Classification and Technical Requirements of CMC Changes of Biological Products

Center for Drug Evaluation of NMPA
Biologics CMC Division
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I. Overview

Implementation of new laws and regulations

- Vaccine Administration Law of the People's Republic of China (Presidential Decree [2019] No.30)
- Drug Administration Law of People's Republic of China (Presidential Decree [2019] No.31)
- Provisions for Drug Registration (No.46 in 2020)
- Provisions for the Post-Marketing Changes of Drugs (Interim) (No.8 in 2021

- Risk management
- Strengthen the life-cycle management of drugs

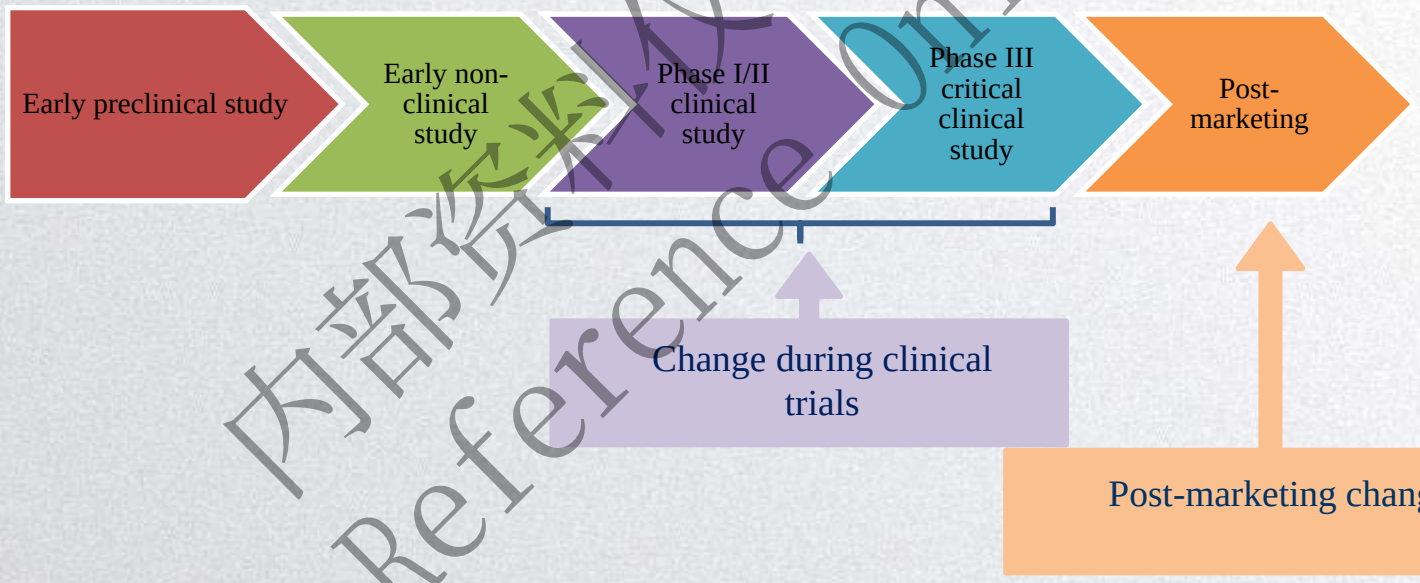
Two technical guidelines have been drafted as technical support

- Technical Guidelines for CMC Studies and Changes of Biological Products during Clinical Trials (interim), which have been submitted to NMPA for approval
- Technical Guidelines of CMC Changes of Marketed Biological Products (interim), issued

I. Overview

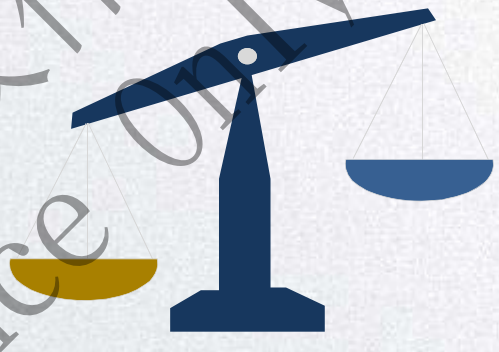
CMC change and life-cycle management of biological products

