Brief Discussion on the Enlightenment of FDA's Comparability Protocol to the Post-Approval Change Management of New Drugs in China

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Abstract

Objective To discuss the flexible supervision and communication mode in the post-approval change (PAC) of drugs, to explore how to ensure the quality and availability of drugs during the changes, and to provide some suggestions and reference for promoting the timely marketing of drugs. **Methods** Based on the comparability protocol guidelines issued by the US FDA in October 2022, the regulatory status quo of PAC between China and the US was compared to explore the feasibility of implementing comparability protocols in China. **Results and Conclusion** According to the specific situation of post-approval of drug change supervision, some suggestions were put forward to optimize the PAC management procedure, such as establishing the communication pathways between holders and health authorities, publishing relevant guidance and strengthening training, so as to provide reference for the implementation of comparability protocols in China.

Keywords: post-approval change; quality risk management; risk assessment; comparability protocol; pharmaceutical quality system

Post-approval change (PAC) refers to changes after a drug is approved for marketing, mainly including the change of the manufacturing process of drug substance, excipients in preparations, manufacturing process of drug product, source of drug substance used in drug product manufacturing, batch scale up/down, the change of approved specification, packaging material and container, expiration date and storage condition, and the introduction of new strength and/or manufacturing site [1]. The marketing authorization holder (MAH) should carefully evaluate PACs in conjunction with the pharmaceutical quality system (PQS) [2] and quality risk management (QRM) [3] to minimize the risk that might be brought by relevant changes [4]. The rigor of the risk assessment should be commensurate with the complexity and/or criticality of the changes [5]. If the management of PACs is cumbersome and time-consuming, it is not conducive to encourage the Holders to continuously improve the quality of drugs, nor is it good for securing the supply of drugs. FDA's newly published (October 2022) comparability protocol (CP) guidance offered the Holders an official way to communicate the planned/proposed chemistry, manufacturing and control (CMC) relevant PACs [6] with the agencies, which brought a lot of convenience to holders and the agencies. It is

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worth referring to in China.

1 Introduction to PAC submissions in the US

According to the Code of Federal Regulations (21 CFR 314.70) [7], PACs are classified as major, moderate, and minor ones based on the severity of deleterious impact on safety or effectiveness of the drug product. Major changes should be submitted through a prior approval supplement (PAS), and the products under the changes cannot be distributed until holders get an official approval from FDA (usually 4 months, but 6 months in some cases). Moderate changes are submitted by filing a change being effected in 30 days (CBE 30) or Change Being Effected (CBE 0) supplement. 30 days after receipt of the supplement (for CBE 30) or the day of formal receipt of the information (for CBE 0) by FDA, the product under the change can be distributed. Minor changes, as the impact on product safety and efficacy is minimal, are generally submitted through annual report (AR), and the effect/implementation of relevant changes is controlled by the holder's PQS.

2 FDA's CP

2.1 Introduction to CP

In October 2022, the U.S. FDA published the "Comparability Protocols for PACs to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA". The guideline aimed to enhance communication between holders and the agency to expedite the implementation of PACs which would ultimately benefit the patients. The publication of this guidance is a build-up and further extension of the draft guidance issued by the FDA in 2003 and 2016 and is a combination of iterative technology and constantly updated regulatory concepts (see Fig. 1) [8].

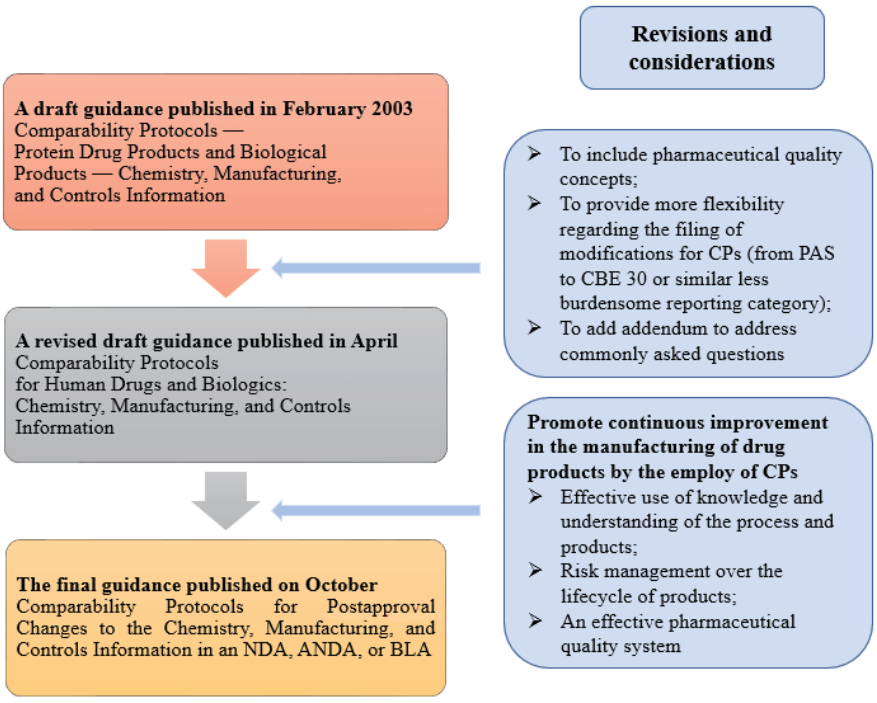

Fig. 1 The iterative process of the official guidance of the comparability protocol

