appendix

创新药（化学药）临床试验期间药学变更技术指导原则（试行）

I. Overview

Innovative pharmaceutical research is characterized by graduality, stages and uncertainty.

The breadth and depth of its research continues to advance with the progress of clinical trials. Regular opening

In development mode, the R&D process of APIs is ahead of preparations and usually follows the following rules:

law:

For APIs, the synthesis routes and processes in early clinical trials are relatively

For immature products, the key quality attributes such as physical and chemical properties and impurity behavior of raw materials have been determined.

The understanding is limited, based only on preclinical safety trials and relatively limited preparation experience.

Established an initial quality control strategy and a broader

Quality Standard. With the advancement of clinical trials and in-depth understanding of critical quality attributes

Understand, based on the needs of enlarging production, improving quality, improving quality control, etc.,

Continuously optimize process routes, conduct in-depth research on impurity behavior, and strengthen understanding of key physical and chemical characteristics

understanding of the nature and its potential impact on formulations, combined with multi-batch production

Experience adapting quality control strategies. Determined for commercialization during pivotal clinical trials

Synthetic routes and processes, based on systematic quality risk assessment, determine key processes

Steps and key process parameter ranges, and develop reasonable process control and intermediate control

system, based on historical batches (especially safety trial batches, critical clinical trials

batch) production information, quality characteristics, stability research results, etc., to improve the raw materials

Drug quality standards, packaging, storage conditions, validity period/retest period, etc.

For preparations, in the early clinical trial stage, based on the evaluation of the drug itself

limited knowledge of the physicochemical properties, safety and effectiveness of

Preparation forms with relatively simple processes (such as oral solutions, raw materials and excipients mixed with powder directly)

filled capsules, etc.), based on preclinical safety trials and relative

Limited preparation experience, establish broader quality standards suitable for its development stage,

Based on limited stability, compatibility (if necessary), compatibility (if necessary)

The research information initially determines the packaging, storage conditions and clinical usage of the preparation. back

As clinical trials continue to advance, preliminary human data are obtained, and for the drug

Have a certain understanding of their own characteristics and internal behaviors, and initially accumulated production experience

On this basis, we will optimize dosage forms, specifications and prescription processes, and strengthen preparation prescriptions.

Research on process and degradation impurities, and improve quality control based on existing knowledge and information.

In the critical clinical trial stage, based on sufficient human safety and effectiveness information,

Information and production information, determine the dosage form, specifications and prescription process to be commercialized, and conduct

Systematic quality risk assessment to determine key process steps and key process parameters,

Develop sound process controls and intermediate controls, based on historical batches (especially

Safety test batches, critical clinical trial batches) information and stability, compatibility

research results on properties and compatibility, and improve preparation quality standards, packaging, storage conditions,

Validity period and clinical usage, etc.

Based on the above research and development rules, due to the different pharmaceutical research stages of innovative drugs,

Different research objectives determine that the research process will inevitably be accompanied by a large number of pharmaceutical changes.

Pharmaceutical changes may introduce quality risks in clinical samples, which may in turn

It will affect the safety of subjects and/or the scientific validity of clinical trial results, so it is necessary to

Comprehensively and prudently assess the quality risks introduced by changes and conduct relevant research to support

These changes should be applied to the preparation of clinical samples.

Pharmaceutical changes described in this guideline refer to changes that occur (or are expected to occur) in clinical

Changes in sample production, quality control, packaging and storage conditions. This refers to

The guidelines are applicable to the clinical practice of innovative chemical drugs and improved new drugs (except radiopharmaceuticals).

Medication changes during the trial. Taking into account the stages and stages of pharmaceutical research on innovative drugs,

The diversity and complexity of scientific changes, this guiding principle mainly explains the innovative drugs

General principles for evaluation and research of chemical changes, only some common major changes and

Examples of general changes are given, and the research ideas and research under such changes are briefly described.

Research content. For other forms of changes not explicitly listed, applicants may refer to this

guiding principles or other relevant guiding principles, and conduct assessments based on the specific circumstances of the change.

and research.

