Guiding Principle Number:

Technical Guiding Principles for Pharmaceutical Change Research on Marketed Biological Products (Trial)

国家药品监督管理局

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1. Foreword This

guiding principle is mainly used to guide holders of marketing authorization for biological products (hereinafter referred to as the holders) to conduct research on pharmaceutical changes after the marketing of biological products. Post-marketing pharmaceutical changes of biological products refer to changes in production, quality control, etc. of biological products that have obtained marketing authorization. It is for the holder to continuously optimize the production process, maintain process stability and advanced control, and ensure the safety and effectiveness of biological products. and important means of quality control. Change research is the research and validation work performed on proposed changes. In order to guide holders

to carry out targeted research on pharmaceutical changes after the release of biological products, strengthen the full life cycle management of biological products, and ensure the safety, effectiveness and quality controllability of biological products after changes, according to the "Drug Administration of the People's Republic of China" This guideline is specially formulated for the relevant provisions and requirements of the Law, the Vaccine Administration Law of the People's Republic of China, the Measures for the Administration of Drug Registration, the Measures for the Supervision and Administration of Drug Production, and the Measures for the Administration of Post-Market Changes of Drugs (Trial).

This guideline aims to explain from a technical perspective the basic ideas and focus of research on changes in registration management matters for biological products after they are launched on the market. It is applicable to preventive biological products, therapeutic biological products and in vitro diagnostic reagents managed as biological products. Since

biological products are complex and diverse, even if the same change is made, the risks will be different under different circumstances. The holder needs to conduct change research based on the product characteristics and the actual change, and fully evaluate the impact of the change on the safety, effectiveness and quality of already-marketed biological products. The regulatory impact will be affected, and supplementary applications, filings or reports will be made in accordance with relevant regulations. The requirements for each specific research work can be found in the promulgated technical guidelines related to biological products.

Preventive vaccines (hereinafter referred to as vaccines) are widely used in healthy people and involve major public health issues. It is recommended that holders fully evaluate and plan for post-marketing changes in advance to minimize unexpected risks caused by changes.

For post-market changes to biological products such as vaccines and cell therapy products, in addition to conducting research with reference to these guidelines, any other regulations and technical requirements should also be followed.

This guideline only reflects the current scientific understanding of biological products. As scientific research progresses, relevant content will be continuously improved and updated. When applying this guideline, you should also refer to the relevant requirements of relevant guidelines such as the International Conference on Harmonization of Technology for the Registration of Pharmaceuticals for Human Use (ICH).

2. Basic considerations

(1) Subject Responsibility and Continuous Compliance

Holders are the subjects responsible for post-market change management of biological products, undertake the full life cycle management obligations of biological products, complete the continuous research work on biological products, and ensure that biological products meet current technical requirements after they are launched on the market. The holder should establish a post-market change control system for biological products in accordance with the relevant requirements of drug regulatory laws and regulations, and be responsible for all post-market pharmaceutical change research, self-evaluation of research results, and ongoing dynamic change management of biological products.

Strict implementation of Good Manufacturing Practices (GMP) and effective Pharmaceutical Quality Management System (PQS) are prerequisites and necessary conditions for implementing post-market pharmaceutical changes of biological products. On this basis, the holder should strictly implement the company's internal change procedures to ensure that the production process continues to comply with regulations, and ensure that the production and inspection of biological products are organized in accordance with the approved production process and quality standards.

(2) Change risk assessment and management Post-

marketing pharmaceutical changes of biological products will bring different potential risks due to different characteristics of biological products, different change matters, and different degrees of change. Therefore, the holder must have sufficient knowledge accumulation and the ability to identify, assess and manage risks. When implementing changes, the holder shall proactively design change plans based on risks, and conduct sufficient research and necessary verification. In addition to assessing the potential risks of the change itself, risk assessment should also consider the uncertain risks associated with implementing the change.

Research on post-marketing changes to biological products should be based on research and data accumulation during the previous product registration stage and the actual production process. The more systematic and in-depth the research work is, the more sufficient the data accumulated during the production process will be, and the more helpful it will be for the study of pharmaceutical changes after the release of biological products.

The holder is encouraged to continuously improve and optimize the production process and continuously improve product quality, but it should be proved that the changes will not have an adverse impact on the safety, effectiveness and quality controllability of the product. Change management tools can make the implementation of post-market changes to biological products more planable, predictable and transparent, enabling strategic planning and efficient management of post-market changes to biological products. Holders can freely choose to use change management tools, such as Established Conditions (ECs), Post-Approval Change Management Protocols (PACMPs), Product Lifecycle Management (PLCM), etc. The specific implementation methods and requirements for change management tools will be stipulated in another document.

(3) Change comparability study

Conducting change comparability studies is an important step in the evaluation of pharmaceutical changes after the marketing of biological products.

foundation and key to success. The strategy and scope of the comparability study should be determined based on the changes and categories, the expected impact of the changes on the product, and the assessment of the potential impact of the changes on product safety and effectiveness. Through a series of comparative and comprehensive assessments of the production process, quality and stability data of relevant products before and after the change, we determine whether the changes are comparable before and after. Changing the comparability study is a progressive process. In addition to conducting pharmaceutical comparability studies, it should also include non-clinical or/and clinical bridging studies in some cases. The key considerations for pharmaceutical comparability research are as follows:

1. Research samples and comparability acceptance criteria In

order to support major pharmaceutical changes after the launch of biological products, comparability research samples should generally include at least three consecutive batches of commercial-scale production products after the change. If the number of study batches is reduced (using the bracketing method, matrix method, etc.), or the scale of the study is reduced (except for changes to increase the scale), sufficient justification should be provided based on science and risk assessment.

Comparability acceptance criteria are not the same as quality criteria. Acceptance criteria for comparability should be set based on historical data on process and product quality, and any exclusion of data should be justified. Typically, comparability acceptance criteria are more stringent than quality criteria. For quantitative verification projects, appropriate statistical tools should be used to develop comparability acceptance criteria. For product quality attributes not included in the release criteria (e.g., extended physical, chemical, and biological characteristics, etc.), data from early process development, expanded process research, and validation can be used to formulate acceptance criteria. If for some reason, the pharmaceutical data before the change are missing and the comparability acceptance criteria cannot be determined, necessary non-clinical and/or clinical studies should be considered.

2. Process comparability research

Process comparability research is mainly to compare the process steps, process parameters, process control results and historical data in the batch production process after changes. In addition to comparing process control parameters in conventional production, necessary additional process control parameters should also be compared, paying attention to the comparability of the removal capabilities of relevant substances, impurities and exogenous factors in the production process before and after the change.

For pharmaceutical changes in biological products that affect the production process and process control, post-change production process verification should be carried out to confirm the robustness and batch-to-batch consistency of the process. If there is evidence that a simple change has no impact on subsequent process stages, or on intermediates produced in subsequent steps, validation can be limited to the affected process steps.

Careful consideration should be given to the potential impact of proposed changes on subsequent steps and related process control parameters. If necessary, corresponding intermediate controls should be strengthened on the changed process. It should be confirmed that the process and intermediate products before and after the change are comparable, and that the process control capability after the

change is not lower than before the change. 3. Quality

and stability comparability studies Quality comparability can be studied by comparing the results of batch release and extended characterization with historical data. If changes to the stock solution will affect the formulation, data on both the stock solution and the formulation should be collected to support the conclusion of comparability. For multi-component biological products (such as combination vaccines, etc.), consideration should be given to whether process changes in one component will have an impact on other components. Attention should be paid to the applicability of detection methods, etc. For changes that may introduce new process impurities, it should be confirmed that existing methods can detect impurities that may appear in the products after the change.

Stability studies can detect subtle differences that cannot be detected through conventional quality analysis, and conduct stability comparability analysis of products before and after changes.

Helps evaluate the impact of changes on product quality. Stability comparability test plans should be formulated scientifically. Accelerated and forced degradation stability tests can help determine the degradation trend of the product and are a powerful tool for direct comparison of products before and after process changes. If changes to the original solution may affect the stability of the preparation, forced degradation and/or accelerated stability comparable studies and long-term stability investigations should be conducted on both the original solution and the preparation. When conducting stability studies in accordance with the relevant requirements put forward in this guideline, consideration should be given to whether the research work and research results can fully reflect the stability changes of the drug after the change. If necessary, it is necessary to increase the research batches or extend the research time. For some minor changes, if it is confirmed that the change does not affect stability based on full evaluation, it may not be necessary to conduct a stability study on the change. If the changes are proven to be comparable, full-validity approval can be supported based on limited post-change long-term stability data and post-

approval stability study protocols.

4. Comparability bridging study If the production process, quality and stability studies of the products before and after the change are sufficient to prove comparability, there is no need to conduct non-clinical and/or clinical studies on the changed product. However, when the relationship between a specific quality attribute and safety and efficacy has not been established and differences in quality attributes of the product before and after the change are observed, non-clinical and/or clinical bridging or confirmatory studies should be performed. The manner and extent of non-clinical and/or clinical research should be combined with the results of pharmaceutical comparability, the level of knowledge about the properties of the product, completed relevant non-clinical and/or clinical research data, and the use of the drug, and be analyzed based on specific issues. determined by the principles. It is encouraged to carry out change research through pharmaceutical and non-clinical methods. If comparability cannot be proven on this basis,

further consideration should be given to clinical research. Certain changes that may have a significant impact on biologics, su

For major batch changes, changes in key excipients of special preparations, etc., non-clinical and/or clinical bridging studies should be considered.

(4) Related changes

Pharmaceutical changes after the marketing of biological products often do not occur independently. One change may be accompanied by or trigger other changes, which is called an associated change. For example, changes in the production site may be accompanied by changes in production equipment and production processes, and changes in existing pharmaceutical excipients in prescriptions may be accompanied by or trigger changes in drug quality standards. Related changes need to be researched separately with reference to each change requirement, and an overall change comparability study must be carried out, and classified according to the highest change category. When multiple lower-risk changes are related, it may increase the risk of the overall change. It is recommended to pay attention to the superimposed impact of multiple related changes on drug safety, effectiveness, and quality controllability.

(5) Changes in excipients and packaging materials

This guidance covers post-market changes to excipients and packaging materials for biological products, and Changes in suppliers of excipients and packaging materials. For excipients and packaging materials production process changes, changes in quality standards, etc. that may affect their quality and thus affect biological products, registrants of excipients and packaging materials and holders of biological products should follow the "State Food and Drug Administration's Notice on Further "Announcement on Improving Matters Related to Drug-related Review, Approval and Supervision" (No. 56, 2019) stipulates that change research and change management should be carried out.

3. Change Classification

Changes are classified according to the degree of risk and impact that pharmaceutical changes may have on the safety, effectiveness and quality controllability of biological products. According to the degree of risk and impact, they are divided into: major changes, medium changes, minor changes from high to low.

Even.

For major changes, it is necessary to prove through a series of studies that the changes will not have an adverse impact on the safety, effectiveness and quality controllability of the product; for moderate changes, it is necessary to prove through corresponding studies that the changes will not affect the safety and effectiveness of the product. , and does not reduce the quality controllability of the product.

If there are moderate changes and minor changes associated with major changes, they should be stated together when submitting the major change application. There are minor changes associated with medium changes and should be stated when submitting a medium change request.

Post-market changes to biological products may be made based on relevant management regulations, technical review or The review requires timely production site inspection, standard review or sample inspection.

4. Communication

Due to the complexity and variety of pharmaceutical changes after the marketing of biological products, this guideline cannot list all changes one by one. Holders are encouraged to follow the relevant requirements of the "Measures for the Management of Post-Marketing Changes in Drugs (Trial)" and communicate through communication channels on the expected marketed changes. Communicate with the corresponding drug regulatory authorities and technical units on key technical issues regarding pharmaceutical changes to marketed biological products that are not covered by the guiding principles such as the category of pharmaceutical changes to biological products, comparability plans and research content to support the change, and post-marketing change management plans, especially for Significant changes that affect the quality of biological products.

