Comparison and Suggestions on the Registration and Regulation of Biosimilars between China and the USA

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Abstract

Objective To put forward some suggestions for improving the registration and regulation, the efficiency of evaluation, and approval of biosimilar in China so as to promote the development of biopharmaceutical industry and increase the accessibility of therapeutic drugs in China. **Methods** Literature related to the registration and regulation, evaluation and approval of biosimilars were sorted out to analyze the differences in China and the USA. **Results and Conclusion** Based on the analysis of the current situation of registration and regulation of biosimilars between China and the USA, it is suggested to improve the registration and regulation of biosimilars in China from the following four aspects: Establishing a biosimilar regulatory department, expanding the professional evaluation personnel, scientifically simplifying the registration and approval procedures, and constantly refining the types of communication meetings.

Keywords: biosimilar; registration and regulation; review; approve

"Biosimilars" also known as "follow-on biologics", is a kind of biological drugs highly similar to the approved original drugs. In recent years, with the expiration of original biological drug patent, the research and development of biosimilars has attracted much attention from the industry. In 2021, the global market size of biosimilars reached $20 billion, and the average annual growth rate will maintain above 15% in the next 10 years. Among the sales of the top 20 biosimilars in the world, the U.S.A has more than 60% of the market, occupying a dominant position in the global biosimilar drug market [1].

China has invested heavily in the research and development of various biosimilar products. Though China has the largest number of varieties and enterprises in the world, but there is still a significant gap between China and the USA in terms of market size. The development and application of biosimilar products play an important role in improving the accessibility of biomedicine [2], so improving the review and approval efficiency of biosimilars in China and accelerating their marketing process will help to address unmet medical needs and achieve the goal of healthy China.

1 Overview of registration and regulation policies of biosimilars in China and the USA

In 2009, the United States Congress passed the "Biologics Price Competition and Innovation Act (BPCIA)", which provided a legal basis for the approval of biosimilars. In 2018, FDA issued the "Biosimilars Action Plan (BAP)" to deal with the slow

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development of biosimilars [3].

The United States is cautious about biosimilars because the first biosimilar product approved by FDA is 10 years later than those in Europe, and only a few biosimilars have been successfully launched in the United States. In recent years, FDA has actively promoted the development of biosimilars by issuing a series of guidance documents that are highly scientific and demanding. Besides, it emphasizes the overall data, which can provide comprehensive and scientific data for indication extrapolation and substitution. It also stipulates strict post-marketing safety monitoring [4].

The registration and regulation of biosimilars in China started late, but the development speed is very rapid. In March 2015, China Food and Drug Administration issued and implemented the "Technical Guiding Principles for the Research, Development and Evaluation of Biosimilars (Trial)", which established the basic principles for the evaluation and management of biosimilars. As the European Union and the United States began to focus on the marketing of biosimilars, China timely participated in the global research and development.

With the passage of time, China's drug regulatory agencies have successively issued a number of guidance documents based on their own experience and lessons from foreign successful cases [5]. The legal system of registration and regulation for biosimilars in China is generally similar to that in the United States, with a few differences in key points and details (Table 1).

Table 1 Comparison of the legal systems of biosimilars between China and the USA

Contrast project	China	The USA
Guidelines for biosimilars	"Technical Guiding Principles for the Research, Development and Evaluation of Biosimilar (Trial)" "Guiding principles of similarity evaluation and indication extrapolation of Biosimilar" "Technical guidelines for clinical pharmacology research of Biosimilar", et al. 11 guiding principles for single species biosimilars	"Scientific Considerations in Demonstrating Biosimilar to a Reference Product" "Quality Considerations in Demonstrating Biosimilar to a Reference Protein Product" "Clinical Pharmacology Data to Support a Demonstration of Biosimilar to a Reference Product" "Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry", et al. The guiding principles for single species biosimilars have not been released yet
Basic principles of evaluation	The principle of comparison, gradual progress, consistency and similarity evaluation, but the specific control of the above principles is not clear	"Quality, purity and efficacy" are consistent with the reference drugs, and the specific analysis strategy, evidence integrity strategy and step-by-step strategy are specific
Reference drug selected rule	The listed products or active ingredients obtained from abroad can be used as reference drugs in pharmaceutical and clinical research stage; However, reference drugs entering the clinical trial stage need to be approved for registration in China	Products approved by FDA can be used as reference drugs, and drugs approved in other areas outside the United States can also be used as reference drugs if their comparability through bridge test
Safety and validity requirement	If the difference in previous studies is limited and the biological similarity is inferred from the clinical PK/PD comparison, it can be simplified; When there are safety-related differences between PK/PD and immunogenicity studies, repeated toxicity tests of at least one related species should be carried out	When highly similar, less animal toxicity data can support phase I clinical; When the similarity is not high, a complete repeated dosing test is needed; If biological similarity cannot be inferred from pharmaceutical and animal experiments, it is still necessary to study the safety and effectiveness, but some clinical safety and effectiveness comparisons can be omitted based on scientific argumentation

