临床试验期间生物制品药学研究和变更技术指导原则

（试行）

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目 录

1. Introduction To

standardize the pharmaceutical research and changes of biological products during clinical trials and meet the requirements of different stages

Basic requirements for samples used in clinical trials, speeding up the clinical trials and marketing of biological products,

Promote the management of the entire life cycle of biological products.

The Vaccine Administration Law of the People's Republic of China, the Drug Registration and Administration Measures and the Drug Administration Measures

In accordance with the "Regulations on Post-Market Change Management of Products (Trial)", these technical guidelines are specially formulated.

During clinical trials, the pharmaceutical research of biological products is characterized by gradual and phased development.

Follow the research and development rules of biological products, promote pharmaceutical research and changes, and ensure

Obtaining sufficient pharmaceutical research data support is an important step in the development of biological products during clinical trials.

This is a key goal and also the basis for advancing clinical trials and marketing applications.

This guideline is aligned with the pharmaceutical technical requirements for clinical trial applications for biological products.

With the goal of meeting the pharmaceutical requirements for marketing authorization, we refer to and learn from relevant technical guidelines at home and abroad.

Based on the guiding principles, it aims to explain from a technical perspective how to continuously conduct clinical trials during

Biological product pharmaceutical research, as well as the phased requirements for research content. In addition, by giving examples

Pharmaceutical changes that may increase safety risks during clinical trials, guide and regulate clinical

Pharmaceutical change notification for biological products during clinical trials.

This guideline applies to biological products that have obtained implied approval for clinical trials in China.

Products, including preventive and therapeutic biological products, involve obtaining clinical trial implicit

The entire “clinical trial period” between the time of approval and the submission of a marketing authorization application is the period during which the drug

Changes and/or updates in the science and technology, including raw materials used in production, production processes, quality, stability

Research and changes in qualitative and packaging systems, etc. Gene therapy and cell therapy biological products

The research and changes during clinical trials can also refer to the basic concepts of this guideline for research and development.

At the same time, it is necessary to carry out product-specific change research in conjunction with the corresponding technical guidelines.

This principle does not apply to in vitro diagnostic reagents for blood screening.

Biological products are complex and diverse. This guideline is for the pharmaceutical

General requests for research and changes reflect our current knowledge and opinions only.

When conducting pharmaceutical research and changes on biological products during clinical trials, trial sponsors may refer to

Consider the guiding principles, analyze specific issues based on the characteristics of the varieties, and conduct a thorough assessment

and research to advance the development of biopharmaceuticals for marketing.

II. General Principles

1. Basic considerations

1. Scientific planning

To ensure the orderly development of biological product research and development and reduce the impact of unexpected changes,

Pharmaceutical research and changes during clinical trials should be scientifically planned and managed.

The data are limited, and the early clinical trial stage is mainly based on R&D experience and prior knowledge (such as

With the acquisition of clinical data and the accumulation of pharmaceutical research data

The plan needs to be improved accordingly.

Platform technology helps to quickly develop innovative products and

Provide supporting data for risk assessment of changes during product development.

The platform knowledge in this guideline refers to the phased considerations and the difference from post-marketing changes.

A technology or set of technologies used by manufacturers to develop and/or produce similar products.

Previous products of this technology have been launched or clinical research has been carried out.

The technical product skeleton (may include nucleic acid vector, viral vector, protein skeleton, etc.),

If the production process, key quality attributes and GMP implementation conditions remain basically unchanged, it can be regarded as

A platform. The platform is a collection of previously acquired experience and knowledge, production data (about production

production, control and stability) and method validation can serve as supporting data for faster

Rapidly evaluate and develop new products that fit within platform boundaries and pharmaceutical

Adequate support should be provided for risk assessments using platform knowledge

The evidence is based on the comparative analysis of specific pharmaceutical research data, analysis of the mechanism of action,

Previous clinical research progress, etc.

2. Phased considerations

During clinical trials, the pharmaceutical research of biological products is gradually improved to comply with the regulations of drug development.

Pharmaceutical changes during clinical trials are essentially a process of continuous enrichment and completion of pharmaceutical research information.

Pharmaceutical research and changes during clinical trials and the first application for clinical trials

Pre-test studies and post-marketing change studies are different. The purpose of pharmaceutical research and changes at this stage is

The premise is to balance risks and benefits without increasing the safety risk of clinical subjects.

The early stage pharmaceutical research and development data can support the development of late stage clinical trials and provide a basis for the final development of biological products.

Provide sufficient basis for listing.

In the early clinical trial stage, pharmaceutical research and changes of biological products should focus on safety.

Safety risks, such as the introduction of exogenous factors by raw material changes, and the possible impact of process changes on disease

toxins/bacteria, and maintain biological activity (potency) and purity.

Quantity attributes are comparable.

In principle, changes that have a significant impact on safety and efficacy during clinical trials of biological products

It should be completed before the end of confirmatory clinical trials, and the production process of the stock solution should be basically stable.

The formulation and process should be determined, and the process scale and control should be representative to ensure that the confirmatory clinical trial

The scale and technology of the pilot phase should be more closely connected with commercial production.

Pharmaceutical changes during clinical trials are supported by safety and effectiveness data from clinical trials.

Due to the uncertainty of clinical research and development of biological products, after completing confirmatory clinical trials

Pharmaceutical changes are inevitable. Even so, they may affect the safety and efficacy of biological products.

Pharmaceutical changes with significant impact are generally not recommended to be implemented at this stage unless there are sufficient

Data support.

3. Considerations for different types of biological products

The focus of pharmaceutical research and changes during clinical trials of different types of biological products is different.

same.