CP is a forward-looking written plan that assesses the impact of proposed PACs on the quality attributes of a drug product (including biologics), such as identification, strength, quality, purity, and potency. Because these quality attributes are related to the safety and efficacy of a drug, they are critical items in the change impact assessment. The CP should include information such as a description and justification for

the change, supporting information, analytical data, risk assessment, implementation plan for the change, and, if applicable, the proposed reduced reporting category. The CP can be applied to new drugs, generic drugs, and biologics for any foreseen changes, and can be submitted in the original application (OA) or through the PAS [9].

FDA evaluates and approves CPs based on the holder's prior knowledge [10] and current understanding of the product and process, the risk of proposed changes, and the fitness of the current control strategies [11]. Once the CP is approved, holders only need to submit the data through the reduced reporting category. And this data is generated per the protocols which have been approved by the agency. The preparation and submission of the comparability protocol is provided in Fig. 2. The adoption of a CP is a valuable and practical attempt for both holders (speeding up the implementation of changes and lowering reporting categories, bringing drugs to market faster, reducing regulatory non-compliance risks, etc.) and regulators (reducing the quality risk and potential drug supply risk brought by the change, reducing regulatory pressure), which can benefit both.

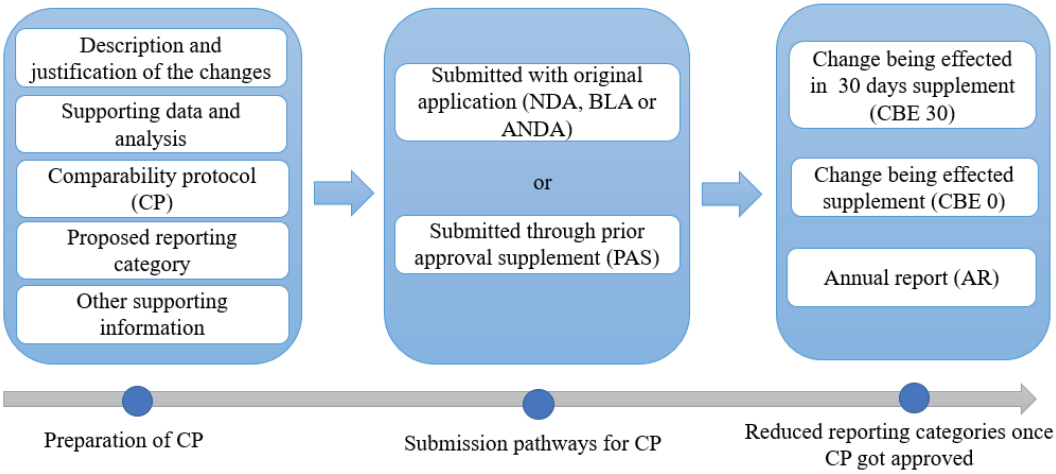

Fig. 2 Preparation and submission of the comparability protocol

The purpose of the CP is to promote innovation in production and continuous improvement of technologies to ensure patients' early access to high-quality products. The protocol emphasizes that holders should establish an efficient PQS, leverage acquired knowledge and experience about drugs and processes, and strengthen the usage of quality risk management throughout the life cycle of the drug to ensure a deep understanding of the impact of changes on product quality and efficacy. In addition to reducing the reporting category of changes, the CP also makes it possible to enhance the communication between holders and the agency. The holder can discuss the planned changes with the regulators in advance, confirm the studies and data that needed to support the changes and prove it to the agency that the changes would not bring any deleterious impact on product quality. Furthermore, it will facilitate the implementation of proposed changes and reduce potential risks.

2.2 Implementation of CPs in US

Although the final guidance was issued by FDA in 2022, two versions of draft comparability protocols were published online in February 2003 and April 2016 separately for industry's reference. In the final guidance, it also states that the comparability protocol is an equivalent concept to the PAC management protocol (PACMP) [12] listed in ICH Q12.