Furthermore, pharmacy changes often do not occur in isolation. For example, a production site

Changes may be accompanied by changes in production equipment and production processes, and changes in prescriptions may

It can accompany or trigger changes in drug quality standards, etc. For multiple changes to occur simultaneously

If they are related, you can refer to the basic ideas of this guideline to carry out research separately.

According to the research, in general, relevant change support can be carried out according to the change categories with higher technical requirements.

conduct ongoing research work and pay attention to the possible overlapping effects of multiple changes.

The applicant is responsible for the evaluation and investigation of pharmaceutical changes during clinical trials.

body responsibility. When conducting research on pharmaceutical changes, it is first necessary to clarify the reasons for the change,

The changed items and the extent of the change, and then combined with the characteristics of the variety and the specific changes

Content, based on the idea of risk assessment, evaluates the impact of changes on drug quality and clinical trials

Based on the possible impact on the safety of test subjects and the scientific validity of clinical trial results,

Based on this, determine whether the change is a major change or a general change, and conduct corresponding research.

work to assess the feasibility of the change.

2. General principles for evaluating pharmaceutical changes during clinical trials

When pharmaceutical changes occur during clinical trials of innovative drugs, the applicant should follow

Risk assessment principles, combined with the clinical research stage, subject population, and

Variety characteristics, existing knowledge of drugs, and preliminary research on changes, etc., scientific research

Assess the possible impact of changes. Specifically, it can be considered from the following aspects:

consider:

1. The clinical stage in which the change occurs (early clinical research stage, critical clinical stage

clinical research stage): Pharmaceutical changes occur throughout all stages of drug development, usually

Changes are more likely to occur in the early stages. In early clinical stages, the drug's

Human safety has not yet been fully established, and it needs to be mainly combined with non-clinical safety evaluation results.

and early clinical study protocols to assess whether pharmaceutical changes are safe for subjects.

The impact it can have. For example, will changes in the production process of APIs introduce new

Impurities (such as mutagenic impurities), whether changes in the preparation production process will cause the same

Changes in in vivo exposure at equal doses. During the pivotal clinical study phase, subjects

The quantity increases, the medication time is extended, and the clinical trial results are higher than the risk when the product is launched.

The main basis for risk-benefit ratio evaluation. Pharmaceutical changes that occur at this stage need to be focused on

In addition to paying attention to the safety of subjects, it is also necessary to take into account the scientific nature of clinical trial results. Compare

If the dosage is determined based on the results of phase II clinical trials, in the phase III clinical stage

To add new specifications, it is necessary to conduct in vitro studies (pharmaceuticals) based on the characteristics of the product.

scientific comparison, etc.) and/or in vivo tests (such as BE, PK, etc.) to evaluate

Evaluate the compatibility between the new specifications and the original specifications.

Usually, in the process of innovative drug research, the more changes occur in the later stages of research, the more

The greater the need for detailed and in-depth research to demonstrate the acceptability of changes. Innovation

After the drug completes key clinical studies to support marketing, if major pharmaceutical changes occur

Please consider carefully.

2. Subject population involved in the change: The subject population involved in the clinical trial does not change.

The risks that may arise from changes are different. If the production process of raw materials is changed, the

Contains mutagenic impurities, which poses a higher safety risk to healthy subjects;

For specific subjects (such as patients with advanced tumors), based on benefit-risk

Based on hazard analysis, the risk may be relatively small. Prescription changes for the same, e.g. for use in children

subjects, you need to carefully evaluate whether the changed excipient type and dosage are suitable for

Are there any safety risks for children?

3. Variety characteristics: The complexity of the drug structure/components and preparation process are also

Important factors to consider in your assessment. For example, compared to small molecule compounds,

High molecular polymers, synthetic peptides, polysaccharides, biological source extracts and other structures/

When process changes occur for compounds with more complex components, evaluate the impact of the changes

The impact may be relatively difficult, the ability to control risks is relatively weak or the risk assessment

The uncertainty of the estimate is relatively high. For special preparations (liposomes, microspheres, etc.),

The impact of changes in the prescription process may not be proven through pharmaceutical comparison alone.