For innovative biological products, enterprises are encouraged to adopt the Quality by Design

Design, QbD) framework for overall design and development. Due to the relative lack of prior knowledge, innovative biological products require more risk analysis and experimental design (Design of Experiments, DOE), gradually determine the critical process parameters (CPP) and key In the early clinical trial stage, safety-related CPPs and in process control (In process controls, IPCs) items, acceptance limits, and conduct Necessary monitoring is carried out. With the advancement of pharmaceutical research, the understanding of drugs and production processes continues to improve. In the confirmatory clinical trial stage, it is encouraged to Adopt the process of commercial production scale, and update and improve the quality standards.

For modified biological products, the following criteria can be considered: The relevance of the information and other information, combined with the research and development strategy during the clinical trial, timely complete the pharmaceutical Research and change.

For biological products that are applied for according to marketed biological products (including biosimilars), Similar products can be used as reference, and it is recommended to conduct comprehensive preclinical comparative studies. On the basis of commercial production scale, we focus on local adjustment optimization and connectivity research. When the requirements for phased clinical trials and human data are waived, if there is a serious Pharmaceutical research data should not only ensure the safety of subjects, but also support Evaluation of drug effectiveness.

4. Considerations for different types of biological products

Traditional preventive vaccines (such as live attenuated vaccines, inactivated vaccines, etc.) usually have a material base. The clinical trial population is different from the treatment population. Therefore, the requirements for pharmaceutical studies and changes during clinical trials should be consistent with other The products are different, but the basic concepts and principles are the same. When there is a change with a significant impact, in addition to conducting a pharmaceutical comparability study, it is recommended to further conduct non-clinical Bridging studies, such as immunogenicity and necessary safety comparisons, etc. Although the evaluation indicators of vaccines

The correlation with protective efficacy needs to be confirmed by confirmatory clinical studies, but in the early clinical trial stage

While focusing on safety, pharmaceutical changes during this period should also take into account factors that affect effectiveness evaluation.

Pharmaceutical research, such as comparative analysis of humoral immunity, cellular immunity and other efficacy data.

For vaccines with low-dose, the pharmaceutical research of each active ingredient (antigen) should be gradually improved during clinical trials.

research and conduct comprehensive assessments of vaccine safety and effectiveness.

There are many types of genetically engineered recombinant protein products, including antibodies, fusion

Proteins, peptides, and coupled/modified proteins or peptides.

The primary structure should be highly purified and the currently available advanced analytical methods should be used to gradually and comprehensively confirm the

structure, higher order structure, post-translational modifications, biological activity (potency), product-related substances and

Impurities, etc. For products such as coupled/modified proteins or peptides, please refer to relevant technologies.

The guidelines study the quality attributes of the modification/conjugation site and ratio.

When changes occur during the period, when pharmaceutical comparability studies are not sufficient to exclude the safety of changes

When risks are identified, appropriate nonclinical/clinical comparability bridging studies should be conducted.

Human plasma used in the production of blood products is a scarce resource due to its potential pathogenic

Virus contamination risk, virus safety control is the core content of blood product quality control.

The development of blood product technology should focus on the virus safety, product potency and other quality issues.

on the other hand, the effects of the quality attributes of the

Scale and batch size can be considered comprehensively in combination with improving comprehensive utilization rate and representative process.

5. Correlation between stock solution and preparation

The stock solution and the preparation are an inseparable whole in the pharmaceutical research of biological products.

The risks will be reflected in the samples used in clinical trials.

Changes should be gradually improved as clinical trials progress.

Therefore, during clinical trials, pharmaceutical research and changes should focus on the stock solution and preparation research.

If the change of stock solution has an impact on the finished product, both the stock solution and the finished product need to be tested.

If the change of stock solution does not affect the preparation, the preparation research does not need to be carried out.

2. Pharmaceutical Change Risk Assessment and Comparability Study

To ensure the safety of the subjects, the non-clinical/clinical studies before the bridging change should be fully evaluated.
Assess the impact of pharmaceutical changes on quality, safety, and effectiveness, and conduct comparability studies
The research was confirmed.

1. Risk Assessment

During clinical trials, the quality control system of biological products has been gradually improved, making them safe and effective.
Clinical trial data are gradually obtained, even for the same change, in different clinical trial stages and different
Risks also vary among types and classes of biologics.

In the early clinical trial stage, the sponsor has accumulated knowledge about the process and product.
The human safety of the drug has not been fully established, and it may not be possible to conduct risk assessment for changes.
Comprehensive, it is necessary to combine the results of non-clinical safety evaluation and early clinical studies to evaluate pharmaceutical changes
The possible impact on the safety of the subjects. The clinical trial results are the risk factors for the product when it is put on the market.
The main basis for risk-benefit ratio assessment is the accumulation of knowledge, and the risk assessment system is gradually improved.
In the confirmatory clinical phase, in addition to focusing on
In addition to paying attention to the safety of the subjects, the scientific nature of the clinical trial results must also be taken into account.
When conducting risk assessment on changes after clinical trials, the quality management system of the drug should be
At the same time, the risk assessment should include a review of all changes,
Identify the reasons for the change and consider the risks of the potential impact of the change.

Therefore, we should follow the principle of specific analysis of specific situations, comprehensively analyze and judge the biological
Potential risk factors and associated impacts of product changes. It is encouraged to refer to relevant guidelines such as ICH Q9
Conduct scientific risk assessment based on guiding principles.

2. Comparability study

Comparability studies in clinical trials are often affected by the development process, applicability of analytical methods,
Impact on the knowledge of process and drug etc. All pharmaceutical
Changes should be considered in light of the stage at which the change occurs, the extent of the change, etc., and refer to ICH Q5E.

Conduct appropriate comparability studies to evaluate the impact of the changes on drug quality, safety and efficacy.