2.3 Applicability of CP

A good understanding of the product and process, as well as the ability to identify and assess the risks brought by the proposed changes, are

prerequisites for the approval of PCs. The holder is required to prepare comparability protocols based on prior knowledge of products and processes (publicly accessible or internally accumulated), experience in the development of drug substance and their manufacturing processes, experience in developing drug product and its manufacturing processes, experience in process validation (including process design, process performance validation, and continuous process validation) and quality risk management activities.

In general, CMC changes, such as changes in drug substance, drug production processes, quality control, equipment or facility that need to be submitted through prior approval supplement, CBE 30 filing or CBE 0 filing can be considered for submission of comparability protocols. However, some cases are not applicable to the protocols. For example, some CMC changes that have no clear scope, or changes in the formulation that cannot be evaluated by predetermined tests, studies, or methods, or acceptance criteria, or non-clinical, pharmacokinetic (PK) or pharmacodynamic (PD), and clinical trials are needed to evaluate the safety and efficacy of the changed product, or the approved labeling should modify the information on safety or efficacy, or the change of the source of the drug substance and this drug substance manufactured by the new manufacturer has not been used in any approved product. Other cases where an initial new drug (IND) application should be considered.

3 Management of PAC in China

3.1 Classification and filing pathway for PAC

PAC management [13] is an important part of drug lifecycle management, and the quality after the change is of particular concern to holders, patients and regulators.

Article 77 of the "Provisions for Drug Registration" stipulates that PACs of drugs shall be subject to categorical management according to the risk and degree of impact on the safety, efficacy and quality controllability of drugs, and shall be divided into prior approval changes, notification changes and reporting changes [14]. Pre-approval supplements are for major changes in the production process, and such changes need to be submitted to the National Medicinal Products Administration (NMPA) for review and approval, and the review timeline is 60 days. Moderate changes in the production process are supervised by the Medical Products Administration of each province, and the holder should submit the filing dossier before the implementation of the change, and the review time is generally 30 days [15]. For minor changes in the production process, the holder can first implement the changes, and then include relevant information in the annual report of the product.

3.2 Comparison of PAC management between China and US

Firstly, whether in China, Europe or the United States, the classification principles of change are based on risk, because specific changes will bring certain risks to the quality, safety and efficacy of drugs with corresponding levels of impact on patients. Therefore, there is a great similarity in classification (Table 1). However, due to the peculiarities of China's regulatory environment, it has national supervision and provincial supervision. There are great differences in communication with holders/regulators and filing pathways. In China, the major changes are approved by NMPA, and the notification and annual report categories are approved/reviewed by the provincial regulatory authorities. Segmented supervision has its regulatory advantages, such as making full use of the familiarity of provincial regulatory authorities with enterprises in their jurisdictions, strengthening management, and serving enterprises, but sometimes it is easy to have faults in management convergence. For example, when determining the reporting category of a change, if there is a dispute between the holder and the provincial regulatory authority (the two parties do not agree with each other), in accordance with Article 21 of the current "Regulations for the Administration of Post-approval Changes of Drug Products" [15], the

holder should file the submission as pre-approval supplement, and there is no further communication channel or possibility. The implementation of CPs can effectively prevent this from happening.

Table 1 Comparison of change classification between China and US

Classification based on risk	China	US
High	Prior approval (major)	PAS
Medium	Notification (moderate)	CBE 30, CBE 0
Low	Annual report (minor)	AR

3.3 Risk in the implementation of PAC

Although the "Technical Guideline for Post-approval Changes in Drug Products" has clear provisions on the classification of changes, it is not easy for holders to confirm the reporting category of changes without deep understanding of the specific product, process and the change itself. To achieve accurate classification, it is necessary for the holder to apply the concept of quality risk management, reasonably select risk assessment tools, and thoroughly analyze the proposed changes based on the data, knowledge and understanding of the product and process. Besides, the holders should reduce subjectivity and bias as much as possible in risk management activities. In this way, the source of hazards can be correctly identified, risk analysis and risk assessment can be carried out, and finally appropriate risk control strategies can be advised. Correctly identifying the risks brought by changes is a prerequisite for accurate classification of changes. If the holders define the classification of changes based on a limited understanding and submit the dossier, it is likely that the regulatory authority will deny the classification proposed by the holders and require the holders to cancel the changes which might be effective at that time. Cancelling the implemented changes or even recalling the already released products will bring great challenges to holders, patients and regulators.