In some cases, in vivo bridging tests and/or necessary non-clinical safety tests are required.

Comprehensive evaluation through comprehensive testing. In addition, different routes of administration, their own safety

The degree of risk is also different. For example, compared with oral solid preparations, injections need to be fully considered.

Bacteria-related risks.

4. Limitations of existing knowledge: Pharmaceutical change management during clinical trials is

As part of the full life cycle management of drugs, research work is usually more systematic and in-depth.

The more research data is accumulated, the more sufficient research data is accumulated to evaluate the possible impact of the change.

The more scientific the estimate. Based on the general rule of gradual progress in innovative pharmaceutical research, clinical

Awareness of the product's critical quality attributes during testing (e.g., impurity profiling studies,

The influence of the physical and chemical properties of raw materials on the quality of preparations and in vivo behavior, etc.) may exist

Limitations: Change studies in the clinical trial phase may also have certain limitations.

For some potential impacts, it is difficult to assess possible risks with limited data.

Or changes that cannot be proven to have consistent quality before and after through simple pharmaceutical comparison, basically

Considering the risks, it is recommended to treat it as a major change, carry out in-depth research, and accumulate

More adequate data.

Generally speaking, based on pharmaceutical changes, the safety of clinical subjects, clinical trials

The possibility of scientific impact of test results can be used to change pharmaceutical changes during clinical

Divided into major changes and general changes. Major changes are those that are assessed to have a significant impact on

affect the quality of clinical samples, which may in turn affect the safety or safety of clinical trial subjects.

Changes that have a significant impact on the scientific validity of clinical trial results. Applicants should review

Carefully assess the risks associated with such changes and conduct relevant research to support them

It is also used in the preparation of clinical trial samples. General changes refer to changes that may be assessed to

The quality of clinical samples, the safety of clinical trials and the scientific nature of test results

For changes that have no obvious impact, the applicant may conduct relevant research as appropriate.

Changes that the applicant assesses may increase risks to subject safety should

When a supplementary application is submitted in accordance with the "Drug Registration Management Measures", it is considered that it will not affect the trial

can be directly implemented and reported in the security update report during development

tell.

3. Research on changes to raw materials

1. General principles for research on changes to APIs

Changes to raw materials need to be carried out in light of their impact on the quality of the corresponding preparations.

Assessment and research. Specifically, it is necessary to focus on changing the key physical and chemical properties of raw materials.

The influence of characteristics, impurity behavior, etc. is unfolded. The key factors affecting the performance of pharmaceutical preparations

Changes in physical and chemical properties may lead to changes in the behavior of the experimental drug in the subject's body,

This will further affect the scientific validity of clinical trial results (data) and may also increase the number of subjects

safety risks; changes in the types and levels of impurities may increase clinical trials

test the risk of expected/unexpected adverse reactions and bring safety risks to subjects.

1.1 Key physical and chemical properties

Generally speaking, the key physical and chemical properties of APIs such as crystal form, particle size and particle size Distribution, solubility, etc. may affect the quality of clinical trial drugs. These The physical and chemical properties are often related to the final purification (such as salt formation, crystallization, etc.) process, The separation method, drying, crushing, mixing and other operating steps are closely related. certain feelings Under such circumstances, significant changes in impurities in the materials to be refined may also lead to the closure of the API. Changes in the physical and chemical properties of bonds. Therefore, after relevant process changes, it is necessary to conduct risk assessment based on Compare the key physical and chemical properties of the raw materials before and after the change, and conduct stability testing as appropriate. Research and re-confirm the structure if necessary. Key principles of drug substance when changed If the chemical properties change, its impact on the formulation process (such as flowability, compressibility, mixing uniformity, solubility, etc.) and formulation properties (e.g. oral solid Dissolution, disintegration, content uniformity, etc.) of the preparation, based on risk assessment Conduct research on the results, and if necessary, consider in vivo bridging studies of corresponding preparations.