CMC changes run through the whole life cycle



I. Overview

- Risk-based change management
- Subject of liability
  - Scientific planning
  - Risk management capability
  - Platform knowledge
- Compliance
- Related changes



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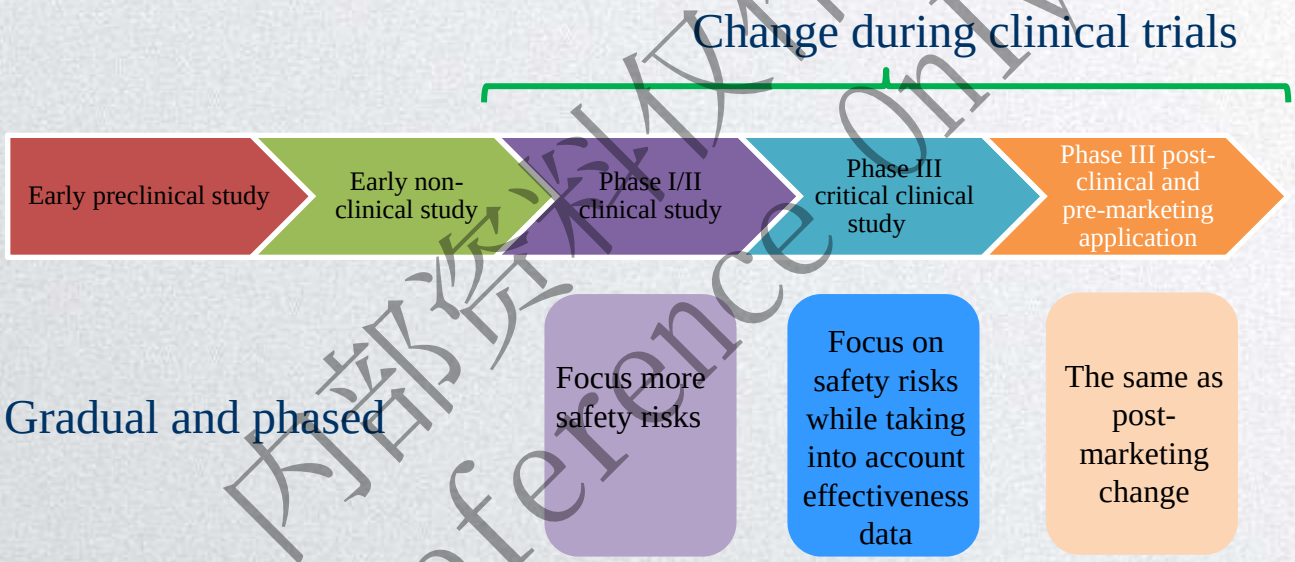
II. CMC Changes during Clinical Trials

Definition and characteristics of change during clinical trials



➢Gradual and phased

II. CMC Changes during Clinical Trials

Basic considerations for changes

- Consideration of stages
  - Complete major changes in confirmatory clinical trial stage
- Biological products of different types
  - Innovative
  - Modified
  - With similar varieties already on the market (biosimilars)
- Biological products of different categories
  - Preventive biological products
  - Therapeutic biological products

II. CMC Changes during Clinical Trials

Legal basis for the classification

- Provisions for Drug Registration: In case of any change to drug clinical trial protocol, non-clinical or CMC change or new finding during a drug clinical trial, the sponsor should fully assess the impact on the safety of subjects according to the regulations and with reference to relevant technical guidelines.

If the sponsor believes that the change has no impact on the safety of subjects upon, it may be implemented directly and reported in the Development Safety Update Report. If the sponsor believes that the change may increase the safety risk of subjects, a supplementary application should be made.