The impact of effectiveness.

In the early clinical trial stage, comparability studies are usually not as comprehensive as those after marketing.

Encourage continuous improvement in quality without negatively affecting safety.

With the accumulation of process experience, the information used for comparability studies will gradually increase.

In other words, the later the pharmaceutical changes are in clinical trials, the more comprehensive and systematic the comparability studies are.

If the change occurs after the confirmatory clinical trial is verified,

Conduct comprehensive comparability studies in accordance with the requirements of ICH Q5E and post-marketing changes.

Comparability studies for pharmaceutical changes can be conducted from IPCs (if applicable), release testing, expansion testing,

Comprehensive evaluation of the characterization studies, stability studies (forced degradation, accelerated and long-term)

Estimate the impact of the change.

If the comparability results show that the pharmaceutical changes may affect the safety or effectiveness of the clinical trial

Negative effects (such as changes in immunogenicity, generation of new impurities, etc.), or when a specific quality

The relationship between the property and safety and effectiveness has not been established and the product quality before and after the change is

When there are differences in sex, nonclinical or even clinical bridging studies are needed before and after the change.

Some changes that may have a significant impact on clinical trials cannot be determined using only pharmaceutical analysis data.

When excluding the impact of changes, nonclinical and/or clinical bridging studies should also be considered, such as new

Changes in main seed batches, changes in special excipients, and extension of the virus seed generation for the production of live attenuated vaccines

wait.

Pharmaceutical changes during clinical trials often do not occur independently; a change may be accompanied by

Or cause other changes. It is recommended to conduct risk assessment according to actual conditions, and generally follow the higher

Even the cumulative risks require relevant comparability research.

3. Communication

Good communication helps the sponsor to integrate changes into the product development process.

Reasonable planning to control the risk of changes and determine the application strategy.

If there is a major change, the sponsor may contact the drug regulatory agency for pharmaceutical research and major changes in biological products.

Technical issues (e.g. whether the impact of the change on product quality and safety requires further clinical research)

To ensure

The quality and efficiency of the communication meeting. Before the communication meeting, the clinical trial of the drug should be submitted.

The research overview during the trial and detailed supporting research data (and literature) for the changes will be

An assessment of the possible impact on the safety and effectiveness of the study and whether the existing research data support the

The clinical trial to be conducted should clarify the meeting theme, issues to be discussed and preliminary solutions.

The consensus reached through communication and exchange can serve as an important basis for subsequent research, development and evaluation.

For details on communication requirements, please refer to relevant management regulations.

III. Phased requirements for pharmaceutical research

(I) Stock solution (3.2.S)

1. Production (S.2)

1.1 Manufacturer (S.2.1)

Specify the name, address and responsibilities of the manufacturer (including production and inspection), including the contract

Each proposed production site (production line) or facility involved in the design, manufacture and inspection of the product.

If the manufacturer is changed during the clinical trial, the original solution process, quality, stability, etc.

Fully assess whether the change brings risks related to drug quality and safety, and conduct relevant

Research.

1.2 Production process and process control (S.2.2)

Define the process flow (diagram) and describe each process step, including scale,

Culture medium and other raw materials and equipment used in production, and provide process parameters and IPCs information.

Confirm the storage and transportation conditions of the stock solution (if applicable). Update the control cells according to the development progress (if

Safety assessment information of exogenous factors involved in the unprocessed harvest fluid (unprocessed crude product) (such as

applicable).

In the early clinical trial stage, process steps and intermediate product control information should be collected.

Monitor/control key materials and reagents added during the process that may affect safety.

During the confirmatory clinical trial stage, the production scale should be determined in combination with the process development.

Improve the items and limits of process and process control, and

Initial acceptance limits are revised retrospectively (if applicable) to ensure that the manufacturing process is effective.

Effective control. Clarify key steps and IPCs.

If a biopharmaceutical that may affect the safety or efficacy of a drug occurs during a clinical trial,

If changes are made to the manufacturing process, scale and/or IPCs, the changes should be evaluated according to ICH Q5E.

The scope of the comparability study should be based on the impact of the change.

Risk assessment and clinical development stage determination. In principle, process changes during clinical trials should

The process is more suitable for commercial production, and the process control capability is gradually improved.

1.3 Material control (S.2.3)

Cell bank/seed batch system: timely update the cell bank/seed batch establishment based on the actual R&D situation.

Verification and storage information. Comprehensive verification of cell banks/seed batches to ensure compliance with the China

Pharmacopoeia, and other relevant technical guidelines at home and abroad (such as ICH Q5A, etc.).

Pay attention to and confirm the monoclonality of the seed batch/cell bank.

Early clinical trials should generally have preliminary data on stability studies.

Comprehensive stability studies should be conducted during the clinical trial phase and reasonable in vitro limits should be established.

Passage times/highest in vitro doubling level. For products such as vaccines and microecological live bacteria products, use

The cell matrix and bacterial/virus strain passage number should comply with the corresponding general and specific monographs of the Chinese Pharmacopoeia.

And other requirements.

If a working cell bank/seed bank (WCB/WSL) is established during the clinical trial,

WCB/WSL or changes that may affect the growth/generation characteristics of WCB/WSL

Furthermore, adequate risk assessment and corresponding comparability studies should be conducted.

Raw materials for production: specify the raw materials and consumables used in the production of stock solution (including but not limited to

Limited to starting materials, culture media, growth factors, enzymes, chromatography media, reagents, etc.) and their use

The production stage of biological materials (including

including raw materials used in the preparation of cell banks/seed batch systems) and key complex raw materials

For materials, the source, production process (if homemade), characteristic identification (if applicable), quality standard

The accuracy and stability of the product should be evaluated, and the safety of adventitious agents (including TSE/BSE risks) should be assessed.