1.2 Impurity behavior

Generally speaking, the types and levels of impurities in raw materials affect clinical Important factors in testing drug safety. Impurities usually originate from the manufacturing process (e.g. Solvents, reagents and catalysts, introduction of starting materials and impurities generated by process side reactions) and self-degradation, etc. API production site, synthesis route, synthesis process and control Changes in manufacturing, packaging and storage conditions may lead to changes in the types and levels of impurities. Change. Applicants need to compare the types of impurities in intermediates or APIs before and after the change and levels, including but not limited to related substances, residual solvents, elemental impurities, potential

mutagenic impurities, etc., and conduct stability studies as appropriate. The impurity test used

The investigation method should be able to effectively separate and detect potential impurities in the changed samples. Original

Therefore, the impurity levels of samples used in clinical research must not exceed those found in animal safety tests.

Levels of corresponding impurities supported by data, potentially mutagenic in clinical study samples

For impurities, toxic reagents, solvents, metal catalysts and other residues, please refer to relevant guidance.

requirements of the principle. If there are exceptions, corresponding security support basis must be provided.

2. Examples and research on changes in classification of APIs

2.1 Change of API production site

Change of API production site refers to the production and production of API for clinical trials.

(or) Change of packaging location.

When the API production site is changed, the process routes and process operations before and after the change need to be

Compare the differences in operation, batch size, production equipment, etc., such as changes in the production site

These changes have occurred at the same time, and the impact of these changes on the raw material drug miscellaneousness needs to be comprehensively considered.

quality type or level, and key physical and chemical properties, and evaluate the impact on the quality of the preparation as appropriate.

Impact. It is recommended that intermediates and/or APIs be inspected before and after the site change.

Comprehensive quality comparison and conduct stability studies where appropriate. If multiple production sites are used

To produce key intermediates or APIs locally, attention should be paid to the uniformity of sample quality between different sites.

Consistency.

2.1.1Major changes

including but not limited to:

• Replace or add manufacturing sites (in early clinical stages, Simple Chemistry

Exceptions may be made for changes in production sites for synthetic small molecule APIs).

2.1.2 General changes

including but not limited to:

• Change the name and address description of the API production site, but the actual address

constant.

• Without changing the quality standards, packaging and storage conditions of APIs

Next, change the API packaging location.

2.2 Changes in API production process

Changes in the production process of APIs generally include: changes in synthesis routes (such as abbreviation

shorten, extend or change the synthesis route, etc.), changes in production conditions (such as: materials,

Feeding amount, reaction temperature, reaction time, stirring time, post-processing method, precision

production conditions, drying methods, etc.), etc.

Such changes may have an impact on the impurities and physical and chemical properties of the drug substance. one

Generally speaking, the closer to the last step of the synthesis route (limited to the formation or cleavage of co-

Changes in the reaction of the valence bond are more likely to affect the quality of the raw material drug, thus affecting the corresponding clinical

impact on the performance and quality of clinical trial drugs. In a comprehensive evaluation of the current change step

The behavior of the impurities in the step and the suitability of the analytical method can be compared to assess the changes involved.

The quality of the intermediates obtained can be considered equal if there is no difference. If there is a difference, the

Defer evaluation to the next intermediate until deemed equivalent. When such changes occur,

It is necessary to conduct detailed evaluation and research on the changed process steps, and analyze the changes before and after

Comprehensive comparison of intermediates in this step and subsequent intermediates and/or APIs,

Pay attention to the analysis of impurity profiles in raw materials before and after the change (reaction by-products and newly added Toxic reagents, solvents, catalysts, etc.), impurity transformation and removal research results must be Adjust impurity control strategies when necessary. When the last reaction step (limited to covalent bonds formation or cleavage reaction), the final purification/saltization step and its subsequent process steps When a sudden change occurs, it is necessary to compare the quality of the product and the quality of the API before and after the change. If necessary, it is also necessary to compare the performance of the preparation products produced before and after the change of the raw material drug. and quality to comprehensively evaluate the overall impact of this change on clinical trial drugs, certain In this case, it is also necessary to consider in vivo bridging studies of the corresponding preparations.

