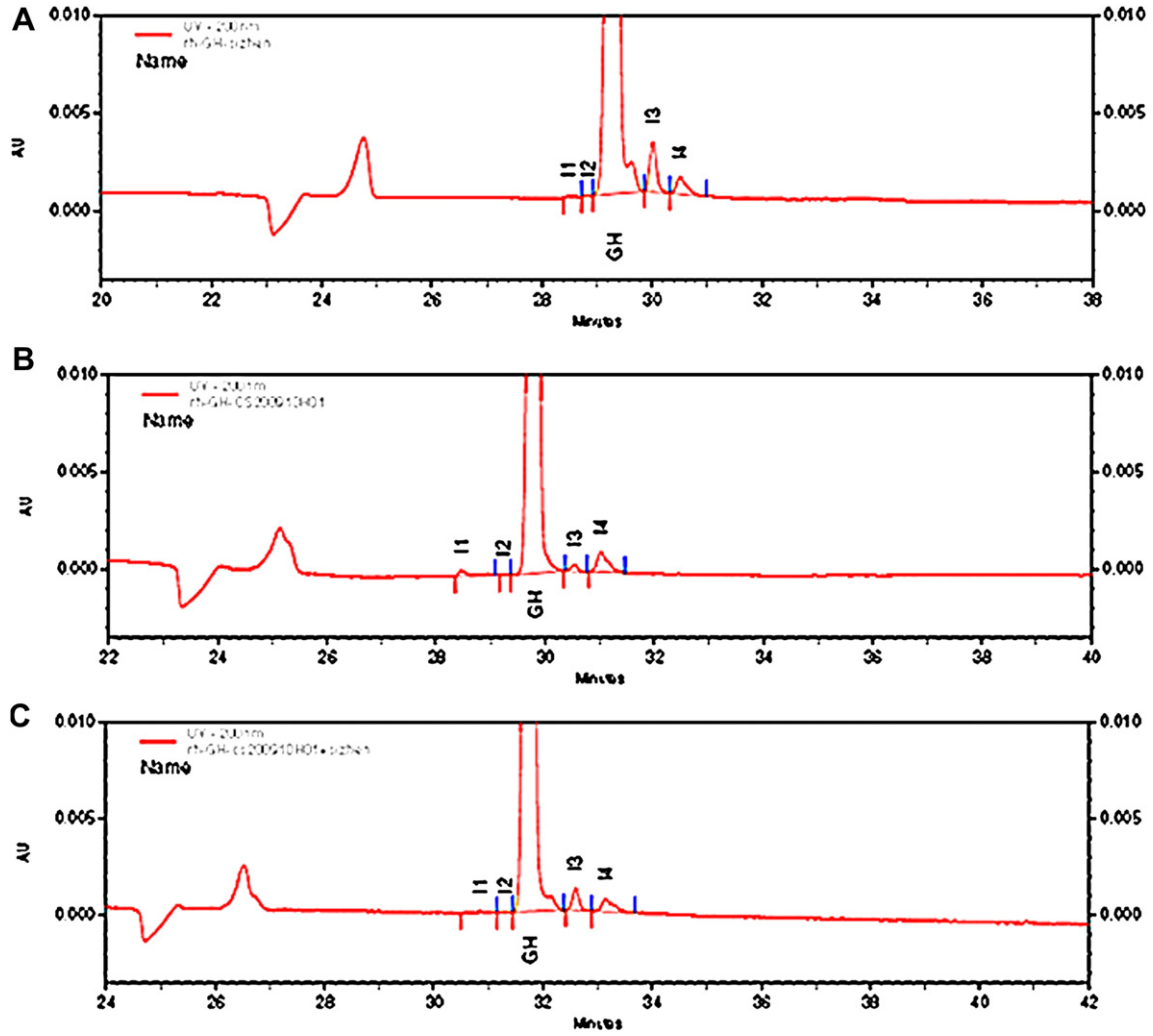


**Fig. 2.** Comparison of rh-GH using capillary electrophoresis (CE). A. Saizen®. B. Domestic rh-GH product. C. A mixture of the Saizen® and the domestic rh-GH product.

and prompting them to develop new 'non-innovator product' based on the comparative approach.
- Strengthening the documentary requirements for the pharmacy section and developing technical guidelines for PK/PD for 'non-innovator products'.