2 Evaluation of the registration and regulation policies of biosimilars in China and USA

A clear, sound, scientific and reasonable registration policy will be reflected in the efficiency of review and approval. Therefore, the number and speed of the review and approval of biosimilars are compared to evaluate the implementation effect of the registration and regulation policies between China and the United States.

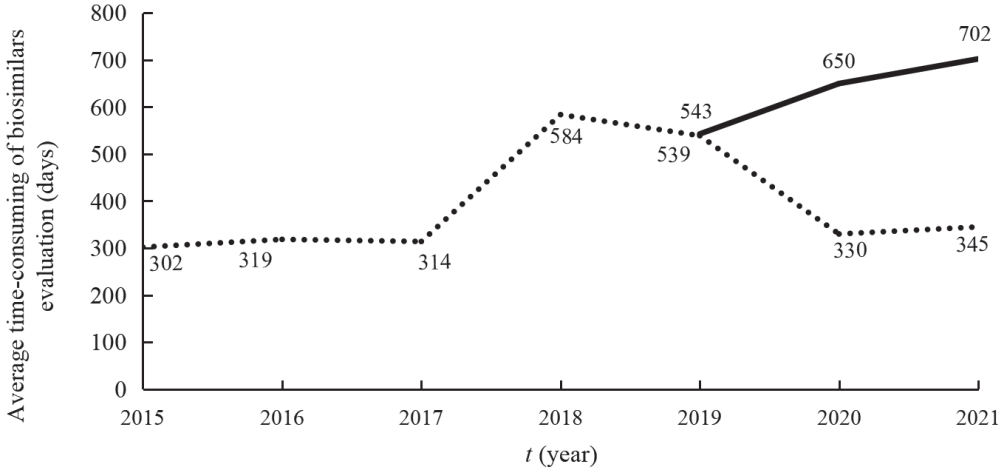
2.1 Number of registered and approved biosimilars

On March 6, 2015, FDA approved the first biosimilar product, Zarxio (filgrastim-sndz) developed by Novartis. In 2018, FDA issued and implemented the "BAP", and carried out a refined reform of the biological product review department. The corresponding number of reviewed biosimilars reached a peak from 2018 to 2019, and the reviews of rituximab, trastuzumab, and pefepristine were completed. As of December 2022, there were 42 biosimilars approved by FDA.

In 2015, China issued and implemented the first guiding principles for biosimilars. However, on February 22, 2019, National Medical Products Administration (NMPA) approved the first domestic biosimilar product, Hanlikang ® (Rituximab injection) developed by Fuhong Hanlin. Since then, the annually number of reviewed biosimilars in China has increased year by year. China can catch up with Europe and the United States in terms of biosimilars after 2021. As of December 2022, 39 biosimilars had been approved in China.

2.2 Speed of reviewing and approving biosimilars

The time-consuming of review biosimilars can reflect the evaluation speed. First of all, from 2015 to 2021, among all the biosimilars that had been reviewed, the longest review time in the United States was 1 631 days, and the shortest review time was 180 days. Meanwhile, the longest time was 2 312 days, and the shortest time was 307 days in China. In addition, as shown in Fig. 1, the average time of review biosimilars in the United States is significantly shorted than that in China. There is still much room for improvement in the approval speed of biosimilars in China.



Data sources: FDA official website, CDE official website, and insight database.

Fig. 1 Average time-consuming of biosimilars evaluation in China and the USA (2015−2021)

3 Status and comparison of biosimilars' registration and regulation in China and the USA

3.1 Registration and regulation agency of biosimilars

3.1.1 Registration and regulation agency in the USA

The FDA is responsible for drug regulation in the United States. The FDA has several branches, among which the Center for Biological Products Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) are closely related to the regulation of biosimilars [6].