5. Common change categories and technical requirements for biological products

This chapter gives examples of common pharmaceutical changes to biological products. Based on science and risk, it defines the categories of specific changes, the prerequisites and basic technical requirements that need to be met, and tries to make them as consistent as possible with international biological products. Post-marketing pharmaceutical change guidance harmonization. If all prerequisites for the corresponding change are not met

case, the change should belong to a higher category until all prerequisites are met (e.g.

If all the prerequisites for a moderate change are not met, the change shall be classified as a major change.

Even). This guideline directly involves drug registration approval documents and their attachments.

Minor changes to the matters or contents stated in the document shall be managed according to the filing requirements (such as

Minor changes in registration standards should be managed according to filing).

In order to facilitate declaration, this guideline covers the pharmaceutical changes of various common biological products.

The updated items are marked with the Common Technical Document (CTD) chapters they involve to connect with the CTD

declaration.

(1) Original solution (3.2.S)

A. Expression vector, seed batch and cell bank

Main content of change matters	Prerequisites	Reference Category	Technical Requirements
Expression vector	Expression vector change ÿ	Major ÿ Major ÿÿÿ Moderate	1-14
seeds for production Batch and cell bank ÿ 3.2.S.2.3 ý	New master seed batch	ÿÿ Moderate ÿÿÿ Minor	1,5-11,13,14
		5,13	1,5-10,13,14
	New job seed batch		1,5-11,13,14
	new master cell bank	Major	1,5-11,13,14
		ÿÿÿ Medium	1,5-10,13,14
	New working cell bank	ÿÿ Medium	1,5,6,11,13,14
		ÿÿÿ Tiny	5
	Bacterial (toxic) species/cell bank Cryoprotectants	ÿ small	1,13
	change seed lot/cell bank quality Standard changes	ÿ small	1,11

Prerequisites:

ÿ Neither the target gene nor the host cell has changed.

ÿ If it is a biological product for preventive use, the new main seed batch should be produced by the previously approved

Produced from the original seed lot or from an approved master seed lot.

ÿThe new master seed batch/new master cell bank shall be composed of the previously approved original seed batch/cell bank.

from a cell bank or an approved master seed lot/master cell bank. ÿNew working seed batch/new

working cell bank shall be obtained from the previously approved main seed batch/

Master cell bank preparation.

ÿThe number of new working seed batches/new working cell bank generations shall not exceed those previously approved

Generations.

ÿ The preparation method remains unchanged, and the quality standards for seed batches/cell banks are tightened or unchanged.

ÿOnly the

animal-derived components contained in the working cell bank, such as newborn bovine blood, are removed

clear.

ÿAdd new testing items or tighten acceptance standards to comply with pharmacopoeia and other national

Relevant internal and external norms and guiding principles.

ÿThe passage number of the new master seed batch/new cell bank does not exceed the approved passage number.

Technical requirements:

1. Explain the reason for the change. Detail the content, basis and advantages of the changes. 2. Explain the name,

origin, structure and genetic characteristics of the expression vector. Describe the carrier composition and function. When using

special carriers with limited knowledge at present, the application in human body should be explained, and its safety and advantages of use

should be evaluated.

3. Detailed description of expression vector construction and screening methods. Are the enzyme digestion identification results

correct? Provide sequencing color pictures of the nucleotide sequences inserted into the control regions at both ends of the gene and expression

vector, and compare and explain whether the results are consistent with the designed (theoretical) sequence. If gene manipulation is performed

on an expression vector, the expression regulation status of the introduced auxiliary gene (such as GFP), the residual amount of the expression

product, and the potential impact on the safety and effectiveness of the product should be evaluated. 4. Describe in detail the introduction of

the recombinant expression vector into

the host cell (bacteria) and the

Long screening and confirmation methods. Based on risk, analyze the status of the target gene and related control elements in the host cell (whether integrated into the chromosome), copy number, and genetic stability after the host and vector are combined. Methods and expression levels used to initiate and control the expression of target genes in host cells.

5. The preparation, management and verification of seed batches and/or cell banks should comply with the "Regulations on the Management of Bacteria (Viruses) for the Production and Verification of Biological Products" and/or the "Regulations on the Preparation and Verification of Animal Cell Substrates for the Production and Verification of Biological Products" in the Pharmacopoeia and other related requirements. If applicable, describe in detail the seed batch/cell bank passage process, preparation method, preparation scale, etc. Provide complete test reports for seed batches/cell banks.

6. Clarify the storage locations, methods and conditions of seed batches/cell banks at all levels. If relevant, provide passage stability study data for the seed batch/cell bank. Analyze and determine the maximum allowable number of doubling generations or passages in the large-scale production process.

7. Conduct process verification for three consecutive batches of commercial production-scale stock solution and preparation (if it affects the preparation). Confirm the suitability of the seed batch/cell bank through the consistency of consecutive batches of products, and prove that the risk of contamination and variation by exogenous factors can be avoided. For seed batches of multivalent vaccine intermediates, the holder can appropriately reduce the research batches (using bracketing method, matrix method, etc.), or use reduced scale to conduct research, but should Have sufficient basis. 8. Except for special requirements, provide the results of commercial production scale stock solution and preparation (if it affects the preparation) under acceleration and/or degradation conditions for at least 3 months before and after the change (or until it is unqualified). Provide stability study data under real-time/actual conditions for at least 3-6 months before and after the change of commercial production scale stock solution and preparation (if it affects the preparation), or until it is unqualified. Accelerated and/or forced degradation of stock solutions and formulations before and after changes (e.g. impact on formulations) and real-time/actual conditions

Comparability studies were conducted on the stability under different conditions. The data before the change can be the historical stability test results.

9. Develop a stability research plan. Long-term stability studies continue to be conducted to confirm shelf life/expiry of the bulk solution and formulation (if affected). Commitment to report nonconformities arising from long-term stability studies. 10. When the pharmaceutical comparability study data are insufficient

to support the comparability change, non-clinical and/or clinical bridging studies should be conducted, or foreign research data should be available to evaluate and ensure the safety and effectiveness of the changed product, or provide a basis for exemption. . 11. If involved, update the seed batch/cell bank quality standards. Provide variations

Basis and inspection results of sub-batch/cell bank quality standards.

12. If involved, clarify the source and characteristics of the bacterial (virus) species. 13.

Carry out comprehensive testing of the final production generation and/or super-production final generation seed batches/cell banks, including testing of the genetic stability and microbial contamination of cells and bacterial (virus) strains during production. The testing results should comply with the " "Chinese Pharmacopoeia" and other relevant international guidelines.

14. Provide quality comparability studies before and after the change of three consecutive batches of commercial production-scale raw solutions and preparations (if it affects the preparations).

B. Changes in culture media and raw materials for

production	Main content, prerequisites, reference categories, technical requirements			
medium ÿ3.2.S.2.3ÿ	Ingredient changes		Major 1-11,15,17,18	
		ÿÿ	medium	1-7,9,10,11,15, 18
		ÿÿ Minor 1,6, 16 Major 1-8,15,17,18		
Materials of animal origin (3.2.S.2.3)	source change		Medium 1,3-7,15,18 ÿÿ/ÿÿ	
		ÿÿ	Minor 1,2,6,8,11,15,16	
		Major 1,3-7 ,15,17,18 medium		
Materials of non-animal origin (3.2.S.2.3)				
		ÿÿ		1,3-7,15,20

		ÿÿÿÿ ÿÿÿÿ	small	1, 6,7,15,16
Inspection of raw materials for production defined projects and standards ÿ3.2.S.2.3ÿ	Reduce items/put wide standard		medium	1-3,5
		ÿÿ ÿÿÿ	small	1,2,16
	Add items/abbreviate tight limit			1
		Mediumÿÿÿÿ Tiny		1
Human blood produced overseas albumin raw material plasma ÿ3.2.S.2.3ÿ	Pulp collection station/testing location Address addition/replacement	ÿ Medium		12-14
	of pulp collection station/testing Address reduction		small	
	introduces virus markers Detection of objects	ÿ	major	19

Prerequisites:

ÿChanges in key components, such as adding, removing, replacing, increasing, decreasing,

Supplier changes.

ÿDoes not affect the key quality attributes of the product.

ÿ Changes in non-key components, such as adding, removing, replacing, increasing, subtracting

Few, suppliers change.

ÿReplace with materials of non-animal origin, such as raw materials derived from tissue or plasma.

More recombinant products, replacing animal sources with plant sources, etc.

ÿReplace with animal-derived materials that meet pharmacopoeia standards, such as newborn calf serum, etc.

ÿThe detection of virus markers is introduced because it has a significant impact on virus risk assessment.

Measurement.

ÿNon-culture medium components. Structural complexes such as polyethylene glycol (PEG) and fatty acid chains

Miscellaneous production raw materials are excluded.

ÿFor example, change from A salt to B salt with a similar mechanism of action; or do not change

Substance types only change suppliers.

ÿ Changes in raw material standards do not cause the quality standards of the raw liquid to exceed the approved

Scope and Limits.

ÿThe changes in raw material standards have not caused the changes in impurities in the raw solution to exceed the approved range and limits, and no new impurities have emerged. ÿThe test items

are reduced due to inapplicability. ÿThe change is not related to

recurring deviations or stability concerns in production. ÿ Changes in testing items will not affect the key quality attributes

of the product (such as purity, impurities

quality, key physical and chemical properties, etc.).

ÿExcept for testing items of human raw plasma. ÿThe new/replaced

human blood plasma collection station has been approved in the country of origin, and the raw plasma collection method will not change.

ÿ Remove antibiotics from production according to pharmacopoeia requirements. Technical

requirements: 1.

Explain the reasons for the change. Clarify the source of raw materials used for production, changes in active ingredients before and after changes, and quality similarities and differences. Provide quality verification reports and evaluate the quality and stability of raw materials for production in conjunction with verification reports of key raw materials. If changes to analytical methods are involved, methodological verification/validation needs to be carried out.

2. If involved, evaluate the safety of viruses of animal or human origin materials. Bovine-derived substances should have a certificate of origin from an epidemic-free area, conduct a TSE safety risk assessment, and comply with relevant national regulations and the "Guidance Notes on Minimizing the Risk of Transmission of Animal Spongiform Encephalopathy through Human and Veterinary Medical Products" (EMA). Encourage the use of recombinant products to replace animal-derived raw materials to minimize product safety risks.

3. Conduct process verification for three consecutive batches of commercial production-scale stock solution and preparation (if it affects the preparation). Conduct process control and product quality comparability studies before and after changes. Prove the original solution and preparation before and after the change (if it affects the preparation)

Comparability.

4. If involved, revise the quality standard of the original solution and conduct testing on the new analysis method.

Learn to verify.

5. Except for special requirements, provide the results of accelerated and/or degradation conditions for at least 3

months before and after the change of commercial production scale stock solution and preparation (if it affects the preparation)

(or until it is unqualified). Provide stability study data under real-time/actual conditions for at least 3-6 months before and after

the change of commercial production scale stock solution and preparation (if it affects the preparation), or until it fails. Conduct

comparability studies on accelerated and/or forced degradation and stability under real-time/actual conditions before and after

changes to the bulk solution and formulation (if affecting the formulation). The data before the change can be the historical

stability test results.

6. Raw materials for production should meet production needs and comply with the "Quality Control Procedures for

Raw Materials and Excipients for the Production of Biological Products" in the "Chinese Pharmacopoeia" and relevant

international guidelines. 7. In

principle, the use of toxic and harmful materials to the human body should be reduced as much as possible during

the production process. When it must be used, the removal effect of the subsequent process should be verified, unless the

verification results indicate that the residual amount of process-related impurities is far lower than the specified requirements, or

there is evidence to prove that the residual amount is within the acceptable range of the human body. This should usually be

done during preparation calibration or appropriate testing. The intermediate product control stage sets the verification items for this residue.

8. If involved, research should be carried out with reference to relevant international technical guidelines.

research, provide a biosafety assessment or statement.

9. Conduct culture medium suitability inspection tests to analyze and verify the impact of changes in culture medium

components on active ingredients.

10. The production medium must not contain substances that may cause adverse reactions in the human body.

Penicillin or other beta-lactam antibiotics should not be used. If it involves replacing a medium containing animal-derived components with a medium with a clear chemical composition, attention should be paid to the impact of the medium on growth curves, products, etc.