II. CMC Changes during Clinical Trials

Change classification

- Based on whether increase the risks to subject safety:
  - **Major CMC change**
  - **Non-major CMC change**
- related change
- Complexity of biological products
- Limits on recognition of innovative biological products

II. CMC Changes during Clinical Trials

Change classification

Major changes during clinical trials (examples)

- Change in production process affecting virus inactivation/removal
- Change in production process affecting impurity removal
- Major change in quality control affecting the safety
- Any new CMC information (e.g., identification of new impurity and increase of TSE risks) affecting the safety

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II. CMC Changes during Clinical Trials

Basic considerations of technical requirements

- Facilitate the previous CMC development data to support the conduct of later clinical trials on the basis of ensuring the safety of subjects and provide sufficient support for the final marketing of biological products.
- The technical requirements for comparability study are appropriate to the development stage and related to the product type.
- For any CMC change or any CMC information related to safety identified, no matter whether it is a major change, appropriate and comparability study should be carried out.
- Comparability is not equivalence, it is encouraged to improve the product quality in the development stage.

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III. Post-marketing CMC change

Basic considerations of post-marketing changes

- Changes should be based on previous studies and data accumulation
- Change comparability study is the basis and key to the success of post-marketing CMC change evaluation
- MAHs are encouraged to continuously improve and optimize the production process and continuously improve the product quality, but should prove that the change does not adversely affect the safety, effectiveness and quality controllability of the product
- MAHs can choose to use change management tools

III. Post-marketing CMC change

Legal basis for post-marketing change management

- Vaccine Administration Law of the People's Republic of China
- Drug Administration Law of the People's Republic of China
- Provisions for the Post-Marketing Changes of Drugs (Interim)

III. Post-marketing CMC change

Change classification

- According to the degree of change risks and the impact caused, changes can be divided into: major changes, moderate changes and minor changes from high to low.

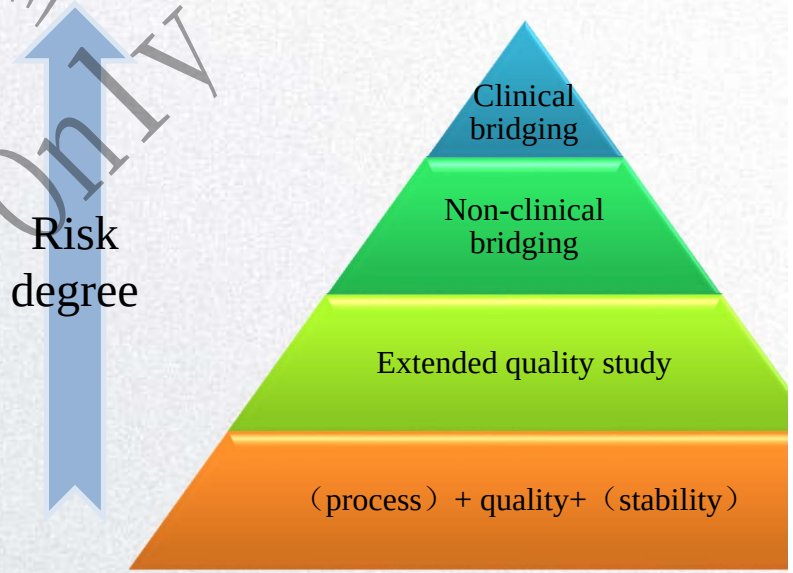
China	US	EU	WHO
Major	PAS	II	Major
Moderate	CBE30/ CBE0	IB	Moderate
Minor	AR	IA/IA_{IN}	Minor

