

Preparing for Volume-Based Procurement of Biologics: A Benchmarking Study of Biosimilar Policies in the EU and USA

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Abstract

Driven by the centralized procurement of biologics in China, it is forcing an urgent evolution of the regulatory policy for biosimilars to break the zero-sum game at present. By benchmarking the relatively mature regulations of biosimilars in Europe and the United States, some decisive factors influencing the quality of biosimilar registration, review and approval are found. In order to ensure the safe and effective use of biologics and interchangeable products under the promotion of the centralized procurement process, and foster the development of biotechs and biopharmas, it is essential to reform the supervision of biologics, promote an entire competition in the market, and secure clinical medication for patients.

Keywords

Biosimilars, Regulatory Systems, Policy Benchmarking, Biologics Industry Insight

1. Introduction

Biologics is known as the “sunrise industry that will never decline.” With the division and cooperation of the global pharmaceutical industry chain, China's biologics industry is accelerating innovation to achieve leapfrog development. Under the normalization and institutionalization of national centralized drug procurement, promoting the reform of medical service supply has become an essential focus of Chinese biopharmaceutical industry supervision and policy innovation. Looking at the development pattern of the global biopharmaceutical industry, Europe and the United States have formed a relatively mature and perfect policy system for registering and supervising biopharmaceuticals and similar

drugs. The policy practice and experience measures in R&D guidance, review and approval, registration management, and other aspects can provide a reference for the standardized development of the biopharmaceutical industry in China.

2. Analysis of the Regulatory Pathways of Biosimilars in the EU and USA

2.1. Own the Leading Registration and Evaluation Systems of Biosimilars

2.1.1. Optimizing Review Approval Procedures

Europe and the United States have increased the listing speed of biosimilars by establishing standardized, simplified, and standard review and approval procedures for biosimilars. Regarding the completeness of review and approval procedures, the EU has adopted the “centralized procedure” for registering, reviewing, and approving biosimilars and comprehensively evaluating clinical trials, thereby systematically improving the evaluation quality. The European Drug Administration requires that a Clinical Trials Authorization (CTA) thoroughly evaluate and approve each clinical trial protocol. During the evaluation, the applicant must provide all the quality, safety, and effectiveness data of the biosimilars to ensure the effective implementation of the evaluation (EMA, 2014).

Concerning the simplification of review and approval procedures, the UK’s Medicines and Healthcare Products Regulatory Agency issued the MHRA Guideline on the Licensing of Biologically Similar Drugs in 2020, introducing a simplified licensing approach for bio-similar drugs, encouraging the development of bio-similar drugs in a step-by-step manner, eliminating the requirement for partial comparison effectiveness tests, reducing the need for clinical test data on bio-similar drugs, and speeding up the listing of bio-similar drugs in the UK (MHRA, 2020). With the practical consideration of the interchangeability of similar biological drugs, the United States established a simplified approval two-level regulatory approach for similar biological drugs and similar biological drugs with interchangeability in the Biologics Price Competition and Innovation Act (also known as “BPCIA” or “BPCI Act”) in 2019.

In order to further clarify the examination and approval requirements for biosimilars, the FDA issued policy documents such as Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, and Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry, to provide guidance and reference for the specific evaluation procedures and evaluation criteria of biosimilars.

Simultaneously, to better support the development of similar biological drugs, the FDA issued the “Purple Book” for biological drugs for the first time in 2014. In 2020, the FDA upgraded and launched the “Purple Book” online database.

Taking this as a reference, building public information retrieval tools and creating information publicity channels played an important role in supporting the development of biosimilars.

2.1.2. Clearing Definitions and Principles

The development of biological analogs is intended to be “highly similar” to the original investigational drug in terms of quality, safety, and effectiveness, with no differences in clinical significance. For this reason, European and American countries have adopted the principle of “comparison” throughout the whole development process of biosimilars, and issued policies, regulations, and technical guidance specifications one after another, requiring the research, development, and production of biosimilars to strictly and gradually carry out a comprehensive comparison in terms of biological activity, pharmacokinetics and pharmacodynamics in vivo of experimental animals, and pharmacokinetics in clinical trials, efficacy and safety.