### 3.2. Developing a Chinese guideline for SBPs

Directly led by the SFDA, a group of NRA's officers and experts has been organized to prepare the Chinese guideline for SBPs. The future guideline will be drafted based on basic scientific principles and considering both the local situation in China and the general WHO framework.

### 3.3. Quality assessment being carried out by NIFDC

- Many divisions of NIFDC are actively conducting the comparability assessment of the quality of new 'non-innovator products' and carrying out comparability studies for some of the marketed 'non-innovator products' which were licensed using the route for new drug applications.
- NIFDC is continuing efforts aimed at developing advanced analytical methods for the quality control of biological products.
- Biological products manufacturers are being motivated to strengthen the safety evaluation for impurities and related substances produced during processing and/or storage.
- Methods for obtaining some RBPs for quality comparability exercises by purification from original preparations are being developed.
- Opportunities to be involved in collaborative studies aimed at producing international standards sponsored by WHO are being actively encouraged.

## 4. Examples of quality evaluation for being developed SBPs in China

Some examples of comparability exercises in quality assessment for SBPs and RBPs which have been carried out by NIFDC or manufacturers are described below.

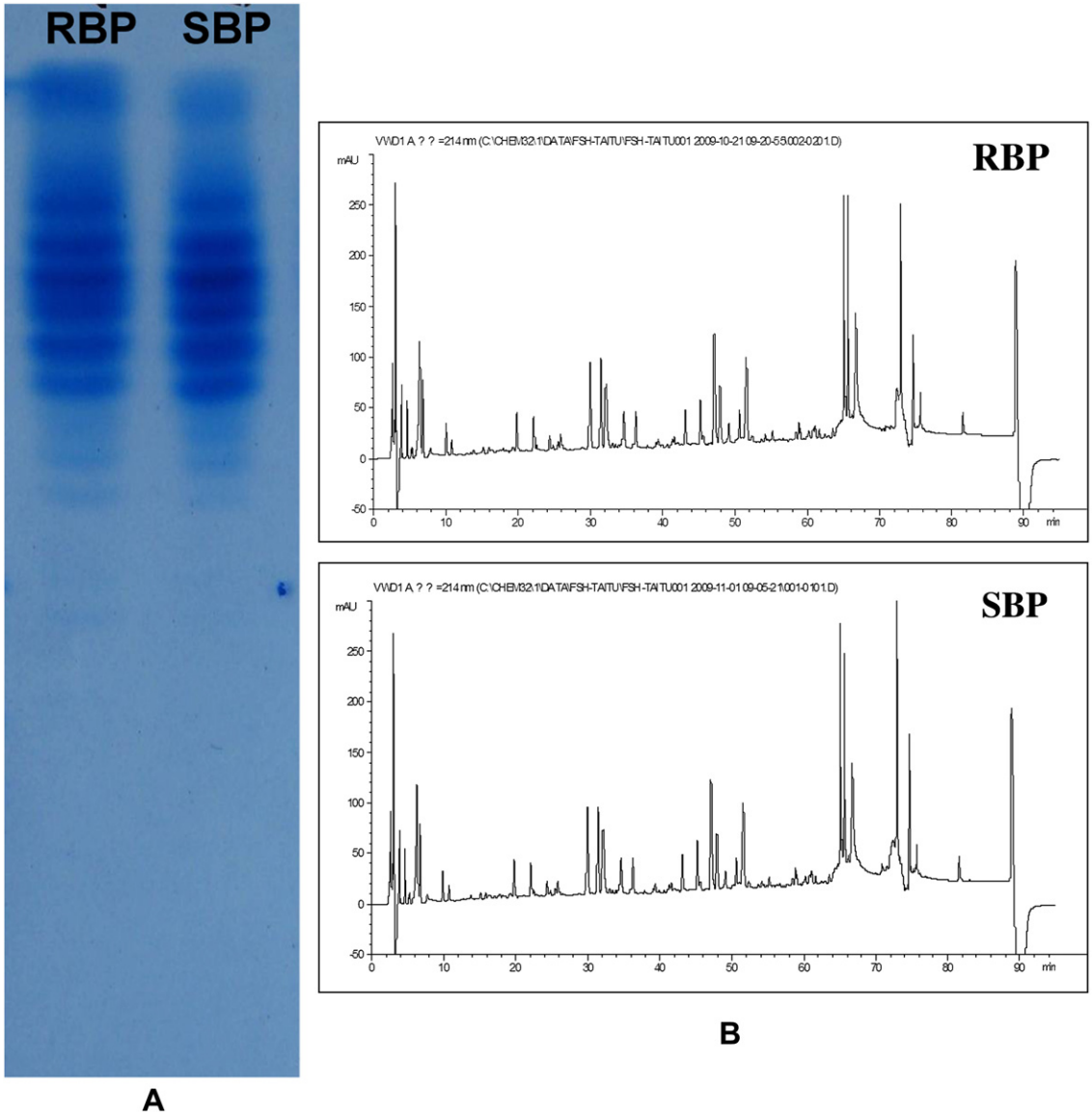


**Fig. 3.** Comparison of an SBP and RBP rh-FSH using IEF PAGE. A. IEF-PAGE profiles of a domestic product (SBP) and a Reference product (RBP). Sample volume is approximately 20 μg/lane. B. Peptide mapping of the RBP and SBP. These were trypsin treated after removing the sugar chain.

### 4.1. Recombinant human growth hormone (rh-GH)

The first rh-GH was marketed in China in 1998. Until recently, there were several rh-GH products licensed in China, which were produced by different domestic manufacturers. Comparability data is shown for some quality characteristics of the developing domestic rh-GH product and the somatropin standard of the EP or Serono product Saizen®.

According to Fig. 1, the molecular weigh of the rh-GH produced by Chinese domestic manufacturer is basically the same as the EP somatropin standard. No additional mass peaks different from those found in the individual samples have been detected in the mass spectrum of the mixture sample. Furthermore, Fig. 2 showed that the profiles of the impurities tested by CE are similar for the domestic rh-GH product and the Serono product Saizen®. There are no additional peaks of impurities seen in the profile of the Chinese rh-GH compared to that of Saizen®. Based on the comparability exercise, it can be concluded that the rh-GH marketed in China is similar to the brand product in quality.