2.2.1 Change of synthesis route

2.2.1.1Major changes

including but not limited to:

• Change the synthesis route and possibly change the impurity behavior and key principles of the API have a significant impact on chemical properties.

• Change preparation methods (e.g. replacement of chemical synthesis and fermentation processes, Replacement of peptide solid-phase synthesis and liquid-phase synthesis, etc.).

2.2.1.2 General changes

including but not limited to:

• Extend the synthesis route based on the original route and prepare the original starting materials The process is partially or completely incorporated into the production of APIs.

2.2.2 Changes in production conditions

2.2.2.1Major changes

including but not limited to:

• It may have significant effects on the impurity behavior and key physical and chemical properties of raw materials.

Changes in production processes and parameters affected. For example, it may affect the raw materials

Changes in the fermentation process and extraction process (such as bacterial strain changes,

Changes in purification principles); APIs that may affect the in vivo behavior of the preparation

Changes in crystallization conditions, etc.

• Change the sterilization process of sterile APIs.

2.2.2.2 General changes

including but not limited to:

• Types or types of solvents, reagents, and catalysts that do not affect the quality of the API

Dosage adjustment.

• Batch scale-up without affecting API quality.

2.3 Changes in quality standards for raw materials

Changes to API quality standards generally include inspection items, analytical methods and

Changes in acceptance limits that may result in quality-related safety

Changes in the ability to identify or detect sexual risks. Generally speaking, API key

Changes in quality attribute analysis methods, deletion of inspection items or relaxation of limits will not affect the original

The quality control of raw materials and pharmaceuticals has a greater impact. When the analysis method is changed, the method change needs to be

Compare and verify the before and after detection capabilities. If necessary, use the old and new methods.

Inspection of samples for animal safety testing and/or samples for clinical trials

Compare and re-evaluate whether the safety evidence is sufficient, and in principle analyze method changes

The post-detection capability should not be lower than before the change.

In the early stages of innovative drug research, the understanding and knowledge of the varieties being developed is limited.

It is necessary to pay attention to the accumulation of inspection data. Without sufficient data support, do not establish

It is recommended to delete the inspection items or relax the limits beyond the security support.

2.3.1 Major changes

including but not limited to:

• Eliminate key inspection items.

• Relax acceptance limits for key inspection items.

• Change the analysis method (different principles) of key inspection items (if using

TLC method replaces HPLC method to determine related substances).

2.3.2 General changes

including but not limited to:

• Add inspection items (non-safety reasons).

• Tightening of acceptance limits (non-safety reasons).

• Adjustment of analytical methods (within the scope of existing methodological validation or new

The method validation results in equivalent or better validation results).

2.4 Changes in packaging containers and storage conditions

In the early development stage of innovative drugs, due to insufficient understanding of the compounds,

points, limited stability information is available and more conservative packaging is often chosen

and storage conditions. With the accumulation of stability information and understanding of APIs,

With continued enrichment, appropriate packaging and storage conditions will gradually be determined.

Changes in the packaging of APIs may affect the stability of APIs. Apply

One needs to fully assess the possible negative impact of packaging changes on the stability of the API.

impact, select appropriate inspection indicators to carry out new stability tests, and analyze packaging changes

Analyze the stability change trends of APIs before and after the update. For non-solid APIs

When changing packaging, the compatibility of the new packaging with the API must also be considered. Sterile

APIs also need to consider packaging sealing issues.

Changes in storage conditions, especially relaxation of storage conditions, may affect the original

stability of the drug substance, it is generally necessary to provide sufficient stability data to prove the change

There will be no negative impact on the raw materials after changing the storage conditions.

2.4.1 Major changes

including but not limited to:

• The changed packaging may be the same as the API (generally non-solid API)

interaction occurs.

• Strict storage conditions due to safety reasons or better protection during use

packaging materials/containers.

2.4.2 General changes

including but not limited to:

• Changed packaging provides the same or better protection (non-security

reason).