4 Implications from the FDA's CP

4.1 Advantages of CP

The use of a CP has two major advantages. First, it can significantly shorten the review and approval time for relevant changes. For example, for some changes that need to be filed through PAS (generally 4−6 months), if the holder communicates the changes and the supporting data with the agency in advance through the comparability protocol and gets alignment (approval from the agency), then these changes can be reduced to moderate and reported through CBE 30 or CBE 0. The actual review and approval time for the entire change is greatly shortened, and the products involved in the change can be brought to market in time. Furthermore, since the supporting data involved in the change had been communicated through the comparability protocol, regulators and holders had agreed on the content of the study and therefore no extra study would be proposed. Without extra requirements from the regulators also help to reduce the time spent on PACs in another way. Second, it can minimize the potential regulatory compliance risk to holders when the change is implemented, as well as the safety/efficacy risk to patient medication. As the details of the changes, the data to be collected and the studies needed have been approved by the regulatory authorities, the regulatory authorities will not think that the holder has insufficient research or inaccurate classification when submitting data in the future, thus reducing the occurrence of the holder supplementing the research data or canceling the implemented changes, and minimizing the risk of regulatory compliance and quality.

4.2 Issues of PAC management in China

China's PAC supervision has particularity (see Section 3.2), because China's PAC is divided into two

parts, national supervision and provincial supervision. Only after accurately defining the change reporting category, the holder can determine the pathway for dossier submission. However, accurately determining the level of change risk and confirming the classification of change can sometimes be extremely challenging for holders. To facilitate holders to carry out PACs and ensure the accuracy of the classification, various provinces have successively issued "Notices on the Communication of Post-Approval Change Reporting Categories of Drugs", aiming to guide holders to determine categories of relevant changes that are not specified in the current guidelines, or to reduce reporting categories specified in the current guidelines [16, 17]. However, at present, there are no detailed guidelines for such communications, which cannot guide holder to make relevant communication documents. For example, Article 2 of the "Documents List for Change Category Communication" issued by the Shanghai Medical Products Administration requires holders to provide "changes (including comparison before and after changes, self-assessment conclusions, etc.)", and part 4 of Article 3 requires holders to provide "summary of research data and results of the changes in accordance with the requirements of the relevant guidelines for PACs of drugs", which is different from the specific tests and studies to be performed as listed in comparability protocol (focus on results or plans). In addition, there are no documents to illustrate how to reduce reporting categories of changes and how to communicate with national regulators for major changes that require prior approval supplement. Therefore, there is a certain basis for the implementation of comparability protocols in China, but it still needs the support of higher-level guidance documents, and the recently issued guidelines on comparability protocols in the United States provide an example for strengthening the communication of changes in China.

4.3 Suggestions for the implementation of CP in China

For the implementation of comparability protocol in China, the author put forward several suggestions for reference. First, filing/communication pathways should be established. Relevant policies can be issued by NMPA, creating prerequisites for holders and regulators to communicate about PACs, clarifying the filing or communication ways (e.g., through applicant's account, communication meeting, etc.) and submission type (e.g., through original application or supplementary application), and encouraging holders to communicate with the regulators in advance about the planned changes. Second, the relevant provisions in the "Regulations for the Administration of Post-approval Changes of Drug Products" should be revised and technical guidelines with practical guidance in detail should be issued. holders in preparing comparability protocol should be guided with specific guidelines. the circumstances in which the plan applies/does not apply should be clarified, and the technical research data or research plan that needs to be provided in this guideline must be recommended. Direct adoption of FDA's comparability protocol can also be considered, but in view of the differences between the regulatory authorities in China and the United States, special consideration should be given on setting up regulatory agencies and dispute resolution mechanisms for the communication of comparability protocol during the implementation progress. Third, social training should be strengthened. Through the organization of relevant training, more holders and regulators are familiar with and understand the content and significance of the implementation of the comparability protocol. In addition, holders should be encouraged to plan and communicate about applicable changes in advance, which enables regulators to understand the changes earlier and provide specific suggestions. Lastly, with the continuous implementation of ICH-related technical guidelines in China, it is believed that the PAC management plan (PACMP) in the technical and regulatory considerations for pharmaceutical products lifecycle management (Q12) will also provide assistance for early communication and full discussion between holders and regulatory agencies on relevant changes.

5 Conclusion

Communicating with regulators on PACs in advance through the CP and obtaining alignment can help holders reduce reporting category of change without risk and shorten the review and approval time. Because the required research and how to evaluate the impact of changes have been thoroughly discussed with the regulatory authorities before the implementation of the changes, and the potential risks and the risk control strategies to be adopted are known, the product quality can be guaranteed to the greatest extent without being negatively affected by the change. This type of flexible regulation and communication is a win-win situation for both holders and regulators, but it does not exclude the submission of some very complicated changes (such as changes that require preclinical or clinical data to evaluate) through PAS. As the quality risks brought by these changes are unpredictable or unacceptable, the FDA still recommends to file PAS instead of filing a CP. The application of CPs is also based on risks. In the PQS, the holder needs to fully predict the impact of changes combining the knowledge of products, processes and quality risk management, and adopt appropriate quality control strategies to ensure the quality and supply of the drugs after the change.

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