According to different types of biological products, CBER set up three product review offices: Office of Vaccine Research and Review (OVRR), Office of Tissues and Advanced Therapies (OTAT) and Office of Blood Research and Review (OBRR) [7].

In 2018, the FDA implemented the Biosimilars Action Plan, the internal coordination mechanism of CDER was strengthened and improved. The Therapeutic Biologics And Biosimilars Staff (TBBS) was established to be responsible for the technical review of biosimilars and interchangeable biological products, which also formulates relevant research and development & approval policies and manages the CDER Biosimilars Review Committee (BRC) and CDER/CBER Biosimilars Policy Committee (BPC) [8].

3.1.2 Registration and regulation agency in China

Center for Drug Evaluation (CDE) is responsible for the evaluation of biosimilars in China. CDE belongs to NMPA, and its organizational structure is shown in Fig. 2. At present, CDE has not set up separate evaluation departments for biosimilars including pharmaceutical technical evaluation, clinical technical evaluation and the technical evaluation of statistics, clinical pharmacology and bioequivalence tests [9].

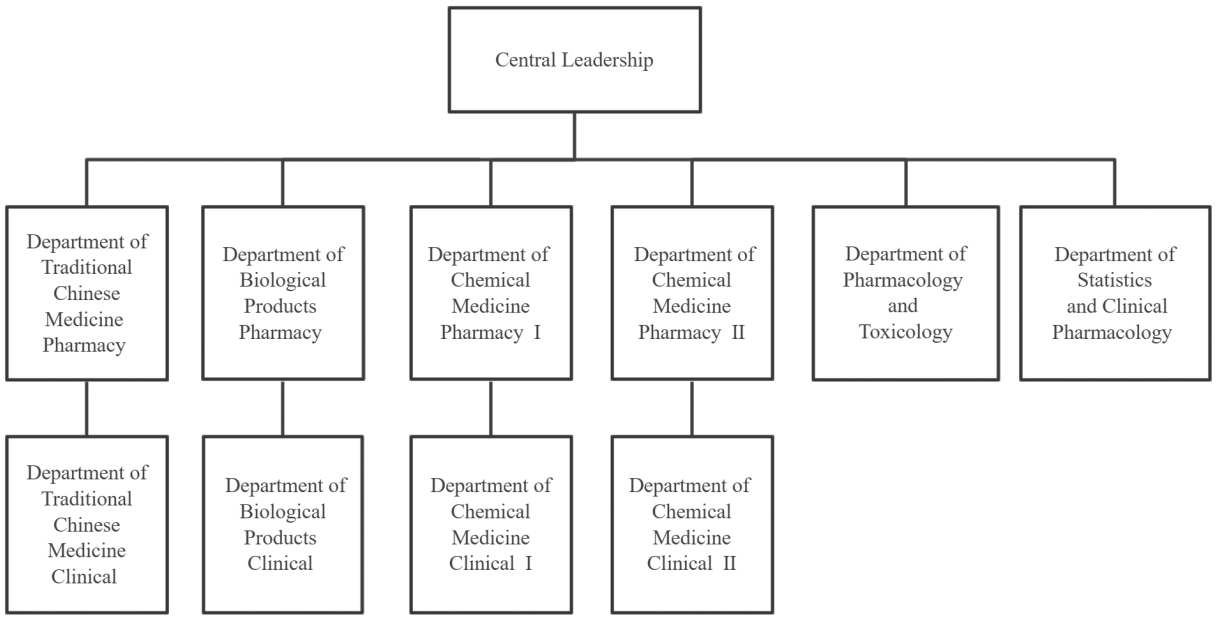


Fig. 2 The organizational structure of CDE

The NMPA is responsible for drug approval in China. NMPA makes approval decisions based on comprehensive opinions, issues new drug certificates if it meets the requirements. Besides, it issues drug approval numbers to applicants who have pharmaceutical production license and production conditions. The organizational structure of NMPA is shown in Fig. 3. When CDE completes the review of biosimilars, Division of Biological Products is responsible for the inspection of research and development, and Division of Supervision III is responsible for organizing and guiding the on-site inspection of the production [10].

3.2 Review staffing of biosimilars

3.2.1 Review staffing in the USA

In terms of quantity, to cope with the rapid expansion of the biosimilars market, by the end of 2022, the number of biosimilars' reviewers in evaluation center had increased from the current 400 to more than 600 in the FDA. At the same time, under the authorization of the federal act, each office under the evaluation center can temporarily recruit less than 100 evaluation staff according to its own situation.