The possible introduction of genotoxic raw materials/intermediates into production should be fully evaluated.

Safety risks of toxic substances.

If there is a change in the raw materials used in production, the above information will be updated accordingly and the possible introduction of

The risks of exogenous factors and impurities should be fully evaluated and necessary research should be conducted.

1.4 Control of key steps and intermediates (S.2.4)

In the early clinical trial stage, the operating range of process parameters should be initially established, and

Can affect the IPCs parameters and acceptable limits related to product safety, and have an impact on non-safety related

The storage time and temporary storage conditions of intermediate products should be

Supported by preliminary physicochemical, bioburden/sterility analysis data (if applicable).

During the clinical trial phase, IPCs parameters and acceptable limits are gradually determined.

Establish CPP and IPCs parameters and acceptable limits. Improve the acceptable standards/limits for intermediate products.

To ensure that the quality of intermediate products can be effectively controlled. Storage time and storage conditions of intermediate products

Existence conditions should be supported by research data.

1.5 Process validation and/or evaluation (S.2.5)

1.5.1 Virus removal/inactivation verification

Virus removal/inactivation validation was carried out in accordance with the Chinese Pharmacopoeia and relevant technical guidelines.

If the virus removal/inactivation platform process validation is used, the relevant technical guidelines should be referred to and the

Fully evaluate and confirm.

For genetically engineered recombinant protein products, the degree of virus removal/inactivation verification depends on

During the drug development phase and before marketing application, comprehensive virus removal/inactivation process testing is performed.

Evidence study and overall process viral safety risk assessment.

For inactivated virus vaccines, continue to study inactivation agents and inactivation processes, and establish

The virus inactivation activity curves of multiple batches of samples are collected to verify the inactivation effect.

Parameters should be determined in combination with validation results and should comply with the requirements of the Chinese Pharmacopoeia when marketed.

If changes occur during clinical trials that have a direct or indirect impact on virus removal/inactivation,

Changes (such as changes in nanofiltration membrane material, changes in inactivation agent type, etc.) should be made to the changed process.

Perform virus removal/inactivation revalidation and safety risk assessment.

1.5.2 Process Validation/Evaluation

Encourage the collection of data throughout clinical trials to establish and support process validation.

To support the completion of process performance confirmation before marketing application

Qualification (PPQ). In principle, a drug should be tested under commercial scale conditions before a marketing application is submitted.

Complete process validation for at least three consecutive batches to ensure process robustness and drug quality.

Consistency.

Typically, upstream culture process validation should focus on cell morphology, growth characteristics, density, viability,

rate, cell metabolism level, target product expression level, cell stability, etc.

For vaccines cultured with virus/virus strains, attention should also be paid to virus titer or cell/bacterial activity (if applicable),

Antigen content and purity (if applicable), etc. For polysaccharide-protein conjugate vaccines, attention should be paid to the derivative

rate, derivatization/binding kinetics, specific carrier protein monomer or polymer form, etc. Purification process

Validation should focus on purity, product-related impurities, and process-related impurity removal capabilities.

For biological products modified by chemical coupling, the degree of modification, free small molecule content, and uncoupled protein content must also be confirmed.

White ratio, yield, etc. Cleaning/storage/regeneration and circulation of ultrafiltration membrane package/chromatographic medium should be carried out

Service life verification, compatibility evaluation and research of equipment/containers in direct contact with the original liquid, intermediate

Storage stability verification, transportation verification (if applicable), etc.

1.5.3 Process development

The development process of the production process should be described, the reasons for the changes should be clarified and the changes should be summarized.

Summarize the batch numbers and uses of stock solutions for representative processes during the development process.

Also conduct corresponding comparability studies to determine the impact of the changes.

2. Characterization (S.3)

2.1 Structure and physicochemical properties (S.3.1)

The characterization studies (including physicochemical properties, biological activity, immunochemical properties, purity and impurities, etc.); explain the choice of the characteristic analysis method used The legal basis and its applicability.

In the early clinical trial stage, we should continue to accumulate knowledge about the structure and physicochemical properties; The confirmatory clinical trial stage encourages the use of advanced technical means and methods for comprehensive characterization. Including primary structure, higher structure, purity and biological activity research, etc., to understand the drug structure It provides a basis for analyzing the relationship between structure and function, determining the CQA of drugs and formulating analytical control strategies.

For vaccines, we will continue to promote the development of vaccines based on their own types and characteristics during clinical trials. Expand quality research to further confirm the protective antigen composition, content and conformation of the vaccine, and accumulate The correlation between the quality of cumulative protective antigens and clinical immune effect. Extended quality studies include but are not limited to Limited to antigen-specific identification, physicochemical properties, structural/sequence variation (if relevant), purity and Impurity analysis, infectivity (if relevant), biological activity related to vaccine immune effect (such as For adjuvant vaccines or multivalent vaccines, Comprehensive studies on the interaction between adjuvant and antigen, the anti- Research on the interaction of the original.

For blood products, it is necessary to consider the product type, formulation type and drug development stage. Related functional components (such as vWF in coagulation factor VIII), drug activation status, and possible effects Extended quality studies are being conducted on components that affect potency (such as fibrinolysin in fibrinogen).

When major process changes occur during clinical trials, the drug should be fully characterized and studied. Research and comparability analysis.

2.2 Impurities (S.3.2)

During clinical trials, the control of drug-related impurities (such as precursors, splicing products,

decomposition products, aggregates, etc.) and process-related impurities (such as host cell proteins, host cell DNA,

The quantitative information of impurities (including the most clinical

If there is sufficient evidence, qualitative research on certain impurities or

For process-related impurities (such as defoamers, etc.), only the degree of removal is evaluated.