To clarify the definition of biosimilars, FDA emphasizes that biosimilars are required to be highly similar to reference listed drugs, and there can be no obvious clinical differences in safety, purity and efficacy between biosimilars and reference listed drugs (FDA, 2009). In addition, the FDA has fully considered the possible problems of biosimilars in clinical practice, and set the criteria of inter-changeability (FDA, 2019), which means that biologics can be replaced by biosimilars in clinic without a doctor’s prescription.

Furthermore, to clarify the principles for review and approval of biosimilars. EMA emphasizes the “comparative test” and “head-to-head principle” and introduced “Guideline on similar biological medicinal products,” “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues,” to recommend a stepwise conduct of non-clinical and clinical studies (EMA, 2014). Meanwhile, FDA emphasizes the integrity of evidence and the principle of gradual progress, and in 2016, it updated the guidance document “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product”, which standardized the overall concepts related to clinical pharmacological trials of biosimilars, formulated the corresponding clinical pharmacological database method, emphasized the practicality of modeling and simulation when designing clinical trials, and pointed out that cross-trial design and appropriate biological analysis methods should be adopted (FDA, 2016).

As the review and approval techniques and processes FDA emphasizes the principle of completeness of evidence and gradual progression. In 2014 and 2016, it issued and updated the Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, which regulates the general concepts related to clinical pharmacology experiments of biosimilars, formulates the corresponding clinical pharmacology database method, emphasizes the practicality of modeling and simulation in the design of clinical trials, and points out that cross-over trial design and appropriate bioanalytical methods should be

adopted.

In the scientific supervision of biosimilars, EMA allows slight differences between biosimilars and reference listed drugs, such as the variation of post-translation modification, which is acceptable, but the rationality of the difference must be proved (EMA, 2014). In 2009, FDA promulgated the BPCI Act, which revised the original PHS Act. In section 351 (k) of PHSA, it was pointed out that biosimilars need to prove highly similar information with reference listed drugs, allowing slight differences in clinical inactive ingredients, but it must be proved that there is no clinical difference in safety, purity and efficacy between biosimilars and the reference listed drugs (FDA, 2009).

2.1.3. Advanced Guidance for Application

At the early stage of review and approval practice, European and American regulatory authorities all required that candidate biosimilars pass comparative studies on physicochemical, functional, pharmacokinetic, and pharmacodynamic aspects before judging the clinical efficacy. However, as the review and approval techniques and processes mature, the “one issue, one discussion” principle has become an essential guiding logic for the review and approval of bio-similar drugs. The review and approval have become a process of gradually proving the heterogeneity between biosimilars and reference listed drugs. Under the principle of “one issue, one discussion,” the smaller the molecular weight of the candidate biosimilars, and the simpler their structure and mechanism of action, the fewer requirements for clinical trials will be, and the corresponding time and financial investments will be reduced.

Taking the review and approval of biosimilars under the EMA “one incident, one discussion” principle as an example, the regulatory authority's review and approval requirements for different biosimilars are entirely different. Examples include Fulphila of Mylan and Pelmeg of Cinfa, polyethylene glycol (pegylated), and non-gefitinib analogs. Since the Pelmeg of Cinfa has been shown to be highly similar to the reference formulation in preclinical studies, only two Phase I clinical trials of Cinfa were conducted before approval. As for Fulphila of Mylan, it was different from the reference preparation in the preclinical study, so one Phase I and one Phase III clinical trial was required to prove that there was no difference in clinical efficacy between the two preparations.

Monoclonal antibody biosimilars have stricter review and approval requirements because of their larger molecules and more complex action mechanisms. The clinical trial scale is relatively large. For example, there were 102 Zirabev (bevacizumab) cases in Phase I and 719 in Phase III. 189 cases were enrolled in stage I and 544 cases were enrolled in stage III of Imraldi (adalimumab).