- Related change
- Complexity of biological products

III. Post-marketing CMC change

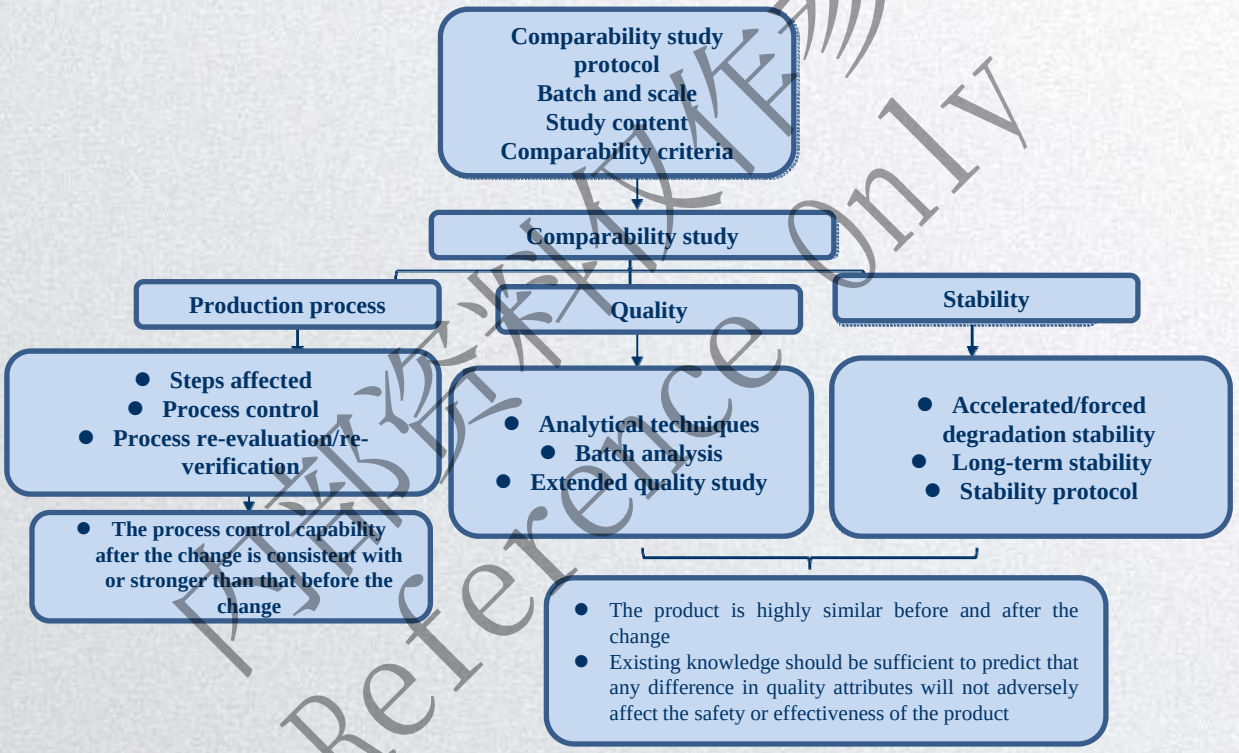
Change comparability study

- Change comparability study is the basis and key to the success of CMC change evaluation of marketed biological products
- Risk-based, data-driven comprehensive evaluation
- Comparability study is a progressive process. In addition to CMC comparability study, non-clinical or/and clinical bridging study should be included in some cases



III. Post-marketing CMC change

Technical requirements for change



III. Post-marketing CMC change

Considerations for change comparability study

- Even minor changes may affect the safety and effectiveness of products. Therefore, the risk level and classification of changes are not only dependent on the changes themselves, but also on the impact of such changes on the safety and effectiveness of products as shown in comparability studies. There must be a comparability assessment on the possible quality impact caused by changes; Rather than simply classifying the changes according to their size.
- The scope and type of non-clinical and clinical studies are determined based on the CMC study results, the cognitive level of the product, and the application of the product. Not all major changes require non-clinical/clinical bridging studies.

III. Post-marketing CMC change

Considerations for change comparability study

- If the CMC is proved to be comparable before and after the change, the limited post-change long-term stability data and approved stability study protocol can support the approval of the whole validity period.

(1) If the change basically does not affect the quality and stability of the product, the limited post-change long-term stability data and approved stability study protocol can support the approval of the whole validity period for the changed product.

(2) If the change may affect the quality and stability of the product, the corresponding period of validity should be proposed according to the long-term stability study data of the product after the change. (e.g., relaxing the restriction on/changing storage conditions, change in type or content of excipients, change in product dosage form, majors change with the CMC comparability study indicating incomparability and stability, etc.)

IV. Conclusions

- Clinical trial sponsors/MAHs should bear responsibilities for the change
- Changes during the clinical trial are gradual and phased, but should not cause adverse effects on the safety of the subjects
- Post-marketing changes should not cause adverse effects on the safety, effectiveness and quality controllability of biological products
- Implement risk-based classification of changes
- Comparability study is the key to the success of changes of biological products

Thanks for Listening