Applicable) Qualitative and quantitative research is required to assess its risks and comprehensively consider the establishment of acceptable

limit.

Before applying for marketing approval, the impurities contained in biological products should be clarified, and the degradation mechanism of drugs should be clarified.

The corresponding changes of drug-related impurities during preparation and storage, and the development of risk control strategies to ensure

Prove drug safety.

3. Quality control (S.4)

3.1 Quality standards and basis for formulation (S.4.1 & S.4.5)

The quality standard of the stock solution should include the CQAs of the drug, such as content, identity, purity and impurities,

Biological activity (potency), physicochemical properties, sterility/microbiological limits, bacterial endotoxins, etc.

During clinical trials, process validation/evaluation data are insufficient, so quality control should not be

Limited to the test items set in the quality standards.

In the early clinical trial stage, the content, identification and purity (main peak) of the stock solution quality standard

The acceptance criteria can be relatively broad, but the “reporting results” approach should not be adopted;

Establish impurity and microbial safety limits; collect sufficient data and combine with drug characterization

Research can establish reasonable limits for quality attributes (e.g., glycoform content, charge variants)

Take the form of a “report of results”.

"Reporting results" in the quality standards during confirmatory clinical trials and before marketing application

The formulation of quality standards should be based on relevant development data, average

platform knowledge, manufacturing information of batches in nonclinical and clinical studies, quality characteristics and stability studies

The research data is the basis, while taking into account the detection capabilities of the detection methods.

For products declared as marketed biological products (including biosimilars), they should comply with

The general technical requirements of the Chinese Pharmacopoeia, in principle, its quality standards shall not be lower than those of the same products already on the market kind.

When quality standards change during clinical trials, previous quality standards should be reviewed. Based on the clinical development stage, the release and stability of the representative samples are adjusted. (if applicable) as support.

3.2 Analytical methods and validation (S.4.2 & S.4.3)

In the early clinical trial stage, the applicability of the detection method is initially confirmed, and the quality The importance of the property and the corresponding methodological research should be carried out in the R&D stage. If involved, a flexible Sensitive, specific, and different detection methods are used to identify new impurities or degradation products and safety analysis, and consider reasonable control strategies based on the safety analysis results. Establish a biological activity (potency) analysis method that can reflect the drug's mechanism of action.

Generally, the pharmacopoeia, Relevant technical guidelines require methodological confirmation or comprehensive methodological validation.

If the analytical method is optimized or improved during the clinical trial, the method should be bridged. Research and evaluation (if applicable), in principle, the detection capability of new analytical methods should not be lower than that of old analytical methods method.

3.3 Batch analysis (S.4.4)

List and summarize the release batch information, including batch number, batch size, production site, production date, Specifications and test results, process versions and batch usage information should be included to support Batch analytical data for pivotal batches of the proposed nonclinical and/or clinical trials.

4. Standard substances (S.5)

The selection and establishment of reference materials is an important part of measuring the performance of different batches of drugs during clinical trials. Key factors for comparability between the proposed drug and the drug used in clinical trials

First, advanced analytical methods should be used to fully characterize the reference materials and verify their biological activity. Although the same standard substance is used for biological testing and physical and chemical properties research

is ideal, but sometimes according to the actual situation, physical and chemical properties, biological activity and related

Different standard substances are used for the research of different substances. It is encouraged to establish internal primary standards as soon as possible.

Materials, working standard materials should be calibrated with primary standard materials.

If there are international or national standard materials, they can be used as primary standard materials and their

It should be noted that the application of some standard materials may be limited to specific

It is necessary to establish detection methods for drug-related substances, drug-related impurities and process-related impurities.

Primary standard material, used to calibrate subsequent working standard materials (if applicable).

If there are no international or national standard materials, primary standard materials should be established within the enterprise.

Internal standard substances prepared by different processes during clinical trials should be fully characterized.

The traceability of the reference materials at different stages is ensured by the characterization and stability test.

Primary reference materials are established from batches of representative processes for clinical trials or batches of process validation.

After the primary reference material is fully characterized, it can be used to calibrate the working standard

substance.

5. Packaging system (S.6)

Identify the packaging system used to transport and/or store the stock solution during clinical trials and demonstrate

The packaging system will not have adverse effects on the quality of the stock solution.

Compatibility and sealing studies of liquid storage containers (if applicable).

If the packaging system of the stock solution is changed during the clinical trial, the impact on the quality,

The impact on stability and conduct compatibility and sealing studies (if applicable).

6. Stability (S.7)

Summarize the stability data of relevant stock solutions, indicating the batch, production date, process version,

Purpose, storage conditions, time points, quality standards and inspection results.

Stability studies can be performed using packaging materials with the same composition as the actual packaging material but on a smaller scale.

Use appropriate analytical methods with stability-indicating capabilities to maximize detection

The purity, impurities and biological activity (potency) of the original solution.

If there is sufficient evidence, the storage period will not be changed.

Variable key quality attributes may not be included in stability studies.

In the early clinical trial stage, gradually accumulate stability research data and stability characteristics.

The data from qualitative research should be able to support the conduct of later clinical trials.

From the confirmatory clinical trial stage to the application for marketing approval, reference should be made to the Chinese Pharmacopoeia, ICH, etc.

Related technical guidelines Continue to complete the long-term stability study of the stock solution and improve the influencing factors

Tests (such as extreme pH, light, vibration, freeze-thaw, high temperature, oxidation, etc.) and accelerated tests,

Identify the potential degradation pathways of the stock solution and fully understand the stability characteristics of the stock solution to prepare for storage period.

Provides a basis for the setting.