In terms of information exchange and communication guidance, in order to solve the confusion of enterprises in the R&D process, the FDA has set up a formal meeting system for developers (the “Formal Meeting of FDA and Developer or Sponsor of Biosimilars and Biological Products” was released in April 2013), which determines the forms and methods of communication between

industry and FDA in the process of developing biosimilars. The smooth information exchange channel promotes the FDA's support and encouragement for enterprises in the R&D of biosimilars.

3. Improve Clinical Medication Access to Biosimilars

3.1. Optimizing Payment Environment

The development of biosimilars is complex, costly, and long-term. There are obstacles to introducing new drugs, resulting in inadequate market competition after the listing. The pricing difference between biosimilars and their originally developed drugs is relatively small. The patent cliff effect caused by listing biosimilars on the originally developed drugs is insignificant.

In France, the price of a bioequivalent drug depends on the outcome of negotiations between the manufacturer and the Economic Committee for Health Products (CEPS) based on the clinical added value (ASMR, Class V by default for bioequivalent-no additional clinical value), the price of the drug in other European countries, and sales projections. The price of biological similar medicine in France is 10% to 20% lower than that of its original research medicine. Payers in Italy and Spain emphasize the impact of medicines on national and regional health budgets. The two countries focus on price control and intervention of manufacturers for biosimilars, stipulating that the price of biosimilars cannot be higher than that of their corresponding original research drugs. Similar drugs in Spain are generally 25% to 30% lower in price than the corresponding original medicines, while similar drugs in Italy have a 15% to 22% reduction in price (Rovira et al., 2011). The price of similar biological drugs in the United States decreased by 15% to 37% compared with reference listed drugs after their listing. The overall price reduction effect was much lower than that of chemical generic drugs compared with that of chemical original drugs.

However, the situation will soon change because of insufficient competition. On the one hand, doctors' understanding and trust of biosimilars are rising rapidly. In 2020, a plan targeting American oncologists (N = 323) showed that more than 60% of physicians had prescribed biosimilars for Herceptin, Avastin, and Rituxan20, the doctor's approval directly led to the increase of biological similar medicine market share. On the other hand, in the future, more and more BCDs will be certified as "Interchangeable BCDs" by the FDA. For example, in October 2021, BLINGER INGERHAN's Cyltezo, the adalimumab biosimilar, became the first FDA-certified "interchangeable biosimilar." It is expected that the marketing of this product will form a more robust alternative to the original research drug.

3.2. Introducing Incentives

In order to further improve the accessibility of biosimilars, European countries also linked the interests of doctors to the use of biosimilars. Taking Germany as an example, Germany has formulated a set of doctor-centered incentives for the use of biosimilars to strengthen the stimulation for clinical use, making Germa-

ny the country with the highest market share of biosimilars in Europe.

Germany's clinical incentives policy covers two key initiatives. First, physicians are encouraged to prescribe bio mimics by setting budget quotas and monitoring prescriptions. For example, according to the requirements of different regions, the prescription quota of EPO bio-similar drugs formulated by outpatient hemodialysis center should account for 18% - 60% of the total prescribed drugs (Renwick et al., 2016). From 2009 to 2015, under the influence of introducing the prescription target of bio-similar drugs, doctors' prescriptions increased significantly, and the market share of EPO bio-similar drugs increased by 50% (Birkner and Blankart, 2022). Secondly, it emphasizes the need to strengthen the propaganda to doctors. The measures adopted include organizing forums and training regularly to popularize the potential differences between biosimilars and biologics in clinical effects, adverse reactions and long-term safety.

3.3. Improving the Quality Supervision after Listing

The United States has established a robust pharmacovigilance system for post-marketing surveillance of bioequivalent drugs to monitor adverse events. The FDA requires all biotherapy and biologics, including biologicals, to include an FDA-designated suffix after the International Non-Patent Drug (INN) name. This naming convention is designed to enable the FDA to accurately track adverse events for specific manufacturer products, ensuring that monitoring systems accurately detect safety signals for specific products throughout their life cycle.