11. If involved, the trypsin used to digest cells should be proven to be free of exogenous or endogenous viral contamination. Unless otherwise specified, eggs used for the preparation of chicken embryos or chicken embryo cells should come from specific pathogen free (SPF) flocks. The use of antibiotics and preservatives during the production process should comply with the relevant requirements of the Chinese Pharmacopoeia.

12. Raw plasma should not be collected from people at high risk of blood infectious diseases. Provide the prevalence of confirmed positive seroconversions among new plasma donors for at least 6 months at the raw plasma collection center (based on the number of plasma donors and the number of blood donations) and the prevalence of confirmed positive seroconversions among new plasma donors. Study statistics. Provide review and inspection quality review and risk assessment data for raw plasma. 13. Have complete

information and qualification certificates of the pulp mining organization. There are contract documents between the production enterprise and the pulp supply organization. Products produced overseas should have proof that the raw plasma comes from non-mad cow disease-affected areas/countries. The collection, inspection, storage and transportation of raw plasma should comply with relevant regulations.

14. An information exchange system should be established with the plasmapheresis station to exchange information in a timely manner when situations arise. A traceability system for raw plasma should be established to ensure that each raw plasma can be traced back to the donor, and can be traced back to the raw plasma collected during at least the quarantine period before the last plasma collected by the plasma donor, or the plasma donation. staff's blood samples. The plasma donor will no longer donate plasma after a certain plasma donation, and his blood sample can be used for testing. Only when the plasma donor is qualified can the raw plasma before the quarantine

period be released. 15. If applicable, develop a stability study plan. Continue to conduct long-term stability studies to confirm the storage time/availability of the stock solution and formulation (if it has an impact on the formulation)

Validity period. Commitment to report nonconformities arising from long-term stability studies.

16. If applicable, conduct process validation of at least one batch of commercial production scale stock solution and preparation (if it affects the preparation) (such as the batch size covers regular production, the production process meets the predetermined process control standards, the product meets the quality standards, etc.) and conduct Comparison of process control and product quality before and after changes. Demonstrate the suitability of the raw materials from both sources and the comparability of the bulk solution and the dosage form (if affecting the dosage form). 17. If involved, provide non-clinical and/or clinical research data, or possess foreign research data, to evaluate and ensure the safety and effectiveness of the changed product. Otherwise, the basis for exemption must be provided. 18. If applicable, conduct genetic stability studies through cell passage. Analyze and determine the maximum number of cell doublings or passages allowed during commercial scale production. At the end of the production cycle, monitor the characteristics of the host cell/vector system, such as cell viability, plasmid (target gene) copy number, exogenous factors, restriction endonuclease digestion patterns, target gene expression levels, and nucleic acid sequencing analysis, etc. , confirming the genetic stability of the cells (bacteria) during production. Provide comprehensive testing data of exogenous factors in the final generation of production.

19. Provide reasons for changes and supporting data. 20. For changes involving chemical drug raw materials, the relevant review requirements for raw materials shall be followed. Please provide relevant materials.

C. Main content of production site, scale and process

change matters, prerequisites, reference category technical requirements				
Production site (3.2.S.2.1)	Change production plant/factory/ production line		Major 1-18, 21	

		ÿÿÿ Medium		1-6,8,10,13ÿ16ÿ 17
Production scale ÿ3.2.S.2.2ÿ	Fermentation culture scale changes Even		major	2-10,12-15,18, 21
		ÿÿÿÿ ÿÿ	medium	2-10,13,14
	Purification scale change		Major 2-9,12-15,18,21	
		ÿÿÿÿ ÿ	medium	2-9,13,14
microbial fermentation or cell culture process ÿ3.2.S.2.2ÿ	critical process changes		major	2-11,13,14,18, 20,21
	Non-critical process changes	ÿÿÿ Medium	2-11,13,14,20	
		ÿÿÿÿ ÿÿÿ	Tiny 2,8,9,11,13,19	
Separation and purification chemicals Art (3.2.S.2.2)	Critical process changes (e.g. For example, virus removal work technical ability or raw liquid miscellaneous Mass spectrometry has a major impact changes)		major	2-9,11,13,14, 18,20,21
	Non-critical process changes	ÿÿÿ Medium		2- 9,11,13,14,18,20
		ÿÿÿ ÿÿ	Tiny 8,9,11,13,18,19	
Other process steps ÿ3.2.S.2.2ÿ	Major changes in key steps 2-11,13,14,21			
	Non-critical step changes ÿÿÿ Medium 2-6,8-11,13,14			
Production process equipment ÿ3.2.A.1ÿ			major	3-10,12-15,18, 21
		ÿÿ Medium		3-6,8,10,12- 15,18
		ÿÿ tiny		8,12,13,15,18, 19

Prerequisites:

ÿ The new production plant/factory/production line is to produce raw liquids of approved similar products.

production site.

ÿ Production line duplication (excluding substantial changes in production technology and/or process control). ÿThe new production plant/factory/production line is under the same quality control as the current production plant Quality assurance/quality control (QA/QC) system. ÿThis change will not affect the effectiveness of the virus removal and/or inactivation process. ÿ No new impurity peak appears. The product does not exceed approved limits for impurities. ÿ The number of passages remains unchanged or the number of passages is within the approved limit. ÿ Changes will not affect the purification process. ÿThe quality of the original solution does not exceed the approved standard range and limits. ÿThe fermentation scale is changed, but the same bioreactor is still used. ÿThe amount of production raw materials changes linearly with the scale; the process parameters are still approved within a quasi-range or linearly with scale.

ÿThe change is not related to recurring deviations or stability concerns in production. ÿThe quality should not be adversely affected, and it is more suitable for commercial scale production.

Produce.

ÿ After changing the equipment, the process parameters shall not exceed the verified range. Does not reduce sterility levels/microbiological limits.

ÿEquivalent equipment (equivalent equipment has similar design, the same operating principle, and is manufactured with the same or higher grade product contact materials. Equivalent equipment should provide the same quality products as those processed by the previous equipment.) Replacement of existing equipment. Non-production process related equipment, equipment changes that do not affect the production process and registration information are managed in accordance with GMP. ÿEquipment changes will not affect other equipment. The materials or operating principles of the equipment in contact with the original solution before and after the change will not change.

Technical

requirements: 1. Explain the reasons for the change. A detailed description of the change in production site, including the name (full name), address (specific to the factory/workshop, production line, geographical location, etc.) and functions of the production plant. 2. If

involved, clarify whether there have been any changes in equipment and production raw materials (grades, verification methods, quality standards), production scale and processes, quality standards (analysis items, methods and limits), packaging materials and containers in direct contact with drugs, etc. Pay attention to the matching of the performance, working principle, production capacity, etc. of the production facilities and equipment with the production process before and after the change. If relevant, provide supporting information.

3. Conduct production process verification for three consecutive batches of commercial production scale raw solutions and preparations (if it affects preparation quality). Analysis of the batch size (whether it is consistent with the design production capacity) and the representativeness of the production process (for example, whether it can cover the range of conventional production scale) should be clearly verified. Process validation should include analysis of continuous production batches meeting their predetermined process control standards and quality standards; analysis and verification of the impact of the process on the types and contents of product-related impurities; when necessary, the verification content may also involve verification of virus inactivation/removal effects , verification of the storage time of intermediate products, research on the service life of filter membranes and

chromatography media, etc. 4. Develop a plan for changing the comparability study. Except for special requirements, quality analysis and research (identification, biological activity, purity, impurities, contamination, etc.) should be carried out on at least three batches of original solutions and preparations at commercial production scale after the change (if it affects the preparations), and compared with the data before the change. Comparability studies.

5. Except for special requirements, provide the results of accelerated and/or degradation conditions for at least 3 months before and after the change of commercial production scale stock solution and preparation (if it affects the preparation) (or until it is unqualified). Provide commercial production scale stock solutions before and after changes to

Less than 3-6 months of stability study data under real-time/actual conditions, or until it is unqualified. Conduct comparability studies on accelerated and/or forced degradation and stability under real-time/actual conditions before and after changes to the bulk solution and formulation (if affecting the formulation). The data before the change can be the historical stability test results. If involved, transport stability studies should be performed. 6. Develop a stability research plan. Post-approval long-term stability studies will continue to confirm the shelf life/expiry

date of the bulk solution and formulation (if affected). Commitment to report nonconformities arising from long-term stability studies.

7. When pharmaceutical comparability study data are insufficient to support changes in comparability, non-clinical and/or clinical bridging studies should be conducted to confirm comparability. Otherwise, the basis for exemption must be provided.

8. Describe in detail the reasons for the change and the specific changes (production equipment, process routes, production process control, acceptable range, etc.). A comprehensive study should be conducted on changes in the raw solution production process, and the impact on the quality of the raw solution should be analyzed based on risk assessment. (or have an impact on the quality of the drug product) and describe the rationale for classifying the change as major, moderate, or minor. 9. Provide production process flow diagram,

indicating process steps and process control parameters,

Display material joining link. Briefly describe the proposed production process. Clarify the fermentation process model, scale, process, process and process parameters, and process control requirements (microbial contamination monitoring, cell density and dissolved oxygen, etc.). Describe the purification process flow, process and process parameters (such as medium, buffer, eluent, flow rate, packing capacity, peak closing conditions, etc.), and process control requirements (such as recovery rate, etc.).

10. If the change leads to a change in generation, end-of-production exogenous factor detection and genetic stability should be carried out in accordance with the requirements of the Chinese Pharmacopoeia and other relevant international guidelines.

Qualitative research. Bacteria/yeast should be tested for purity of bacteria/yeast at the end of production and total number of viable bacteria. 11. If

involved, provide information and evidence that there are no potential risks of BSE/TSE in the production of raw materials, such as the name of the supplier, the species and organization from which the raw materials come, the origin of the animal, and the usage. The use of organic solvents and the regulations on residual limits during the production process should be strictly in accordance with the provisions of the "Chinese Pharmacopoeia" and ICH "Residual Solvent Determination Method", avoid using the first type of solvents, and limit the use of the second type of solvents. If organic solvents or other substances are used for extraction, purification or inactivation, the subsequent purification process should ensure that the organic solvents or other substances in the product can be effectively removed, and the removal process should be verified. 12. If involved, clarify the information about the equipment to

be changed, and carry out the settings before and after the change.

Comparison of similarities and differences in equipment operating principles and key technical parameters.

13. If involved, describe the production process and process control information in detail. Make changes

Comparison of before and after technology and process control.

14. If involved, fully verify the production process and/or equipment after the change,

Including verification of aseptic production and sterilization processes.

15. If involved, the feasibility of shared equipment in contact with the product should be confirmed and

Describe the specific cross-switching procedure.

16. When necessary, animal safety, animal safety, and

Effectiveness assessment.

17. Blood product production plants should be able to ensure the prevention of cross-over after verification.

Multi-product production without contamination should in principle be an independent building and use dedicated production facilities and equipment.

18. Where involved, single-use systems should have supplier quality assurance/quality

measurement system and core verification documents. Holders should validate single-use systems in conjunction with biologics production, including aspects such as chemical compatibility, adsorption capacity, bacterial challenge, particulates, extractables and/or leachables. If the types and contents of extractables and/or leachables change from before the change, the impact of this change on the production process (including downstream processes) and products should be further evaluated, and the newly emerged extractables and/or leachables should be studied. Will the substance interact with the drug?

19. Confirm the production process of at least one batch of commercial production scale raw solutions and preparations (if it affects the quality of the preparations) (such as the batch size covers regular production, the production process meets the predetermined process control standards, the products meet the quality standards, etc.), and conduct Comparison of process control and batch analysis data before and after changes.