### 4.2. Recombinant human follicle stimulating hormone (rh-FSH)

A domestic rh-FSH product has been approved for conducting a clinical trail in China. Because the heterogeneity in charge and the structure are key attributes of glycoproteins, isoelectric focusing-PAGE (IEF) and peptide mapping were picked as examples of techniques to demonstrate the similarities between the Chinese domestic rh-FSH product and the originator product. The RBP shown below is the rh-FSH sample purified from Gonal-F® produced by Serono and the SBP is the bulk product produced by a Chinese manufacturer.

As shown in Fig. 3A, the profile of bands produced using the rh-FSH produced by the Chinese domestic manufacturer were similar to that found for the Serono product when analyzed using IEF. No significant differences were detected between the RBP and the SBP in the profiles of their peptide maps. That is to say, the rh-FSH product produced in China is similar to the originator product.

## 5. Discussion and suggestion

### 5.1. A relatively flexible guideline for SBPs should be considered

There are no essential differences between China and elsewhere in terms of quality control and evaluation of SBPs. We propose the use of comprehensive comparability exercises as long as RBPs are available. A flexible approach can be adopted regarding pre-clinical and toxicological studies; for instance, we would conduct extensive studies depending on literature reports. Since the clinical modes of action and indications of the originators are well understood, these could be picked for initial development.

Intellectual property issues and technical barriers often make it difficult for developing countries to obtain reference branded products. Therefore, we suggest that the ‘non-innovator products’ which are already licensed or registered in China can be chosen as RBPs on condition that their quality and safety have been thoroughly established by the data collected from the marketplace.

### 5.2. Alternative approaches should be allowed in the licensing for SBPs

For some products with complex and heterogeneous structure such as glycoproteins, therapeutic antibodies and PEG modified protein, the requirement for a head-to-head comparison is not currently adopted in China and some other developing countries due to the extreme difficult in obtaining the RBPs. We propose alternative approaches for these kinds of products so that development of biological products is not hindered. Given that the molecular structure of the product has been defined, it is not necessary for a new applicant to submit a full data package of a head-to-head analysis. Comparison of specifications and the key quality characteristics with the RBP should be enough. But complete clinical trials should be required to ensure the safety and the efficacy of these products.

**Conflict of interest**

The authors have disclosed no potential conflicts of interests.