(II) Preparations (3.2.P)

1. Product development and production (P.2 & P.3)

1.1 Prescription composition and batch prescription (P.2.1 & P.3.2)

Clarify the dosage form, prescription (batch prescription) and the origin of all components in the prescription during the clinical trial.

If any new excipient is used, there should be sufficient justification and

Safety data support. Clarify the batch information of representative batches of samples during clinical trials. If applicable

For use, the source, prescription and quality standards of the accompanying diluents and excipients should be clearly stated (if

and).

Before confirmatory clinical trials, the formulation and dosage form of the drug should be determined.

The formulation of certain preparations for drug release should generally be consistent with the drug to be marketed.

New drug delivery devices used in clinical trials should be subject to safety assessment and verification and should be compatible with the drug delivery devices to be marketed.

Be consistent.

Changes in prescription and delivery device may affect drug quality, stability, and safety

and clinical use, etc., any changes in the clinical trial phase must be justified and have corresponding

Supported by research data.

1.2 Manufacturer (P.3.1)

Specify the name and address of the manufacturer (including production and testing) of the drug used in the clinical trial and responsibilities, including contractors, production and inspection involved in each proposed production site or facility.

If the manufacturer is changed during the clinical trial, the manufacturer should be fully considered in terms of process, quality, stability, etc. Evaluate whether the changes bring risks related to drug quality and safety.

1.3 Production process and process control (P.3.3)

Clarify the process flow (diagram), describe each process step, and provide process parameters and IPCs information, and gradually improve IPCs test items and acceptable limits.

If applicable, the amount of active ingredient or active unit added should be specified.

For vaccines with adjuvants, research on the necessity and dosage of adjuvants should continue.

Sterile filtration, focusing on the maximum acceptable bioburden before filtration.

If changes occur in the manufacturing process and IPCs of the drug product during clinical trials (such as freeze-drying, adsorption, Lipid encapsulation/packaging), necessary comparability studies should be conducted according to ICH Q5E.

1.4 Control of key steps and intermediates (P.3.4)

During the clinical trial stage, the process parameters and limits of key steps should be confirmed step by step.

In the early clinical trial stage, the control strategy should focus on safety-related IPCs and establish Acceptable limits for safety-related IPCs should be established; other IPCs should be monitored.

For intermediate products, there should be sufficient reasons, and the storage time and storage conditions should be supported by data.

During the confirmatory clinical trial phase, the IPCs items in the process and the acceptable Identify and confirm CPPs step by step, subject to standards/limits. Determine production batch and scale.

1.5 Process validation and/or evaluation (P.3.5)

Usually, process validation is completed at the intended production scale before the marketing application to confirm and Assess process robustness and batch-to-batch consistency. If applicable, describe aseptic filling process and Validation of the freeze-drying process.

For sterile or non-sterile drugs in multiple-dose packaging systems, if the prescription composition and Changes in pH and packaging system may affect the test method or antibacterial effect.

The antibacterial efficacy test method should be reconfirmed/validated and the long-term stability study should be

Monitor the antibacterial efficacy at the key time points of the study.

For drugs that require a process, revalidation should be performed if process changes may affect the terminal virus inactivation process.

2. Control of excipients (P.4 & A.3)

Generally, excipients listed in the pharmacopoeia should be used, the requirements for preparations should be met, and internal control standards should be established.

For human or animal derived excipients, information on safety assessment of exogenous factors should be clearly stated, and

TSE/BSE risk-free statement.

It is recommended to refer to relevant technical guidelines at home and abroad for research and to

The research was continuously improved during the experiment.

3. Quality Control (P.5)

3.1 Quality standards and formulation basis (P.5.1 & P.5.6)

The basic principles of preparation quality research and control are the same as those of stock solution.

At least the content, identification, purity, and biological activity (potency) tests should be included.

Consider the control of key excipients, special excipients, adjuvants and other functional components added to the prescription.

Sterile drugs need to be tested for sterility and bacterial endotoxins.

Identify and quantify impurities not covered (e.g., introduced during drug production and/or storage)

control.

Early clinical trial phase, based on limited development and nonclinical and clinical research batches

Set preliminary acceptance standards. For some verification items, the “report results” method can be adopted.

In principle, the impurity level of samples used in clinical trials should not exceed that of samples obtained in animal safety studies and preliminary

Corresponding impurity levels supported by clinical trials or prior knowledge (such as platform knowledge), if any

If necessary, an upper limit for impurities should be set.

During the confirmatory clinical trial phase, the relevance of quality standards and production processes should be fully considered.

Stability, compatibility, historical batch data for preclinical and clinical studies of bulk solutions and formulations

The quality standards of the preparations should be improved and determined based on the characteristics of the analytical methods and other factors.

The content, purity, and quality of each active ingredient should be evaluated in combination with the clinical dosage.

Establish quality standards for the biological activity (potency) of

For multi-dose/multi-portion preparations, the accuracy of the dosage and the period of use should be ensured.

Antibacterial effect between the two groups (if applicable). For sustained-release preparations, controlled-release preparations, enteric-coated preparations and transdermal patches

For drugs such as sedatives, drug dissolution/release studies should be conducted. For vaccines, if applicable,

Vaccine characteristics include detection indicators that can comprehensively characterize the effects of humoral immunity or cellular immunity.

For combination vaccines, the interaction between the components and the effect of adjuvants on the active ingredients and the detection

to study the impact of.

For biological products that are registered as marketed biological products (including biosimilars),

It complies with the general technical requirements of the Chinese Pharmacopoeia. In principle, its quality standards shall not be lower than those of the drugs already on the market.

Same variety.

When quality standards change during clinical trials, previous quality standards should be reviewed.