20. If involved, conduct a risk assessment of contamination by external factors or contamination by bacteria. estimate.

21. When necessary, conduct special safety tests (involving allergies, hemolysis and vascular stimulation, etc.).

D. Main contents of process control

change matters		Prerequisite Reference Category	Technical Requirements
Process control parameters and scope (3.2.S.2.4)	Replace process control parameters and range limits	major	1-4,7,10ÿ 11,12,
		ÿÿ Medium ÿÿÿÿ Tiny	1,2,3,7
		ÿÿÿ	1,5,7
	Delete process control parameters and range limits	major	1,2,7,10ÿ 11,12,
		ÿÿÿ Medium and tiny	1,2,7
		ÿÿ ÿÿÿÿ	1,5,6,7
	widen range limits	major	1,2,3,7,10ÿ 11,12,
		ÿÿÿ medium ÿÿÿÿ tiny	1,2,3,7
			1,5,6,7

		ÿÿ		
	Add process control parameters and scope limits	ÿÿ Medium	ÿ ÿÿ	1,2,3,7
		ÿ	small	1,5,7
	Tighten range limit	ÿ ÿÿ ÿÿ	small	1,7
	Change process control/inspection site land	ÿÿÿÿ ÿÿÿ	small	1,8
design space	Establishment of new design space	Significant expansion of approved		1,9
	design space	Significant reduction of approved design space ÿÿ Minor		1,9
				1,9

Prerequisites:

ÿ Does not involve safety and quality issues.

ÿThe change is not related to recurring deviations or stability concerns in production.

ÿUse pharmacopoeia testing methods or other verified testing methods.

ÿThe new detection method does not belong to the biological/immuno/immunochemical method or the The method is not a method for detecting biologically active substances using biological reagents (not including pharmacopoeial microbiological testing methods).

ÿThe detection method is still the same, or the changed detection method is inferior in accuracy, The accuracy, specificity and sensitivity are better than the original detection method.

ÿThe quality of the original solution does not exceed the approved scope and limits.

ÿProcess control parameters do not affect the key quality attributes of the product.

ÿThe impurities do not exceed the approved range.

ÿ Have sufficient historical data to support deletion or relaxation of process control on products No substantial impact.

ÿThe changes in process control parameters do not exceed the approved range limits.

skills requirement:

1. Explain the reasons and sufficient basis for the change.

2. Provide process control and batch analysis data for three consecutive batches of commercial production-scale stock solution and preparation (if it affects the preparation), and perform comparability analysis on the data before and after the change.

3. If involved, provide updated raw solution quality standards, including calibration items and analysis methods. If applicable, provide updated analytical methods and methodological validation information.

4. When the inactivation/removal of viruses is involved in the production process, the specific steps and parameters of the inactivation/removal process should be determined and the process verified to ensure the inactivation/removal effect.

5. Confirm the process of at least one batch of commercial production scale raw solutions and preparations (if affected) (such as the batch size covers regular production, the production process meets the predetermined process control standards, the product meets the quality standards, etc.), and perform process control before and after changes Compare with batch analysis data.

6. Prove that the process control parameters will not affect the critical quality attributes of the raw solution. have an impact.

7. Detail the changes to the production process control parameters and scope. If applicable, compare the production process control parameters and scope before and after the change.

8. Detail the change information of relevant parts. 9. Provide

comparative information on the design space before and after the change. Provide research data to support establishing or changing the design space, including release of sterile product changes to process parameters. Provide a sufficient description of the risk assessment tools and findings used to establish the design space.

10. Except for special requirements, provide the results of commercial production scale stock solution and preparation (if it affects the preparation) under acceleration and/or degradation conditions for at least 3 months before and after the change (or until it is unqualified). Provide commercial production scale stock solutions before and after changes

At least 3-6 months of stability study data under real-time/actual conditions, or

Until unqualified. For the original solution and preparation before and after the change (if it affects the preparation)

Accelerated and/or forced degradation and stability under real-time/actual conditions can be

Comparative research. The data before the change can be the historical stability test results.

11. Develop a stability research plan. Continued post-approval long-term stability

Research to confirm the shelf life/expiry date of the stock solution and formulation (if affected).

Commitment to report nonconformities arising from long-term stability studies.

12. When pharmaceutical comparability study data are insufficient to support changes to comparability,

Animal safety trials and/or clinical bridging studies are required. If you apply for exemption,

There should be sufficient reasons and basis.

E. Quality control

Main content of change matters	Prerequisites	Reference Category	Technical Requirements	
Test items and standard limit (3,2.S.4.1)	Delete test items and/or standard limit		Major	1-4
		ÿ	Moderate	1-4
	Change release check to process control		major	1-5,13
		ÿ	small	1-5,13
	Added inspection items and regulations	ÿÿÿ	medium	1,2,4,5,12
	The standard limits are determined according to the domestic and foreign pharmacopoeia versions caused by updates or additions Standard revision	ÿ	medium	3,4,6,7
	lower (relax), adjust Standard Limits		major	1-4
	Raising (Tightening) Standards limit	ÿÿÿ Medium		2,3,4,12
Test method (3.2.S.4.2)	Analysis method replacement		major	1,2-6,8-10, 12-14
		ÿ	Medium 2,5,6,8,12,	
	Analyzing from within the company	ÿ	Medium 2,6,8,12,13,14	
	Method changed to pharmacopoeia analysis method Law	ÿÿÿÿ ÿ	medium	2 ,6,8,12

	Improved acceptance criteria for analytical	ÿ	small	8
	methods Testing methods for plasma viral markers	ÿ Moderate		2,5,8,13,14
Testing site (3.2.S.2.1)	Substituting changes in testing sites related to biological activity		Major	11
		ÿ Moderate		11
Standard/reference product ÿ3.2.S.5ÿ	See Preparation Standards/Reference Materials			

Prerequisites: ÿ The

deleted items are redundant in the quality standards of the original solution. The original solution itself did not undergo any changes. Changes in standards should not cause a reduction in product quality control levels. ÿ Adding test items to the

standard due to changes in pharmaceutical properties does not fall within the scope of such changes. Usually adding inspection items, increasing the limit range or improving the specificity of inspection methods can better control and ensure product quality. The newly added testing items do not belong to biology/immunology/immunochemistry testing methods or methods for testing biologically active substances using biological reagents (excluding pharmacopoeial microbial testing methods).

ÿThe changed standard limits should be consistent with the relevant official standards and/or relevant technical guidelines, and the changed standard limits should not exceed the approved range. ÿThe change does not correspond to

deviations that occur repeatedly during production (such as unqualified new miscellaneous materials). impurities, or the total amount of impurities exceeds approved limits) or stability concerns.

ÿ The additional inspection items are not due to the generation of new impurities, and the tightened limits should be within the recognized or approved acceptance limits (for example, Class 3 residual solvents are within the ICH limits or within the scope of pharmacopoeia requirements).

ÿ After the method is changed, the standard limits are still within the approved standard limits.

Inside.

ÿThe analysis methods are the same, or based on the same technology and principles (such as changing color

column length or temperature rather than a different column or method) and no new impurities were detected.

ÿThe changed analytical method maintains or improves the analytical precision, accuracy, specificity and sensitivity. ÿThis change

does not involve activity or potency testing. ÿThe changed

method is the same as the original method or has a stronger guarantee. Or change one test method under the same test item in the Pharmacopoeia to another test method. No changes in biological activity detection methods are involved. ÿThere is no

change in the analysis method.

ÿThe detection method has the same or higher detection sensitivity and specificity. The window period remains the same or is

shortened. ÿ Changes in testing sites related to the biological activity of biological/immunological/ immunochemical methods, but do not involve laboratory animal

testing. Technical

requirements: 1. Explain the reasons for the change and provide

supporting evidence. 2. If involved, update the raw solution quality standards, including verification items, limits and method. Compare old and new quality standards.

3. Detailed evidence to maintain quality and production process consistency. Changes to standard limits need to be based on calibration data of historical batches of products. Explain the reasons and details of the changes to the original solution standards and process controls (if involved). May control product quality Changes that have an impact on the system (such as relaxing standard limits, deleting some test items, changes involving biological activity/immunogenicity, etc., or changing the precision, accuracy or specificity of the method, etc.) should be comprehensively analyzed to prove that the changes will not Cause a reduction in product quality.

4. In principle, the registration standard shall not be lower than the requirements of the Pharmacopoeia, and shall not be lower than the requirements of similar products on the market. The acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, Class 3 residual solvents are within ICH limits or within the scope of pharmacopoeia requirements). Quantifiable quality standards should set specific limits.

5. If applicable, describe the new analytical method in detail and evaluate the new analytical method. scientific verification or provide materials proving the applicability of new analytical methods.

6. For existing pharmacopoeia methods, the analytical method should be confirmed before being used for the first time. recognize.

7. Compare the standards before and after the change. Provide the basis for standard changes. Examine the applicability of the updated pharmacopoeial version to the original solution. Quality standards with quantitative indicators should set upper and lower limits.

8. Prove that the proposed analytical method is equivalent to or better than the approved

one. 9. If involved, prove that test animal test results before and after the change are comparable. Animals used for testing should have health certificates. The animals used should comply with relevant regulations on microbiological and parasitological testing requirements for experimental animals.

10. Unless otherwise specified, experimental animals should be animals of clean grade or above. Accurate chemical, physical or cellular methods can be used to replace animal testing for quality verification of biological products. 11. Explain the reasons for the change. Detail the change of verification site information,

including name (full name), address (specific to the factory/workshop) and functions, etc. Provide support methods

Technical information on transfer of

learning. 12. If relevant, use revised methods and/or criteria to evaluate stability study results. Commit to continue to conduct long-term stability testing using the revised method and/or standard to ensure that the revised method is suitable for monitoring the stability of the original solution during storage

changes, and the stability of the original solution during storage can meet the post-change standards.

13. If relevant, provide the verification results using the new method and/or batch release of the commercial production scale stock solution, and compare the data before and after the method change. 14. If the changed method detects new impurities or the impurity content increases, the historical batch samples should be tested to confirm that the change in impurities is due to the increased sensitivity or selectivity of the changed method.

F. Main contents of direct contact materials and container changes

during production, prerequisites, reference categories, technical requirements, changes in disposable liquid storage				
bags, packaging materials and containers, filter membranes, etc.			medium	1-7
		ÿ	small	1,3,8

Prerequisites:

ÿ The equivalent of disposable liquid storage bags, packaging materials and containers, filter membranes, etc. before and after the change (including transfer stability studies, etc.). Changes do not increase extractables/leachables risk. The packaging materials, containers, and filter membrane sterilization processes remain unchanged. Technical requirements: 1.

Explain the content and basis of the change. 2. If involved, update the quality standards (including analysis methods) of direct contact drug packaging materials and containers, explain the basis of the standards, and change the standards or verification methods.

Comparison of laws.

3. If involved, provide details on updated packaging materials and containers (such as appearance, composition, etc.). Demonstrate suitability of packaging materials and containers (e.g. extractables/leachables checks). 4. If involved, transport stability studies need to be conducted. Provide comparative data on product production process control and batch release verification before and after changes. If involved, a quality study of the original solution expansion is required to demonstrate the impact of changes in direct contact materials and containers on intermediate products.

There is no impact on the product or stock solution.

5. If involved, change disposable liquid storage bags, containers, and filter membranes that are in direct contact with each other.

etc., should undergo compatibility studies and risk assessments.

6. Except for special requirements, use at least three batches of packaging containers to be changed to carry out stable packaging

Qualitative study, providing commercial production scale dope and formulation before and after the change (e.g.

agents have an impact) for at least 3 months under accelerated and/or degrading conditions (or do

until unqualified). Provide commercial production scale stock solution for at least 3-6 months after the change

Stability study data under real-time/actual conditions, or until unqualified. right

Acceleration and/or enforcement of dosing solutions and formulations before and after changes (e.g. impact on formulations)

Degradation and stability under real-time/actual conditions were studied for comparability. before change

The data can be the historical stability test results.

7. Develop a stability research plan. Long-term stability studies continue to

Confirm the storage time of the original solution (or intermediate product). Commitment to report on long-term stability

Failures that occurred during the study.

8. If involved, conduct batch production process confirmation (such as batch size covering conventional

Production and production processes comply with predetermined process control standards, and products comply with quality standards

etc.), and compare the process control and batch analysis data before and after the change.