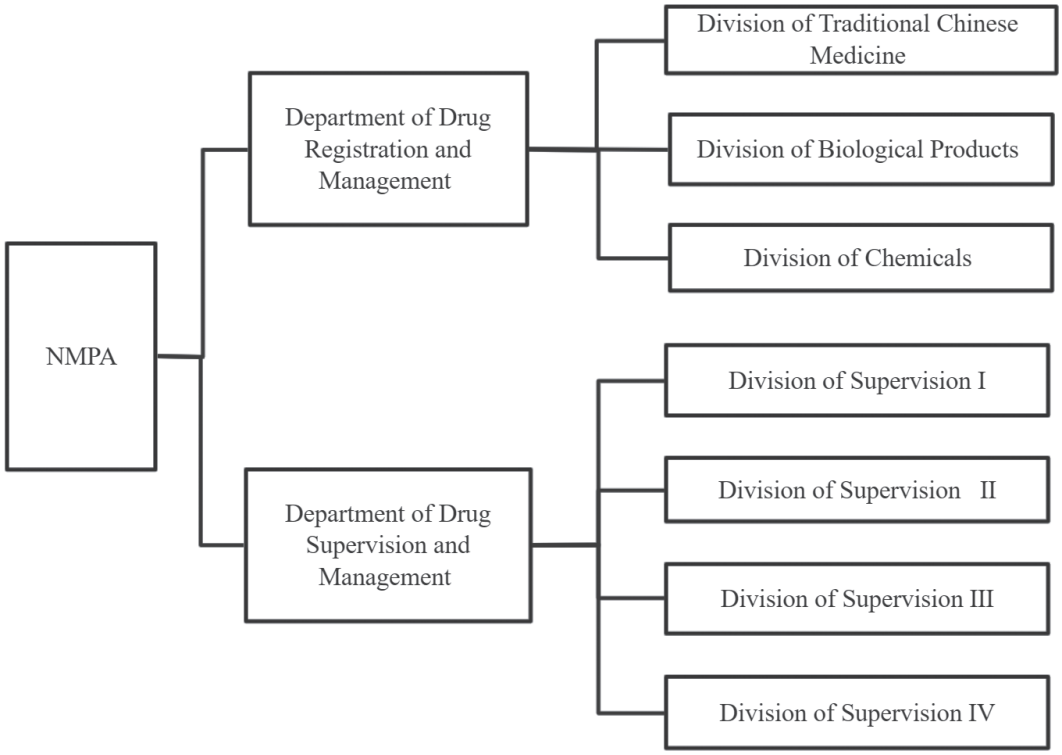


Fig. 3 The organizational structure of NMPA

In terms of academic qualifications, reviewers who usually participate in the work of the evaluation center have at least a doctoral degree in chemistry, chemical engineering or pharmacy or are studying for a doctoral degree.

In terms of recruitment channels, FDA tends to hire people with skilled evaluation experience, and it focuses on candidates with working backgrounds such as R&D departments and research institutions of pharmaceutical companies in resume review. The proportion of new employees who have the ability to review is more than 70%, which enables the center to quickly form a team of reviewers with sufficient work skill at a low recruitment cost.

3.2.2 Review staffing in China

In terms of quantity, although CDE recruits 40–50 people every year, accounting for more than 30% of the total number, the total number of evaluation staff in the center has not reached more than 200 since 2019, which can be inferred that the number of evaluation staff for biosimilar in China is far below 200.

In terms of academic qualifications, for those with intermediate or higher titles, they only need to have a bachelor's degree or above, while for those without intermediate or higher titles, they can also have a master's degree or above in chemical engineering, chemistry and pharmacy.

In terms of recruitment channels, the CDE emphasizes social recruitment to directly obtain evaluation staff with sufficient work experience and skills, which can reduce training time and cost. Therefore, in the recruitment bulletin, it is emphasized that the relevant personnel need to have more than 3 years of working experience in pharmacy and chemical technology-related positions or have intermediate titles, and some key positions require senior titles.

3.3 Registration approval procedure of biosimilars

3.3.1 Registration approval procedure in the USA

The FDA classifies the registration of biological products into two categories: 351 (a) full BLA for biological products with complete research and development data; 351 (k) simplified BLA for biological products with brief research and development data [11].