Based on the clinical development stage, the release and stability of the representative samples are adjusted.

(if applicable).

When the heterogeneity of the target product is inconsistent with the drug used during clinical trials, these changes should be addressed

impact assessments and necessary research.

3.2 Analytical methods and verification (P.5.2 & P.5.3)

Refer to the corresponding content of the stock solution.

3.3 Batch analysis (P.5.4)

Refer to the corresponding content of the stock solution.

4. Standard substances (P.6)

Refer to the corresponding content of the stock solution.

5. Packaging system (P.2.4 & P.7)

The source and standard of packaging materials should be clearly stated, and the qualified information of packaging materials should be available.

The relevant registration status (if any) shall be stated. The packaging material shall comply with the pharmacopoeia or national pharmaceutical packaging material standards.

The materials collected should comply with the relevant technical guidelines of China or other countries.

The packaging material is an atypical drug delivery device such as an inhalation aerosol device, a disposable injection device, or

For drug delivery devices made of new materials, the basis for use must be clear and they must comply with established quality standards.

Early clinical trials should generally conduct preliminary sealing and compatibility studies to demonstrate

The packaging system does not negatively impact the quality of the drug.

During the confirmatory clinical trial phase, comprehensive sealed

Drug delivery devices should complete the research under simulated actual use conditions before the marketing application.

to demonstrate the repeatability and accuracy of dosing and to confirm the packaging system in clinical trials

In principle, the packaging system should be consistent with the packaging system to be marketed.

If the packaging system of the drug product is changed during clinical trials, the impact on drug quality,

The impact on stability and the sealing and compatibility studies were carried out.

6. Stability (P.8)

The basic considerations and phased requirements for the stability study of the preparation can be found in the corresponding section of the stock solution.

content.

When conducting a formulation stability study, the stability profile of the stock solution should be considered.

During the clinical trial stage, stability studies should be able to support the development of phased clinical trials, and confirmatory clinical trials should be able to support the development of phased clinical trials.

During the clinical trial stage, the quality and packaging materials of the drug batches in the stability study should be consistent with those of the drug batches to be marketed.

The products are consistent and comprehensive stability tests are conducted with reference to the guidelines of the Chinese Pharmacopoeia and ICH.

To provide support for the setting of shelf life and drug use.

Different placement orientations (such as upright, inverted, and horizontal) should usually be used for stability.

For separately packaged diluents/adjuvants, in addition to conducting stability tests on each packaging component,

In addition to the above, the stability after dilution/mixing covering the shelf life should also be investigated.

Preparations that are dissolved, diluted, mixed, and placed before use or multi-dose/multi-person preparations need to be used

Stability studies during the period of validity are encouraged.

The stability of the product during use.

IV. Evaluation of pharmaceutical changes and changes that may increase safety risks

According to the Drug Registration Management Measures, during the clinical trial of a drug,

If there are any changes or new discoveries in pharmacy, the impact on the safety of the subjects should be fully evaluated.

Changes that the investigators consider may increase the safety risk of the subjects should be handled in accordance with the Drug Registration Administration.

If the applicant believes that the safety of the subjects will not be affected, the applicant may directly submit a supplementary application according to the relevant requirements of the "Administrative Measures"

The confirmatory clinical trial is completed.

Subsequent pharmaceutical changes to biological products may be submitted before the marketing application or during the marketing application.

Submit together.

During clinical trials, changes in the pharmaceutical performance of biological products that may increase safety risks are usually

As mentioned below, it is recommended that applicants pay special attention to the examples listed, but still need to follow the above-mentioned

Based on the risk classification principle, we will conduct assessment, research and determine the reporting path.

Communicate and exchange divergent suggestions.

The supplementary application materials include newly obtained pharmaceutical safety data,

Updates on the safety of the medicine and to ensure the safety of subsequent clinical trials

Safety update reports should record the clinical trial

All content of pharmaceutical studies and changes during the trial period, including supporting or confirmatory study data,

Pharmaceutical safety review and response to the opinions of the drug review agency (if any), etc.

For potential safety risks that have been identified but not actually implemented on clinical subjects

Pharmaceutical changes of biological products usually do not affect completed or ongoing clinical trials; however,

If a clinical trial is found to have pharmaceutical safety issues or other risks,

The clinical trial should be suspended or terminated, and the safety data of the drug during clinical trials should be reviewed and

Rapid Reporting Standards and Procedures Report potential serious safety risks to drug review agencies

Clinical trials can only be continued after safety issues are resolved or eliminated through supplementary studies.

Test.

Some changes involve changes in the material basis of biological products and need to be considered in accordance with the Drug Registration

Submit new clinical

Application for trials, such as vaccines using new bacterial strains, new adjuvants, etc.

The pharmaceutical changes of biological products that may generally increase safety risks are as follows:

1. Stock solution

1.1 Material Control

1) New master cell bank/master seed batch.

2) Substantial changes in key raw materials.

1.2 Production process

3) Substantial changes in the production site.

4) Changes in the fermentation process that have an adverse impact on safety.

5) Purification process or purification of substances that lead to the production of new impurities/new products

Process changes.

6) Process changes that directly or indirectly affect the virus inactivation/removal capacity.

7) Changes in the scope of safety-related IPCs (relaxation, deletion).

1.3 Quality Control

8) Major changes in the quality standards that affect the safety of the stock solution (addition of safety standards except

outside).

1.4 Packaging materials and stability

9) Changes that alter storage conditions and may adversely affect product quality.

2. Preparation

2.1 Prescription

1) Changes in prescription or dosage form (including changes in active ingredient concentration and excipient composition,

Water injections were changed to powder injections, injections in vials were changed to prefilled injections, etc.).