G. Storage conditions and storage period

Changes	Main content, prerequisites, reference categories, technical requirements			
Storage period (3.2.S.7.1& 3.2.S.7.3)	extend		Medium 1,2,3,4,6 8,9,10	
		ÿ ÿÿÿ	small	1,2,3,4,10
	shorten			1,2,3,4
		ÿ	medium tiny	1,4,7
storage conditions (3.2.S.7.1& 3.2.S.7.3)	Changes in storage conditions		Major 1-4,6,8,9,10	
		ÿ	Medium 1-4,8,10	
		ÿÿ	small	1,4,5
			medium	1,2,4,6,7

Stability study protocol (3.2.S.7.2)	Changes to post-approval stability study protocols or stability study commitments	ÿÿ tiny		1,4,7

Prerequisites: ÿ The

packaging materials and containers in direct contact with the intermediate product and raw liquid have not been changed,

Or change to direct contact packaging materials and containers of the same material.

ÿThe existing long-term stability data covers the proposed storage period/validity period, and the stability data comes from at

least three batches of commercial production-scale intermediate products and stock solutions. ÿAccording to the approved stability study

protocol at the time of registration (or during the initial validity period

Stability data obtained under the storage conditions at the time of approval).

ÿ No significant changes were observed in long-term stability studies. ÿThe change in storage

period is not related to recurring deviations or stability concerns in production. ÿTighten the storage conditions within the

proposed

temperature range. ÿ There are no major changes to the plan (such as changes

in methods, deletion of testing items, reduction of monitoring points, etc.). ÿThe relevant parameter ranges in the changed

stability scheme are more stringent (such

as adding

monitoring points, etc.).

Technical requirements:

1. If applicable, formulate storage conditions and storage period. 2. Clarify the

sample information for the stability study, indicating the sample batch number and production date.

Period, storage container.

3. Complete stability studies under real-time/actual conditions for at least three batches of commercial production-scale

intermediates or stock solutions covering the proposed storage period. If it involves changes in the storage conditions or shelf life of

intermediate products, it should be proven that the storage conditions of the intermediate products have changed or the validity period has changed.

After the storage period is extended, it will not affect the quality indicators of the materials used in the next process or the quality of the original solution (such as the analysis results of three batches of commercial batches).

4. If involved, update the stability research plan. 5. If involved, continue with the original solution and preparation (if it affects the preparation) Long-term stability studies to confirm the storage time/validity period of the original solution and preparation. Commitment to report nonconformities arising from long-term stability studies.

6. If the analytical method changes, the new analytical method should be described in detail and methodological verification should be carried out. Demonstrate that the new analytical method is comparable to or superior to an approved analytical method. 7. Detail the basis for the stability study plan after the change is approved. 8. In principle, raw solutions and intermediate products should enter subsequent processing steps according to the continuous production process. When temporary storage is required while waiting for verification results, appropriate storage methods and conditions should be selected, degradation products, polymers, etc. that may affect safety and effectiveness should be verified and acceptable standards should be formulated.

9. If involved, conduct relevant transport stability verification studies, including in extreme Stability studies at extreme temperatures, etc.

10. Commit to using the original solution at the end of the storage period to be changed to prepare the preparation, and complete long-term stability research data covering the full validity period of the preparation. (2) Preparations **(3.2.P)**

A. Specification

changes	Main content, prerequisites, reference categories, technical requirements,			
Injection specifications change (3.2.P.1)	concentration changes		Major 1-9,11,12,15 Major	
	volume change		1-9,11,12,15 ÿÿÿ Moderate	
		1-5,7,8,11,12 Major 1-12,15		
	Change to new packaging format/delivery device			
		ÿ	Medium 1,5-8,10,11,12	

Changes in specifications for solid dosage capsules (3.2.P.1)	Changes in weight of enteric solvents (or active units)		Major 5,7,8,9,11,14	
	Changes in weight of non-extended-release solid oral dosage forms	ÿÿ Medium		5,7,8

Prerequisites:

ÿ There are no major changes in the production

process. ÿThe approved indications, usage and dosage, and applicable groups remain unchanged.

ÿThe drug delivery device is not in direct contact with the preparation (such as an injection aid for pen refill administration).

pen), the altered device improves durability and precision of drug delivery.

ÿThe preparation formula (composition and dosage of excipients) and preparation process have not changed. ÿThe

dissolution curves are equivalent. The weight change is due only to the capsule weight change and the gum

The capsule is not a critical factor in the release mechanism.

ÿThe materials and types of packaging materials and containers that are in direct contact with the product have not changed

Even.

skills requirement:

1. Describe the specific content of the change in detail. Provide the necessary, scientific and

Reasonable basis.

2. When applicable, detail the composition information of the new batch of prescriptions. Provide the basis for

determining the new batch of prescriptions, including literature information, research information, whether the stabilizers,

buffers, and excipients in the prescription have an impact on the safety and effectiveness of biological products. The batch

prescription should list all ingredients used in the production process of the preparation, the dosage of each ingredient in each

batch, including excess dosage, as well as the source and quality standards of each ingredient. 3. If involved, the process flow

should be clear and the steps

through which the sample enters the process should be shown. Provide semi-finished product preparation methods,

key process parameters and process control scope. Prepare

The process description should reflect the "point preparation" concept. Batch size should be specified. Conduct large-scale production process research and detail new processes and packaging operations that directly affect product quality. 4.

Comprehensively carry out risk-based production processes and product quality before and after the change is comparable sex research.

5. If involved, revise the quality standards. Detail the analytical method and perform necessary methodological validation. 6. Detail packaging materials

and container information. Where relevant, conduct studies on packaging materials and container closure integrity. If the type of packaging materials and containers in direct contact changes, preparation stability studies and packaging material compatibility studies should also be carried out.

7. Except for special requirements, provide the results of commercial production scale preparations under acceleration and/or degradation conditions for at least 3 months before and after the change (or until they are unqualified). Provide stability study data of the commercial production scale formulation under real-time/actual conditions for at least 3-6 months before and after the change, or until it fails. Conduct comparability studies on accelerated and/or forced degradation of the formulation before and after changes and stability under real-time/actual conditions. The data before the change can be the historical stability test results. For multi-dose products, a commitment should be made to provide stability data during the final use period of the preparation after the change, to prove the quality consistency of the changed product during actual multiple uses. After the preparation specification (concentration, volume) is changed, it may be impossible to support the approval of the full validity period with limited post-change stability study data. Stability study data of the post-change preparation that can cover the proposed validity period should be provided to support the full validity period. Approval of validity period. 8. Confirm the validity period of the preparation under normal storage conditions through long-term stability studies, and commit

to reporting any unqualified conditions that occur during long-term stability studies. 9. If applicable, further non-clinical and/or clinical bridging should be considered

Research, or have foreign research data, to evaluate and ensure that the quality, safety and effectiveness of the product after the change are not reduced. Otherwise, a basis for exemption should be provided.

10. Changes to the drug delivery system device should be made based on the characteristics of the drug delivery device. Studies have demonstrated consistent dosing accuracy before and after the change.

11. Conduct process validation of three consecutive batches of commercial production scale formulations. It should be clearly verified whether the batch size is consistent with the designed production capacity and a representative analysis of the production process should be performed (e.g., whether it can cover the range of conventional production scale; whether it can represent the worst process conditions). Verification should include analysis of successive production batches as meeting their predetermined process control limits and quality standards. 12. If involved, revise the relevant content of the drug instructions and packaging labels. 13. Explain the reason for the change and the specific change situation (such as production equipment, production process control methods, standard limits, etc.), and detail the complete production process and process control situation after the change. Batch inspection is conducted according to the current quality standards, and the standard revision is limited to the appearance of the preparation. Compare the dissolution/release behavior of the formulation on at least one batch of pre- and post-change samples. 14. Compare the dissolution/release behavior of the preparations before and after the change of the three batches of samples. 15. If involved, injections should undergo special safety tests (involving allergy, hemolysis, local irritation, etc.). If the dosage of excipients exceeds the commonly used range, there may be certain safety concerns, and corresponding toxicological studies should be conducted or relevant literature should be provided to prove that the dosage is safe.

B. Preparation excipients and adjuvants

Changes in	Main content: Change	Prerequisite	Reference Category	Technical Requirements
preparation excipients (excipients,	the composition or concentration of excipients in the prescription		Major	1-12,14,16,18

Stabilizer, anti-Corrosion, conditioning agent) (3.2.P.4)ÿ	Replace or introduce potential TSE Risky excipients		Major 1-12,14,16,18	
	Replace original excipients		major	1-5,7,8,11,14ÿ 16,18
		ÿ	Medium 1-5,7,8,14	
	Remove excipients		Major 2-5,7,8,11,13,18	
		ÿ	Medium 2-5,7,8,11,13,18	
	Add/replace excipient suppliers		major	1,2,7,8,9,13,14, 16,17
		ÿ ÿ Medium 1,2, 7,8,9,13,14		
		ÿÿÿ	small	1, 9,14
Adjuvant ÿ3.2.Pÿ	Source of		Major 3,5,7,8,11,15,16	
	adjuvant concentration, production process, etc.	ÿ Medium		3,5,7,8,15

prerequisites:

ÿThe safety level and quality standard requirements for excipients after the change shall not be lower than the current requirements Excipients. Changes in excipients will not affect the safety and effectiveness of the preparation.

ÿ Remove the ingredients that are not allowed to be used according to the Chinese Pharmacopoeia or should be avoided as much as possible. Antibiotics, preservatives and other ingredients. And it will not affect the product quality after removal, and it will not be used for manufacturing. adversely affect the safety and effectiveness of the agent.

ÿ Inorganic salts, sucrose and other auxiliaries with simple preparation process and relatively stable physical and chemical properties materials and will not result in changes to the final formulation.

ÿThe excipient supplier is an approved pharmaceutical excipient supplier, or has been registered and For suppliers with status A, if the excipients are not associated according to relevant regulations To declare, an explanation is required.

ÿThe adjuvant type is aluminum adjuvant, and there are no major changes in the production process. The process parameters do not exceed the verified range, and the quality characteristics do not change due to process changes. Variety.

skills requirement:

1. Certification materials for excipients, related declaration information for excipients or explanation that no related declaration is required. Excipients with potential TSE risks should provide documentation proving that they are free of TSE risks. Suppliers who provide excipients should provide verification reports on excipients. For excipients for which internal control standards are formulated, the original quality standards, proposed internal control standards, basis for establishing internal control standards, and inspection reports should be provided. In principle, the excipients of preparations should comply with the relevant provisions of the "Quality Control Regulations for Raw Materials and Excipients for the Production of Biological Products".

2. Explain the role of excipients in the formulation. Excipients with pharmacological activity should generally not be used in preparations. If excipients with certain pharmacological activity are used, the dosage at which they show pharmacological activity should be clearly defined, and their dosage should be controlled within this dosage range. Preservatives should be added in the smallest amount within the effective antibacterial range. For multi-dose products, use an effective preservative based on the potential for contamination during use and the recommended maximum time of use after opening. When antibiotics are used in the production process, antibiotic residues should be detected during finished product testing.

3. If applicable, provide information such as preparation formula, batch formula, production process, control of key process steps and intermediate products, and process verification summary. If the key production process and process control change, provide process control information of key production process steps and intermediate products, and compare the current process with the proposed production process control process. 4. If involved, make necessary revisions to the quality standards.

Due to interference from excipients, etc. or the generation of new impurities, the analytical method should be revised and methodological verification/confirmation should be carried out. 5. If applicable, conduct production verification of three consecutive batches

of commercial production scale. Conduct process and quality comparability studies on the preparation and original solution before and after the change (if it affects the original solution). Focus on inspecting the key properties of the preparations such as impurities, purity, and activity after the change

Whether the quantitative

attributes are comparable. 6. For excipients of human or animal origin, viral safety assessment and risk assessment of exogenous factors (such as the impact on virus clearance studies or BSE/TSE risks) should

be conducted. 7. Except for special requirements, provide the results of commercial production scale preparations and stock solutions (if it affects the stock solution) under acceleration and/or degradation conditions for at least 3 months before and after the change (or until they are unqualified). Provide stability study data under real-time/actual conditions for at least 3-6 months before and after the change of the commercial production scale preparation and stock solution (if it affects it), or until it fails. Conduct comparability studies on accelerated and/or forced degradation of the formulation before and after changes and stability under real-time/actual conditions. The data before the change can be the historical stability test results. For multi-dose products, a commitment should be made to provide stability data during use at the end of the validity period of the changed preparation to prove the quality consistency of the changed product during actual multiple uses. If the formulation of the preparation is changed due to changes in excipients or adjuvants, it may be impossible to support the approval of the full validity period with limited post-change stability study data. Stability study data of the post-change preparation that can cover the proposed validity period should be provided. To support the approval of the full validity period.