4. The Existing Pain Points of European and American Policies

4.1. Clinical Substitutability Has Not Been Effectively Verified

The controversial focus of the clinical substitutability of biosimilars is around the "secondary substitution or switching" and "automatic substitution," which are reflected in clinical application, post-marketing supervision, and market order specification. First, it may lead to immunogenicity risk at the level of clinical application. Second, doctors believe that after allowing pharmacists to carry out "automatic substitution," patients' medication information cannot be followed up, and patients' adverse reactions can not be monitored and recorded in time. Third, the production enterprises and experts believe that "automatic substitution" will affect the safety and effectiveness of listed drug monitoring, since relatively few clinical experiments showed that there was no significant difference in clinical effectiveness and safety between the intervention group and the control group (McKinnon et al., 2018; Cohen et al., 2018; Blauvelt et al., 2018; Griffiths et al., 2017), and doctors do not support automatic substitution and multiple biologics use conversion at the pharmacy level (Aladul et al., 2018). Fourth, the industry is worried that if "automatic substitution" is allowed, drug prices will

fluctuate and decline, further affecting the industry's long-term development. At present, only the United States has put forward specific technical and regulatory requirements for the clinical substitutability of biosimilars, and regulatory agencies in other countries still need to establish technical standards for the interchangeability of biosimilars.

4.2. Fierce Competition Leads to a Decline in the Rate of Return

The ROI on investment in biosimilars projects decreased, making enterprises have to start to rethink the development prospects of biosimilars projects. In the expected substantial decline in the rate of return on investment, many biotechs have announced the contraction or given up biosimilars. The fierce market competition after the listing and the high cost of legal proceedings has made the risks of biosimilars far more significant than those of chemical generic drugs. In the case of the project's low expected return on investment, international biopharmas have readjusted their distribution in biosimilars. For example, Merck sold a biosimilar to Fresenius for \$195 million in 2017; In October 2018, Merck terminated the development project with Samsung on the insulin "Letian" biosimilar (which has been temporarily approved by FDA) and paid a termination fee of 155 million US dollars. In November 2018, Sandoz gave up the application for registration of Rixathon, a bio-similar drug of "Meihua", in the US market. In March, 2021, Pfizer announced that it would stop the production of bio-similar drugs in China and sell the production base to Yaoming Bio. Boehringer Ingelheim is also shrinking the global business of similar drugs, focusing only on the US market.

5. Implications

Combined with foreign policy research and experience, draw the following three research enlightenment:

Firstly, to fully activate the vitality of the development of China's biological medicine market. In order to further improve patient accessibility to biologics and promote the high-quality development of the biopharmaceutical industry, it is urgent to strengthen the entire competition in the biopharmaceutical market in China. However, some problems still need to be solved, such as limited market access and challenging delivery of similar biological drugs in China.

Secondly, the clinical application of biosimilars should be encouraged, and the application risk should be reduced through policy escort. From the point of clinical practice, the clinical substitutability of biosimilars has been continuously demonstrated, but the overall "pace" is in a slow state. First of all, we suggest giving preferential policies to qualified products. Well-argued clinical alternative study results will provide an essential basis for doctors to prescribe similar biological drugs.

Thirdly, to strengthen the supervision of drugs after the listing. From the point of view of drug safety monitoring after marketing, a sound post-marketing

pharmacovigilance system for biological drugs can help promote reasonable and standardized drug use in clinics and avoid the occurrence of drug-derived diseases. In particular, the inherent characteristics of biosimilars require that special attention should be paid to immunogenicity during post-marketing monitoring.

In summary, the primary foundation of the centralized procurement of biologics is to promote the high-quality development of China's biopharmaceutical industry. Additionally, to introduce centralized procurement in the biologics industry and avoid the zero-sum game, the government needs to reform the supervision of biosimilars, promote entire competition in the market, and secure clinical medication for patients. Furthermore, it is legitimate to discuss how to implement a centralized collection of biologics, that is, to bring relevant biological products with significant clinical demand and ample price adjustment space into the national centralized procurement.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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