2) Changes in excipients that may have an adverse effect on the safety of the preparation.

3) Change of adjuvant.

2.2 Production process

4) Substantial changes in production sites, excluding changes in secondary packaging production plants.

5) Process changes that directly or indirectly affect virus inactivation/removal capabilities.

6) Changes in the preparation process that affect sterility and impurity removal capabilities.

7) Changes in the scope of safety-related process IPCs (relaxation, deletion).

2.3 Quality Control

8) Major changes in quality standards that affect the safety of the drug product (except for adding safety control

outside).

2.4 Packaging materials and stability

9) Changes in the packaging system that is in direct contact with the drug (such as material, etc.).

10) Changes that alter storage conditions and may adversely affect product quality.

3. Newly discovered pharmaceutical information that may have an adverse effect on safety (e.g.

Discovery of new impurities, increased TSE risk, etc.).

4. Other major changes that affect safety or drug changes due to safety reasons

Learning changes.

V. Reference Guide

1. Technical Guidelines for Application for Phase I Clinical Trial of New Drugs (National Medical Products Administration, 2018

Appendix to Notice No. 16 of 2018), 2018.1.

2. "Guidelines for Pharmaceutical Research Information for Phase III Clinical Trials of Innovative Drugs (Chemical Drugs)" (National

(Appendix to the Notice No. 48 of the State Food and Drug Administration in 2018), 2018.3.

3. "Technical Guidelines for Pharmaceutical Changes during Clinical Trials of Innovative Drugs (Chemical Drugs)"

(Annex to Announcement No. 22 of 2021 of the Center for Drug Evaluation of the National Medical Products Administration), 2021.3.

4. "Technical Guiding Principles for the Development of Vaccines for the Prevention of Novel Coronavirus (Trial)" (National

(Attachment to Notice No. 21 of 2020 issued by the Center for Drug Evaluation of the State Food and Drug Administration), 2020.8.

5. Application for Clinical Pharmaceutical Research and Technical Data for Neutralizing Antibodies for Novel Coronavirus

Requirements for Guiding Principles (Trial)" (Annex to the Notice of the Center for Drug Evaluation of the National Medical Products Administration), 2020.9.

6. "Technical Methods and Validation Guidelines for Removal/Inactivation of Viruses from Blood Products" (National Drug Administration

Note [2002] No. 160)

7. Technical Guidelines for Stability Studies of Biological Products (Trial) (formerly the National Food and Drug Administration

(Annex to the Notice No. 10 of 2015 of the State Food and Drug Administration), 2015.4.

8. Technical Guidelines for Sealing Research of Chemical Injection Packaging Systems (Trial) (National

(Attachment to the Notice No. 33 of 2020 issued by the Center for Drug Evaluation of the National Medical Products Administration), 2020.10.

9. Technical Guidelines for Compatibility Research of Plastic Component Systems Used in the Production of Chemical Injections

South (Trial)" (Annex to the Notice No. 33 of 2020 of the Center for Drug Evaluation of the National Medical Products Administration), 2020.10.

10. Technical Guidance on Compatibility Study of Chemical Drug Injections and Pharmaceutical Glass Packaging Containers

Principles (Trial) (Annex to Notice No. 40 of 2015 of the former State Food and Drug Administration)

Item), 2015.7.

11ÿFDA Guidance for Industry: IND Meetings for Human Drugs and

Biologics; Chemistry, Manufacturing and Controls Information , 2001.5ÿ

12ÿGuidance for Industry on INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information, FDA, 2003.5ÿ

13 ÿ Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, MOTHER, 2022.2ÿ

14 ÿ ICH Q5C: Stability Testing Of Biotechnological/Biological Products, 1995.11ÿ

15ÿICH Q5D:Derivation And Characterisation Of Cell Substrates Used For Production Of Biotechnological/Biological Products ,1997.7ÿ

16ÿICH Q5E:Comparability of Biotechnological/Biological Products Subject to Change in Their Manufacturing Process, 2004.11ÿ

17 ÿ ICH Q6B:Specifications: Test Procedures And Acceptance Criteria For Biotechnological/Biological Products,1999.5ÿ

18ÿICH Q8(R2)ÿPharmaceutical Development,2009.8ÿ

19 ÿ ICH Q12 ÿ Techinical And Regulatory Considerations For Pharmaceutical Product Lifecycle Management,2019.11ÿ

6. Glossary

Confirmatory Clinical Trials: Confirmatory clinical trials are those that obtain Clinical trials that support core efficacy data for marketing.

Related Changes: A change is accompanied by or triggered by other changes. Even.

Comparability Study In Clinical Trials:

Includes the study design (study samples, analytical methods and pre-defined comparability acceptance criteria)

activities including research implementation and data evaluation to assess whether the product has

Comparability.

Prior knowledge: refers to existing knowledge, including internal knowledge

(e.g. development and manufacturing experience), external knowledge (e.g. scientific publications, including data from suppliers),

of science (e.g., chemistry, physics, and engineering) or established scientific principles (e.g.,

Application of engineering principles).

VII. List of abbreviations

Abbreviations	Full name	Chinese translation
MCB/MSL	Master Cell Bank/Master Seed Lot	Master Cell Bank/Master Seed Batch
WCB/WSL	Working Cell Bank/Working Seed Lot	Working Cell Bank/Working Seed Lot
TSE	Transmissible Spongiform Encephalopathies	Transmissible spongiform encephalopathy
BSE	Bovine Spongiform Encephalitis	Bovine spongiform encephalopathy
I	International Council for Harmonization	International Technical Agreement for Registration of Pharmaceuticals for Human Use Adjustment
PPQ	Process Performance Qualification	
IPC	In-Process Control	Production process control