8. Commit to conducting long-term stability studies to confirm the validity/storage time of the preparation and stock solution (if involved) under normal storage conditions, and commit to reporting any unqualified conditions that occur in the long-term stability studies.

9. Update excipient quality standards and compare with before change. 10. If

involved, describe in detail the basis for formulating excipient quality standards (e.g., demonstrate the applicability of pharmacopoeia monographs in controlling excipients and their potential impact on the preparation)

sex). New analytical methods are detailed and methodologically validated. Batch analytical data for excipients used in commercial production scale batches are provided.

11. When pharmaceutical research data are insufficient to determine comparability, further non-clinical and/or clinical bridging studies should be conducted, or foreign research data should be available to evaluate and ensure the safety and effectiveness of the changed product. Otherwise, the basis for exemption must be provided.

12. If involved, provide the proposed excipient analysis method and relevant methodological verification data. 13. Explain the

reasons for the change. 14. Conduct

comparative analysis on the quality of excipients before and after the change.

15. Explain the reason for the change. If involved, provide information on the evaluation of exogenous factors in the adjuvant before and after the change; provide quality control information on the raw materials used for adjuvant production before and after the change; provide adjuvant production process flow charts before and after the change, clarifying the adjuvant production process steps, key process parameters and processes Control Strategy. Provide process verification data for three consecutive batches of adjuvants, comparative study data on adjuvant quality before and after changes, and comparative study data on stability. Revision of adjuvant quality standards.

16. If necessary, conduct special safety tests (involving allergies, hemolysis and

vascular stimulation, etc.).

17. Provide corresponding information on excipients in accordance with the review and approval requirements

for excipients. 18. If involved, revise the relevant content of the drug instructions and packaging labels. C. Main

content of production site, scale and process changes,

prerequisites, reference category technical requirements				
Production site (3.2.P.3.1)	Changes to preparation manufacturing plants/factories/production lines (including preparation/filling and direct contact with pharmaceutical packaging)		major	1-8, 11, 12, 15,16

		ÿÿÿÿ ÿÿ	medium	1,3-6,8,11,15, 16
	Produced in approved pharmaceutical products Add packaging line/ Labeling line	ÿÿ Tiny		1,8,15,17
preparations (preparation/ filling) scale (3.2.P.3.2)	enlarge		major	1,3-8,11,12ÿ 15,16
		ÿÿÿÿ Medium	1,3-8,15,16	
Process procedures and steps Step (3.2.P.3.3.)	Changes in process steps (including including preparation, filling and freezing etc.)		major	1,3-9,11,12,13,15
		ÿÿÿ Mediumÿÿ		1,3-9,15
		ÿÿ•21	small	8,14
	Add new steps		Major 2-6,8,11,12,15	
		ÿÿ Medium		2-6,8,15
	Operation sequence adjustment		major	3-6,8,11,12, 15,16
		ÿ Medium		3,4,8,15
	Reduce open operations or hands Work procedure steps		small	8,14,15
process control Parameters and ranges (3.2.P.3.4)	Relax process control Scope, delete process Process parameters and range		Major 3,5,6,8,9,12	
		ÿÿÿÿ Mediumÿÿ		3,5,6,8,9,
		ÿÿÿÿÿ	small	8,9,14,18
	Compact process control Parameters and control ranges	ÿ ÿÿÿÿ •18	small	8,9,14
	Replace process control Parameters and ranges		Major 3,5,6,8,9,12,13	
		ÿÿ Mediumÿÿ		3,5,6,8,9
		ÿÿÿÿ ÿÿ	small	8,9,14,18
	Increase process control Parameters and ranges	ÿ		3,8,9
		ÿÿÿÿ	medium tiny	8,9,14

Production process equipment (Including one-time equipment) (3.2.A.1)			major	1,3-7,11,12, 15,16
		ÿ ÿ •19	medium	1,3,4,7,11,15,16
		ÿÿ ÿ Tiny		1,7,14,16
design space	Create/extend new design space between		major	10
	Reduce approved design Space	ÿ	small	10
	process parameter release		major	10

Prerequisites:

ÿThe new production plant/factory/production line is under the same quality assurance control as before the change/ Quality control (QA/QC) system.

ÿThe prescription composition, production process and preparation quality standards have not changed.

ÿ Packaging materials, containers and storage conditions have not changed.

ÿExecute the same, verified production process before and after the change.

ÿThe site uses a production site that has been previously approved for the production of the same category of products. production site, and use the same filling process/equipment to produce the same series of products.

ÿThe equipment used before and after the change remains unchanged or equivalent.

ÿThe reason for changing the production process and/or process control is only due to batch changes. Even.

ÿIt does not involve safety and quality issues, and the changes do not occur repeatedly in production. bias or stability concerns.

ÿThe sterility level/microbial limit level of the preparation will not be affected. If the preparation process There is a virus inactivation\removal process in it, which should not affect the virus removal/inactivation process.

ÿ If a sterilization and filtration step is added, and the added step will not cause the product (such as Antigen) quality changes.

ÿChange the order in which ingredients are added to liquid dosage forms (except for vaccines).

ÿ There is sufficient historical data to support deletion or relaxation of process control that has no impact on the product. substantial impact.

ÿProcess control parameters do not affect key quality attributes (such as content, impurities, etc.). ÿThe impurities in the preparation

do not exceed the approved range. ÿThe quality of the preparation

does not exceed the scope and limits of the approved quality standards. ÿ Use the testing methods

specified in the Pharmacopoeia or other verified methods. ÿ The new detection method does not involve

changes in biological/immunological/immunochemical detection methods or biological active substance detection methods using biological reagents (excluding pharmacopoeial microbial detection methods).

ÿThe detection method is still the same, or the changed detection method is better than the original detection method in terms of precision, accuracy, specificity and sensitivity.

ÿThe materials or operating principles in contact with the preparation will not change. Changing the device will not affect other devices. ÿ Equivalent equipment (equivalent

equipment has similar design, the same operating principle, and is manufactured with the same or higher grade product contact materials. Equivalent equipment should provide the same quality products as the products processed by the previous equipment.) Replacement of existing equipment. Equipment changes related to non-production processes and equipment changes that do not affect production processes and registration information are managed in accordance with GMP. •21 After the change, the process

parameters cannot exceed the verified range. Technical requirements: 1. Explain the reason for

the change and

provide a specific description of the change. If involved, provide the name (full name), address (specific to the factory/workshop, production line) and responsibilities of the production and inspection plant involved in the change; the production facilities and equipment after the change

working principle, production capacity, etc.

2. Clarify the production raw materials and auxiliary materials (manufacturer, grade, verification method, quality standards), equipment, preparation technology (process method, parameters, filling method/volume, etc.) and scale (batch), quality standards (test items, standard limits) and analytical methods), pharmaceutical packaging materials and containers, etc. have been changed. If relevant, provide supporting information. 3.

Conduct process validation of three consecutive batches of commercial production scale preparations. Clearly verify whether the batch size is consistent with the design production capacity and conduct a representative analysis of the production process (for example, whether it can cover the range of conventional production scale; whether it can represent the worst process conditions). Verification shall include analysis of successive production batches as meeting their intended process control and quality standards. If applicable, verify the virus removal effect; verify the filling and freeze-drying process; verify the aseptic process, etc.

4. Provide a change comparability research plan. Provide research data on process and quality comparability before and after

changes. 5. Except for special requirements, provide the results of commercial production scale preparations under acceleration and/or degradation conditions for at least 3 months before and after the change (or until they are unqualified). Provide stability study data of the commercial production scale preparation under real-time/actual conditions for at least 3-6 months before and after the change, or until it fails. Conduct comparability studies on accelerated and/or forced degradation of the formulation before and after changes and stability under real-time/actual conditions. The data before the change can be the historical stability test results. For multi-dose products, a commitment should be made to provide stability data during use at the end of the validity period of the changed preparation to prove the quality consistency of the changed product during actual multiple uses. If involved, transport stability studies should be performed.

6. Develop a stability research plan. Long-term stability studies continue to

Confirm the expiration date of the preparation. Commitment to report nonconformities arising from long-term stability studies.

7. If involved, update the equipment information and provide comparative information on the similarities and differences in the operating principles and key technical parameters of the new equipment and the replaced equipment. Validate or revalidate the device. If involved, provide leaching/extraction study information for the equipment. 8. Provide comparative information on process parameters and control measures before and after changes. 9. If involved, describe in detail the changes to process control parameters and scope and their basis. If applicable, detail any new analytical methods and perform methodological validation. 10. Provide research information to support the establishment or change of design space. 11. If necessary, conduct special safety tests (involving allergies, hemolysis and vascular stimulation, etc.).

12. When pharmaceutical research data are insufficient to determine comparability, further non-clinical and/or clinical bridging studies, or foreign research data, should be considered to evaluate and ensure the safety and effectiveness of the changed product. Otherwise, the basis for exemption must be provided.

13. If involved, update the quality standards of the preparation, including testing items, classification analysis method. If applicable, provide updated analytical methods and methodological validation information.

14. Carry out process validation for at least one batch of commercial production scale preparations (for example, the batch size covers conventional production, the production process meets predetermined process control standards, and the product meets quality standards, etc.), and compare process control and batch analysis data before and after changes.

15. If involved, provide process flow description. Revise key production process steps Information on step and intermediate product control strategies.

16. If involved, the feasibility of shared equipment in contact with the product should be confirmed and Describe the specific cross-switching procedure.

17. Provide production technology, process control, and process verification data for secondary packaging and product batch analysis data. If involved, transport stability studies should be performed.

18. Prove that the process control parameters will not affect the critical qualities of the biological product. Quantitative attributes have an impact.

D. Diluent

Changes	main content	Prerequisite Reference Category Technical Requirements		
Thinner	Diluent process changes			1-6
		Medium ÿÿ Slight Medium		1,2,5
	Replace or add diluent sources		ÿÿ	1-6
		Slight Increase diluent		1,2,3,5
	filling line ÿÿÿ Slight			1,3,5

Prerequisites:

ÿ Refers to water for injection or buffered saline solution, that is, it does not contain active ingredients; And the composition of the diluent has not changed.

ÿ It has no significant impact on the quality of the preparation after reconstitution.

ÿPackaging materials and containers remain unchanged.

ÿThe newly added diluent filling line is equivalent to the approved filling line.

skills requirement:

1. Explain the reason for the change. Draw up a production process flow chart to indicate the process steps, Process control parameters and raw and auxiliary materials used, showing the material adding process. simple Describe the production process.

2. If applicable, develop diluent quality standards.

3. Carry out batch release verification for three consecutive batches of diluents after the change, and compare them with those before the change. Comparability analysis of historical data.

4. Use new diluents to study the reconstitution stability of the product.

5. The diluent for reconstitution of freeze-dried products should comply with the provisions of the Pharmacopoeia. If the Pharmacopoeia does not

Inclusion, technology and standards should be fully demonstrated.

6. Conduct stability assessment during use, that is, reconstitute the preparation and inject it into the dilution bag

Post-stability (for intravenous injection).