The registration and approval of new biological products adopts the way of 351 (a) and the mode of IND-BLA, in which the application of IND (investigational new drug) is equivalent to the application for clinical trials of new drugs in China. BLA (biological license application) is equivalent to the application for marketing new drugs in China. At the same time, the applicant needs to provide complete CMC (chemistry, manufacturing, and controls), non-clinical and clinical research data in the review data requirements.

In 2009, the way of 351 (k) was added to the BPCIA, which stipulated that biosimilars should be simplified for review according to the Simplified Application Path (aBLA). Biosimilars under this path do not need to apply for IND, and after reaching an agreement with the original drug research enterprise on patent issues, the subsequent BLA review can be carried out. At the same time, in terms of review data requirements, the applicant may not provide complete non-clinical trial and clinical research data, but only provide comparative research data that proves it has biological similarity (or interchangeability) with reference biological products [12, 13].

3.3.2 Registration approval procedure in China

On July 1, 2020, the NMPA issued a new version of the "Provisions for Drug Registration". Prior to this, the registration of therapeutic biological products in China was divided into 1−15 categories, and biosimilars were registered as new drugs according to the registration classification 7, 10 and 15 [14]. Since the release of the new version of the "Provisions for Drug Registration", the registration of biological products has been classified into innovative drugs of biological products, improved new drugs of biological products, and biological products (including similar drugs). At the same time, in order to facilitate the registration, declaration and management of biological products, on June 29th, 2020, NMPA issued the "Requirements for Registration, Classification and Declaration Materials of Biological Products". So far, biosimilar products in China have been registered in accordance with the registration classification "3.3 biosimilars".

In the review and approval process, biosimilars are still consistent with new drugs, and applications for clinical trials and marketing licenses must be submitted to the CDE. As for the requirements of application materials, the applicant should put forward sufficient basis for one or some studies that the applicant thinks it is unnecessary to submit the requirements of application materials [15].

3.4 Communication mechanism of biosimilars

3.4.1 Communication mechanism in the USA

There is a very clear and mature communication mechanism between FDA and applicants, including meetings and email consultation. The FDA attaches great importance to the communication before the new drug goes on the market, and strongly recommends that the applicant apply for a meeting at the critical stage of the research and development of biosimilar, so as to review the current research, evaluate the safety and effectiveness of the drug, and confirm that the required information and data can meet the needs of the listing application, thus improving the efficiency of review and approval.

To ensure timely and effective meetings between FDA and applicants and grasp the key points in the process of supervision and R&D, in 2015, the FDA

issued "Industry Guide: Formal Meeting between FDA and Biomimetic Drug Sponsors", which set up five formal meeting types from the main problems faced by the actual work of R&D and registration of biosimilars [16].

(1) Preliminary consultation meeting: Initial evaluation in the very early stage of R&D, to discuss whether the way of 351 (k) applies to the listing of products.

(2) Class 1 meeting: To solve the stagnation of project development or an important security problem.

(3) Class 2 meeting: To discuss specific matters (such as quality attribute hierarchy; Chemical, production and quality control methods as control strategies; Research design or end point; Changes after approval) or problems are discussed, and the FDA provides specific suggestions.

(4) Class 3 meeting: To conduct in-depth data review and making suggestions.

(5) Class 4 meeting: To discuss the format and content of the materials to be submitted and other matters.

3.4.2 Communication mechanism in China

After years of exploration and practice, CDE has gradually formed a review management model of "normative guidance first, communication in the middle, and review decision last". Besides, the range of varieties that can be communicated has also expanded from the special approval procedures varieties to all traditional Chinese medicines, chemicals and biological products.

At present, the forms of communication between drug regulatory agencies and applicants in China include meetings, online platforms (such as general technical questions, telephone calls and emails) and on-site services. Online platform consultation and on-site consultation can help enterprise applicants communicate with the staff of drug supervision departments, but they are mainly used to solve legal and regulatory problems. For the technical problems in the process of evaluating biosimilars, the response time of CDE is usually more than 10 days, and it only provides relatively limited information related to the application materials that cannot guarantee absolute accuracy [17]. For the key technologies that cannot be covered by the current guidelines, the applicant may apply for a communication meeting with the evaluation team of the CDE.

On December 10th, 2020, CDE issued the "Administrative Measures for Communication between Drug R&D and Technical Review", which standardized the workflow and specific requirements of meeting application, review and convening. Therefore, the Measures defined the meeting types of various situations and issues, which were divided into Class I, Class II and Class III meetings [18].