E. Quality control

Changes	main content	Prerequisite Reference Category Technical Requirements		
Test items and standard limit ÿ3.2.P.5ÿ	Delete test items and/or standards limit		Major 1,2,3	
		ÿ	small	1,2,3
	Add new test items and regulations	ÿÿÿ	small	1,2,4,5,14
	The standard limits are determined as the domestic and foreign pharmacopoeia versions are updated. New or supplemented standards change	ÿ	small	6,7
	Change the description method of traits	ÿ	small	1,2
	Lower (relax), adjust standards limit		Major 1-4	
	strict standard limits	ÿÿÿ	small	1,2,4,14
Test method	Analysis method replacement		major	2-5,8,12, 14
		ÿ	small	2,6,8,14
	Change from the internal analysis method of the enterprise		medium	2,6,8,12, 13,14
	More pharmacopoeial analysis methods	ÿÿÿÿÿ	small	2,6,8,14
	Change of experimental animals (species) Genus, age, and genotype determined animal)		Major 9,10,14	
	Change of testing venue		major	11

Verification site (3.2.P.3.1)		ÿ Medium ÿ Tiny		11 11

Prerequisites:

ÿThe deleted items are meaningless in the quality standards. The preparation itself does not occur any changes. Changes in standards will not cause a reduction in product quality control levels.

ÿThe newly added test items do not belong to biology/immunology/immunochemistry methods (Except microbiological testing in the Pharmacopoeia). Changes in pharmaceutical characteristics due to changes in the production process, and adding test items to the standard do not fall within the scope of such changes. domain.

ÿThe changed standard limits should be consistent with the relevant official standards and/or relevant technical guidelines, and the changed standard limits should not exceed the approved range. ÿThe method of character description was changed to describe the preparation more scientifically and accurately, and the preparation itself did not undergo any changes. Changes in the color, shape and other properties of the preparation caused by changes in the prescription, preparation process, etc. do not fall within the scope of such changes.

ÿ Changes in acceptance standards do not exceed the approved scope and limits. ÿ The increased inspection items are not due to the generation of new impurities, and the tightened limits should be within the recognized or approved acceptance limits (for example, Class 3 residual solvents are within ICH limits or Pharmacopoeia within the required range).

ÿThe change is not related to recurring deviations or stability concerns in production. ÿThe analysis method is the same, or based on the same technology or principle (such as changing the column length or temperature instead of using a different column or method), and no new impurities are detected.

ÿThe changed analysis method will not be reduced in terms of precision, accuracy, specificity and sensitivity.

ÿThis change does not involve the potency test. ÿThe

changed method is the same as or better than the original method. Or use the same pharmacopoeia

One detection method under one inspection item is changed to another detection method.

ÿ Tests related to biological activity by biological/immunological/immunochemical methods

Change of venue, but does not include change of experimental animal testing venue.

ÿChange of non-biological activity-related testing sites, and testing before and after the change

Neither the method nor the standard limits were

changed. Technical

requirements: 1. Explain the reason for the change and provide supporting basis for deletion and/or proposed

change of quality

control standards. 2. Updated preparation quality standards (including test items, standard limits and analytical

methods). Provides comparative information on old and new quality standards. For test items that are prone to change

during storage, it is recommended to establish release standards and shelf life standards respectively. 3. Provide information

to maintain quality and consistency of production processes. Changes in test items or methods that may affect

product quality assurance (such as changes in biological activity/immunogenicity testing methods, relaxation of registration

standard limits, deletion of some test items, etc.) should be comprehensively analyzed to prove that the change in standards

will not affect the quality of the product. Reduction in quality control levels.

4. Detail the basis for formulating quality standards and prove the rationality of formulating quality standards. Limit

revisions are generally based on the calibration data of a certain batch of products and the registration standards for similar

products. In principle, the registration standards should not be lower than the requirements of the Pharmacopoeia, and

should not be lower than the requirements of similar products already on the market. The acceptance criteria for residual

solvents are within the recognized or approved acceptance limits (for example, Class 3 residual solvents are within the ICH

limits or the limits required by the Pharmacopoeia). Quantifiable quality standards should set specific standard limits.

5. If applicable, describe in detail the analysis method to be changed, and

Analytical methods were subjected to methodological validation.

6. For existing pharmacopoeia methods, applicability studies should be conducted before first use.

Such as verification of specificity and precision, etc., to prove that the method can be used under actual conditions of use.

Law applies.

7. Provide standard comparison data before and after the change. Conduct research on the rationale for standard

changes. Research work needs to focus on examining the applicability of the updated pharmacopoeia standards. Quality

standards with quantitative indicators should set specific standard limits. 8. Prove that

the proposed analysis method is equivalent to or better than the method before the change. 9. Prove

that the test results obtained by the changed test animals are comparable to those of the approved test animals.

Experimental animals should have health certificates and comply with relevant regulations on microbiology and parasitology

testing requirements for experimental animals.

10. Unless otherwise specified, animals used for verification shall be animals of clean grade or above. Accurate

chemical, physical or cellular methods can be used to replace animal testing for quality verification of biological products

to reduce the use of experimental animals.

use.

11. Detail the information of the changed verification site, including name (full name), address (specific to the

factory/workshop) and functions, etc. Provide approved quality standards and related verification methods. Provide

technical information to support method transfer.

12. If relevant, use new methods to batch commercial production scale formulations

Analyze and compare the data before and after the method change.

13. If the new detection method detects new impurities or the impurity content changes, the historical batch

samples should be tested to confirm that the change in impurities is due to the increased sensitivity or selectivity of the

new method.

14. If stability studies are involved, use the revised standards to evaluate the stability studies.

Research results. Commitment to continue long-term stability testing using revised methods and standards

testing to ensure that the revised standards and methods are suitable for monitoring product stability during storage

changes in nature, and the stability of the product during storage can meet the post-change standards

limit.

F. Standard product/reference product

The main content of the changes shall be based on international		Prerequisite Reference	Category Technical Requirements	
Standard/reference Comparison ÿ3.2.P.6ÿ	(or national) standards. The internal reference product of the product calibration		medium	1
	company is changed from the internal reference product of the company.		Medium	1
	For national or international standards	ÿ Tiny Medium Tiny Medium Tiny		1
	Use approved reference materials to confirm			1
	Certification of new batches of reference products	ÿ		1
	Change the standard confirmation plan and			2
	extend the validity period of the standard	ÿ		3

Prerequisites:

ÿFor physical and chemical examination.

ÿConfirm the new reference product according to the approved plan, including approval and approval

Use an accurate primary reference product to validate new batches of secondary reference products.

ÿAccording to the approved research plan.

skills requirement:

1. Clarify the source, preparation, verification results, and calibration procedures of the standard/reference material.

process and stability studies. Standard/reference product verification includes identification, appearance,

Purity, etc., and evaluate the equivalence of old and new standards/references. Equivalence assessment

Should be based on statistical analysis results. The proposed standard/reference product should be the same as the test product.

The quality should not contain interfering impurities and should be sufficiently stable and highly specific.

sex.

2. Update the reference product validation plan. Detail the basis for changing the reference product validation plan according to.

3. Complete the stability study according to the approved stability plan.

G. Packaging system

Changes	Main content, prerequisites, reference categories	technical requirements	
direct contact with medicine Product packaging materials and container ÿ3.2.P.2.4& 3.2.P.7ÿ	Change direct contact packages Packaging materials and containers (including new coatings, adhesives, Cap/stopper and glass material wait)	ÿ	major	1-6,8,13
	Change the shape of the packaging container shape and size		Major	1-6
		ÿÿÿÿ Minor Medium Minor		1-6
	Change solid dosage form (frozen (except dry dosage form) directly connected Contact packaging materials and containers			2-6
		ÿ		2,5,6
	Replace or add suppliers ÿÿÿÿ		small	1-5
secondary packaging materials (Feature) ÿ3.2.P.7.ÿ	Change does not come into contact with the preparation Any part of the packaging material	ÿÿ Tiny		1
	removed from the outer packaging release agent		medium	11
	Change packaging specifications		small	12

Prerequisites:

ÿThe packaging change of adding a prefilled syringe from a vial is the addition of a new package Installation form changes.

ÿThe materials and types of packaging materials and containers have not been changed.

ÿThe shape and size of packaging materials and containers in direct contact with the preparation have not changed Changes or equivalents (such as increasing the thickness of the glass bottle without changing the internal dimensions) wait).

ÿThe change is not related to recurring deviations or stability concerns in production.

ÿDoes not affect the stability of the product. ÿ Such

changes should not reduce the quality and stability of the product, nor change the characteristics of the original packaging system (for example, the packaging system has the function of preventing children from accidentally opening it, etc.). This change does not cover parts of the packaging material that may affect product transport, use and safety. ÿThe packaging materials have been approved or the

packaging materials have been filed and the registration status is A. Technical requirements: 1. Explain the reason

for the change. Explain

the basis, rationality and applicability of packaging materials

sexual information. Pharmaceutical packaging materials banned or eliminated by the state shall not be used.

2. Provide comparative information on packaging materials and containers before and after the change. If involved, Provides review information related to pharmaceutical packaging materials and containers.

3. Provide the production technology, process control and batch inspection reports for the continuous production of three batches of preparations using the new packaging, and compare them with those before the change. When necessary, an extended quality study of the product should be conducted to prove the product quality before and after changes in packaging materials and containers.

Quantities are comparable.

4. Except for special requirements, at least 3 months' accelerated and/or forced degradation stability data and at least 3-6 months' real-time/actual conditions stability data for new packaged preparations produced on a commercial scale should be provided, and should be compared with the original Compare historical stability data of packaging products for comparability studies. Develop a stability study plan. Long-term stability studies continue to confirm the shelf life of the formulation. Commitment to report nonconformities arising from long-term stability studies.

5. In accordance with domestic and foreign guidelines, conduct research on the sealing integrity of new packaging materials and containers and their compatibility with drugs. Prove the impact of new packaging materials and containers on the quality and safety of preparations through targeted research work.

Influence.

6. If applicable, revise quality standards, instructions, packaging labels and other information.

7. Compare the old and new standards and explain the basis for the revision of the standards.

8. Due to reasons such as permeability, polyvinyl chloride can be used in blood products.

Bag packaging material.

9. If applicable, detail the new analytical methods and methodological validation data.

10. Provide batch analysis data of packaging materials and containers.

11. Explain the reasons for the change. Explain access to facilities that ensure safe and effective medication use

An alternative to the required diluent. Provide revised product information and supporting information

fee.

12. Pharmaceutical packaging specifications should be economical and convenient. There are medicines for treatment,

The packaging specifications should generally be determined based on the course of treatment of the drug. syringe, infusion

When liquid containers or diluents are packaged together with drugs, the outer packaging should be marked with the shortest

validity period.

13. If applicable, conduct special safety tests (such as allergy, hemolysis and blood

tube stimulation, etc.).

H. Storage and transportation conditions and validity period

Changes	Main content, prerequisites, reference categories, technical requirements			
storage conditions ÿ3.2.P.8.1& 3.2.P.8.3ÿ	relax		major	1-7
	more strict	ÿÿÿ	minor	1,2,3,7,8
	Finished product reconstituted/diluted and stored Changes in hiding conditions	ÿÿÿ Medium		2,3, 7
Validity period ÿ3.2.P.8.1& 3.2.P.8.3ÿ	extend		Major	1-7
		ÿ		1,2,4,5,7
	shorten		Moderate	1-7
		ÿ	Major	1,2,3,8
Post-approval stability	Moderate Moderate Post-approval stability studies			1,3,6
The research project may be	Changes to plans or commitments	ÿ Tiny Page 55/65		3

No (3.2.P.8.2)				

Prerequisites: ÿ

Modification of storage conditions should be based on the premise that the stability of the preparation is not reduced. ÿ Shortening of the shelf life and/or changes in strict drug storage conditions are not related to recurring deviations or stability concerns in production; and do not involve major safety concerns question.

ÿThere are no changes in the production technology and process control, prescriptions, standards, packaging materials and containers. ÿ Use at least three batches of commercial-scale preparations, and extend the validity period based on the results obtained from the approved stability study protocol (or under the storage conditions when the validity period was approved), including extending the validity period of the preparation, and use is allowed after opening, dilution or reconstitution time etc. Extension of the validity period due to changes in the production process or pharmaceutical excipients in the prescription does not fall within the scope of such changes; changes in the validity period that change the approved stability study protocol due to changes in the calibration method do not fall into the scope of such changes. category. ÿExcept biological products such as vaccines that must not be stored after reconstitution. ÿThe stability study plan has not undergone major changes (such as deleting items in the stability study plan, replacing analysis methods, or changing storage temperatures, etc.), and the parameter range of the changed stability study plan is more stringent (such as adding monitoring points, etc.) .