(1) Class I meeting: A meeting held to solve major safety problems encountered in drug clinical trials and major technical problems in the development of breakthrough therapeutic drugs, or other specified situations.

(2) Class II meeting: A conference held for drugs at the critical stage of research and development. On the basis of ensuring the safety of subjects, they are divided into three situations: Communication according to law, communication in principle and communication. Before applying for the marketing license for preventive and therapeutic biological products, the applicant shall communicate in principle. It means biologically similar drugs should apply for class II meeting.

(3) Class III meeting: Meetings other than Class I and Class II meetings.

3.5 Comparison of biosimilars' registration and regulation between China and the USA

From the aspects of institutional design, staffing, registration approval procedures and communication mechanism, the main differences between China and the United States in the registration and regulation of biosimilars are compared. See Table 2 for details.

Table 2 Comparison of biosimilars' registration and regulation between China and the USA

Compare dimension	China	The USA
Registration and regulation agency	Office of Therapeutic Biologics and Biosimilars (OTBB) was set up	Biosimilars are supervised according to the categories of biological products, and a special review and approval department has not been established
Review staffing	The number of reviewers of biosimilars is 400−600; Academic qualifications require a doctoral degree or a doctoral degree, and more than 70% of new employees have the ability to evaluate	The number of reviewers of biosimilars is far below 200; Academic qualifications require bachelor's degree or above, emphasizing to have enough work experience and skill level
Registration approval procedure	351 (k) simplified BLA, do not need to apply for IND	Registration by classification "3.3 biosimilars", in the procedure consistent with new drugs (first apply for clinical trials and then marketing licenses)
Communication mechanism	Setting up five meeting types to solve the problems related to the applicant's R&D registration	Meeting applications are based on common conference types I, II and III

4 Suggestions on improving the registration and regulation of biosimilars in China

There is a significant gap between China and the United States in the number and speed of biosimilars review and approval. With a large number of biosimilars under research entering the clinical trial stage, it is expected that the applications for registration of similar drugs in China will reach its peak after 2023. To meet the market expansion demand in China, it is necessary to speed up the process of evaluation, approval and marketing to promote their development.

4.1 Establishing a regulatory department for biosimilars

At present, in order to strengthen the registration and regulation of chemical generic drugs, CDE has specially set up the Department of Chemical Medicine Pharmacy II and Department of Chemical Medicine Clinical II, while NMPA has set up the Division of Supervision II under Department of Drug Supervision and Management. It is suggested that the regulatory authorities should set up a special department for biosimilars with reference to chemical generic drugs, which will make the department responsible for the review and approval of biosimilars, thus promoting the related work and improving the professional capability.

4.2 Expanding the professional review talent team

The number and qualification of reviewers will undoubtedly affect the evaluation efficiency, but at present, the number, education, work experience and evaluation quality of reviewers in China need to be improved urgently.

In order to solve the problem of inadequate talents, it is suggested to speed up the recruitment of reviewers by increasing their salaries and welfare, reducing the turnover rate and stabilizing the outstanding talents. At the same time, it is suggested to attach importance to the training of reviewers, strengthen training, and formulate hierarchical and targeted training plans to improve their professional skills and work capability.

4.3 Simplifying the approval procedures

With the improvement of laws and regulations related to biosimilars, the legal status of biosimilars has been clarified, and it has been stipulated that

they should be declared and registered according to the registration classification of "3.3 biosimilars". However, in the review and approval procedures, the biosimilars are consistent with the original drugs and are not treated differently. To save the cost of research and development and review time of biosimilars, it is suggested to learn from the 351 (k) aBLA of the United States and the BE research of chemical generic drugs in China. Then we should simplify the registration and approval procedures of biosimilars.

4.4 Constantly refining the types of communication meetings

The complexity of biopharmaceuticals makes it impossible for biosimilars to completely replicate reference drugs like chemical drugs, and pharmaceutical companies are faced with various technical challenges in the process of research and development and registration application. In order to ensure full communication between regulators and applicants, and meet the needs of applicants at different stages of project development, we should further refine the types of communication and exchange meetings for similar drugs according to the "Administrative Measures for Communication and Exchange of Drug R&D and Technical Review", improve communication efficiency and R&D quality, and ensure that the evaluation of biosimilars can be completed smoothly.

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