Technical requirements: 1. Clarify the proposed validity period and/or storage conditions. If applicable, provide stability study plan and commitment. The storage of vaccines should generally comply with the provisions of the Pharmacopoeia. Unless otherwise specified, frozen storage is not allowed, especially vaccines containing adjuvanted liquid dosage forms (such as vaccines containing aluminum adjuvants).

2. If applicable, review the content of quality standards, instructions and packaging label samples.

Make the appropriate revisions.

3. If the stability research plan changes, provide an updated stability plan and commitment, and provide a basis for the change. 4. Provide stability study results

covering the proposed validity period under real-time/actual conditions. Study samples should be formulated using a commercial-scale process in three consecutive batches. The packaging method and packaging material of the stability inspection samples should be consistent with those of the marketed products.

same.

5. The validity period of biological products should be based on the long-term stability test results after the change.

If determined, extrapolation results are not applicable to biologics.

6. If a new analytical method is adopted, methodological verification data should be provided to prove

The proposed analytical method is equivalent to or superior to an approved analytical method.

7. If involved, provide stability study data covering the proposed storage time of the commercial-scale preparation after the storage conditions are changed after reconstitution/dilution. The conditions for stability testing should be representative of the actual worst conditions, and the containers/packaging materials used for stability testing should be representative of actual conditions. 8. Commit to conduct

stability research under real-time/actual conditions according to the stability research plan.

Qualitative studies and reporting of non-conformities in long-term stability studies.

(3) In vitro diagnostic reagents managed as biological products

A. Changes in detection reagents based on immunological

methods	The main	Reference Category Technical Requirements	
Antigen, antibody	content is to add the same target antigen or antibody fragment on the original basis. Changes in testing conditions,	major	1-10
Test method, reference value (reference range)	positive judgment values, reference intervals, etc., such as sources, quality	major	3-7
Analytical performance	standards, and suppliers, can improve analytical sensitivity or specificity to medium		3,4,6

Test sample mix number	Add sources of mixed	major	3,4,6
Quality control products	portions, quality standards, suppliers, etc. change	medium	2,3,6,8
Solid phase carrier, coating system system, color development	Moderate changes in quality standards, suppliers, etc.		2-6,9
system buffer, cleaning solution, stop solution	Changes in quality standards, suppliers, etc. (sustained) The essence of the liquid will not change)	Tiny 2,3,6,10	
Check the storage	Add new storage conditions and	medium	3,6
conditions and/or presence of the model Validity period change	validity period for new applicable models (according to stability Plan)	medium	5,6
Production address	Change of production address	Medium 2,3,6,8,11	
Enterprise reference products	change source, matrix or re-establish	small	12
Packaging specifications	add or change	small	12

skills requirement:

1. Provide research information on the main materials such as antigens and antibodies after the change.

2. If applicable, provide production calibration records for at least three batches of changed diagnostic reagents record.

3. Carry out analysis performance evaluation research and analyze the relevant analysis of detection reagents before and after the change. Analyze performance for comparison.

4. If applicable, provide clinical assessment data or historical batches that can support changes Clinical testing data.

5. Provide comparative study data on the stability of diagnostic reagents before and after the change and stability Qualitative research commitment.

6. Provide technical requirements for diagnostic reagents and diagnostic reagent instructions before and after the change and label samples.

7. Provide detailed testing conditions, positive judgment values or reference intervals after the change Identified supporting test data.

8. Provide quality control product change information (if applicable).

9. Provide information on changes to the solid phase carrier, coating system, and color development system (if appropriate).

use).

10. Provide buffer, cleaning solution, and stop solution change information (if applicable).

11. Provide production address change information. Provide quality system (unchanged)

Assessment reports and certificates.

12. Provide relevant change information and supporting materials.

B. Pathogenic microorganism nucleic acid detection reagents

The main contents of the changes are adjustments based on the original		Reference Category	Technical Requirements
Determination of target sequence	target sequence. (such as adding new target sequences, reducing The number of original target sequences, the number of original target sequences Sequence adjustment, etc.)	major	1-10
Test methods, reference values (Reference range)	Testing conditions, positive judgment values or parameters Change the testing interval,	Major 1,3-6,10	
etc., and change the number of mixed portions of the test sample. Increase the number of mixed portions. Significant analytical			1,3-8
performance. Increase the analytical sensitivity or specificity. Moderate.			1,3,5,7
Quality control products	Source, quality standards, suppliers, etc. change	medium	1,2,5,8
Primers, probes, enzymes, Nucleic acid extraction, separation/purification system, color rendering system, Internal standard	Major changes in sources or quality standards1,2,4,5,9		
Changes in buffers, etc.	Changes in quality standards, suppliers, etc. (It will not cause the essential change of the buffer	small	1,5,10
Check model	solution, add new applicable models,	medium	1,5
storage conditions and/or validity Expect	storage conditions, and change the validity period (according to Stability study plan) Production	medium	4,5
Production address	address change	Medium 1,2,4,5,7,11	
Enterprise reference products change source, matrix or re-establish		small	12
Packaging specifications	add or change	small	12

skills requirement:

1. Carry out analytical performance evaluation research and compare the analytical performance of diagnostic reagents before and after the change. 2. If applicable, provide production calibration records of three consecutive batches of changed diagnostic reagents record.

3. If applicable, provide clinical assessment data or historical batch clinical testing data to support changes. 4. If involved, provide comparative study data on the stability of diagnostic reagents before and after the change. and stability research commitments.

5. Provide technical requirements, instructions and label samples of diagnostic reagents before and after the change draft.

6. If involved, provide detailed post-change testing conditions, positive judgment values or Supporting experimental data for determination of reference intervals.

7. Compare the clinical test results before and after the change. The number of clinical samples should be It is statistically significant, and the sample concentration is reasonably distributed within the measurement range. 8. If involved, provide information on changes to quality control products. 9. Provide primers, probes, enzymes, nucleic acid extraction, separation/purification systems, and color development Change information on systems, internal standards, etc.

10. If involved, provide buffer and other change information. 11. Provide production address change information. Provide quality system (constant) assessment Reports and Certifications.

12. Provide relevant change information and supporting materials. 6. References

1. "Technical Guiding Principles for Change Management of Biological Products Production Processes", CFDAÿ2005ÿ

2. "Technical Guiding Principles for Research on Pharmaceutical Changes of Marketed Chemical Drugs", NMPA,2021.2.

3. "Technical Guiding Principles for Quality Comparability Research on Vaccine Production Site Changes", CFDAÿ2014ÿ

4. "Technical Guiding Principles for Stability Research of Biological Products (Trial)", 2015.4. 5. "State Food and Drug Administration's Notice on Further Improving Drug-Related Review, Approval and Supervision" Announcement on Matters Related to Management Work" (2019 No. 56), July 2019.

6. "Technical Guidelines for Research on Sealing of Chemical Injection Packaging Systems (Trial) Action)ÿ(Attachment to the Notice of the Center for Drug Evaluation of the State Food and Drug Administration) 2020.10.

7. "Technical Guidelines for Compatibility Research on Plastic Component Systems Used in the Production of Chemical Injections (Trial)" (Attachment to the Notice of the Drug Evaluation Center of the State Food and Drug Administration) 2020.10. 8. "Research Technology on the Compatibility of Chemical Injections and Medicinal Glass Packaging Containers" Guiding Principles (Trial), 2015.

9. "Technical Guiding Principles for Research on Compatibility of Chemicals and Elastomer Seals" (Trial)" 2018.

10 ÿ ICH Q5C: Stability testing of biotechnological /biological products. November 1995.

11ÿICH Q5E:Comparability of biotechnological/biological products subject to change in their manufacturing process. November 2004.

12ÿICH Q12: Technical and regulatory considerations for pharmaceutical product lifecycle management. November 2019.

13ÿGuidelines for procedures and data requirements for changes to approved vaccines. WHO/BS.2014.

14ÿGuidelines on procedures and data requirements for changes to approved biotherapeutic products. WHO /BS .2017. 2238.

15ÿGuidelines on the details of the various categories of variations, on the operation of the procedures laid down in chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01).

16ÿChemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products. FDA. December 2017.

17. Guidance for industry-CMC postapproval manufactur - ing changes to be documented in annual reports. U.S.-FDA. March 2014.

7. Explanation of terms

Drug Substance: used to make final formulations or semi-finished products

The active ingredient substance or mixture of the product, proinsulin regulated as a biological product

For ingredients and drugs, please refer to the original solution.

Post **approval** Changes: after obtaining marketing approval and any reportable changes that occur after the approved change, such as production

Changes in processes, analytical methods (including quality standards), storage conditions, etc.

Related Changes : Refers to a change that accompanies or causes other changes.

Post-Approval Change Management Protocols (PACMPs): Describe the changes to the production process that the MAH intends to implement in the commercial stage of the life cycle and how to prepare and verify the changes, including the assessment of the impact of the proposed changes and change reporting categories , specific change situations and acceptance criteria that need to be met and other information.

Established Conditions (Ecs): refers to the ability to ensure that the product Legally valid information on product quality, any changes to Ecs need to be reported.

Product Lifecycle Management (PLCM): **The PLCM** file is the central repository of Ecs and related reporting categories for changes to Ecs. The document also includes how the product is managed during the commercial phase of the life cycle, including relevant post-approval CMC commitments and

PACMPsÿ

Design Space : It is the range of multi-dimensional combinations and interactions of input variables (such as material attributes) and process parameters that have been proven to ensure product quality.

Comparability Study : refers to a series of activities such as research design, research implementation and data evaluation to analyze and confirm whether the product quality before and after the change is equivalent or highly similar, and the existing knowledge is sufficient to predict that the difference in quality attributes will not affect the product. adversely affect safety and effectiveness.

Comparability Bridging Study: A study that allows the production of drugs using current processes by providing non-clinical or clinical research data.

Data are extrapolated to drug products produced by altered processes.

In-process Control : Inspections implemented during production to monitor or adjust the production process to ensure that the intermediate or final product meets the appropriate quality standards. Production environment or equipment controls are also considered part of the controls within the production process.

Quality Standard (Specification): It consists of a series of calibration, analytical methods and appropriate acceptance criteria, expressed in numerical limits, ranges or other inspection standards. Quality standards are key quality standards developed by the holder, fully demonstrated, and approved by the pharmaceutical regulatory authorities. Quality standards with quantitative indicators should set specific upper and lower limits. **Reference Standards :**

Sufficiently characterized materials used as a reference when evaluating batches of biological products. These materials are critical to ensuring the quality and consistency of manufacturing of biologics and determining appropriate clinical dosing. **Packaging Materials and Container Closure System :** Packaging materials and containers (including stoppers, etc.) that are in direct

contact with biological products should comply with the relevant regulations and medicinal requirements of the national drug regulatory department and should be non-toxic, harmless, clean and non-toxic. Bacteria should not react chemically with the contents of the drug, and should not affect the quality of the contents of the drug. The integrity of the closure of parenteral containers should be verified by appropriate means. Secondary packaging materials and containers are packaging materials that do not come into direct contact with the drug product (e.g., cartons, pallets).

8. List of abbreviations

abbreviation	full name	Chinese translation
PQSs	Pharmaceutical Quality Systems	of drug quality management system
PACMPs	Post-Approval Change Management Protocols	Post-launch change management plan

ECs	Established Conditions	Default condition
PLCM	Product Lifecycle Management	Product life cycle management
TSE	Transmissible Spongiform Encephalopathies	Transmissible cavernous encephalitis
BSE	Bovine Spongiform Encephalitis No	bovine spongiform encephalopathy
SPF	Specific Pathogen Free World	specific pathogen
WHO	World Health Organization	Health Organization
MOTHER	European Medicines Agency	European Medicines Agency
FDA	Food and Drug Administration	
I	International Council for Harmonization	International Conference on Technical Coordination of Registration of Pharmaceuticals for Human Use
CTD	Common Technical Document	General technical documents
GMP	Good Manufacture Practices	Good Manufacturing Practice for Pharmaceutical Products