2.5 Others

For complex molecules (such as synthetic peptides, small molecule nucleic acids, etc.), complex

Changes in the process (such as fermentation, biological source extracts, etc.) of raw materials,

In vitro assessment of its potential effects on clinical samples may be limited and needs to be done in compliance with

Based on the research ideas according to this guiding principle, combined with the characteristics of the product itself, we carry out comprehensive

Reduce risk assessment and change research work to obtain more change-supportive data

according to.

4. Research on preparation changes

1. General principles of preparation change research

For changes in formulations, the focus should be on changing the formulation performance, safety, and safety of the drug.

Conduct assessment and research on the impact of safety-related indicators. The performance of the preparation changes,

It may lead to changes in the behavior of experimental drugs in subjects, thereby affecting clinical

The scientific nature of the trial results (data) may also increase the risk of subject safety;

Types and levels of impurities or other safety-related indicators (such as sterility of injections,

bacterial endotoxins, visible foreign matter, insoluble particles, etc.), which may increase

Increase the risk of expected/unexpected adverse reactions in clinical trials and bring safety to subjects

All hidden dangers.

1.1 Preparation performance

The formulation performance of a drug refers to the ability of the drug to achieve its intended clinical use.

The combination of pharmaceutical properties is the physical and chemical properties of the raw material, the functionality of the excipients, and the formula

The performance of the comprehensive effects of design, production technology, packaging and other aspects.

The performance of different dosage forms can be characterized by different indicators. For example, mouth

Indicators that can be evaluated for solid preparations (such as tablets, etc.) include hardness, disintegration time,

Dissolution/release, content uniformity, etc.; injections can be tested through reconstitution time,

Characterized by dispersion time, particle size and particle size distribution, microscopic morphology and other indicators; semi-solid

Body preparations (such as ointments, gels, suppositories, etc.) can be prepared through the crystal form of the API and

Particle size, viscosity, content uniformity, in vitro release and/or in vitro skin penetration test

characterized by test indicators.

Generally speaking, changes in dosage forms, specifications, prescriptions, production processes, packaging

Packaging and storage conditions may have an impact on the performance of the preparation.

The research needs to combine the properties of the drug, the characteristics of the dosage form, the characteristics of the prescription process and the changes

Evaluate the possible impact of the change on the performance of the preparation based on specific circumstances, based on the risk assessment

Evaluation results, select appropriate preparation performance-related indicators to carry out change support research,

If necessary, in vivo bridging studies of the formulation should also be considered.

1.2 Security related indicators

1.2.1 Impurity behavior

The type and level of impurities are important factors affecting the safety of drugs in clinical trials.

important factors. Impurities in preparations usually come from impurities introduced by raw materials and excipients, external

Incoming material migration (production components, packaging material compatibility impurities) and degradation impurities, while

Degradation impurities can include degradation impurities of APIs and excipients, APIs and excipients and

(or) Interactive impurities in inner packaging materials. Research on impurities in preparations needs to focus on manufacturing

Degradation impurities during agent processing and storage.

Generally speaking, the preparation production site, formula, production process, packaging and storage

Changes in storage conditions, etc. may lead to changes in the types and levels of impurities. need to be combined

Analysis and evaluation of specific changes in drug properties, dosage form characteristics and prescription process characteristics

Whether it may cause changes in impurity behavior (such as introducing new impurities, causing new degradation

analysis trends, etc.), compare the contents of the preparation intermediates and/or final products before and after the change

Types and levels of impurities, including degradation impurities, residual solvents (if applicable), potential

mutagenic impurities (if applicable), etc., and conduct preparation stability studies as appropriate.

The impurity inspection method used should be able to detect potential impurities in the changed samples.

for efficient separation and detection. In principle, the impurity levels of samples used in clinical studies

The level of the corresponding impurity supported by animal safety test data shall not be exceeded.

Residual solvents (if applicable) and potential mutagenic impurities in samples for clinical research can be referred to

Examine the requirements of relevant guiding principles. If there are exceptions, corresponding security support must be provided

Hold the basis.

1.2.2 Other security-related indicators

For injectables, inhaled preparations, implants, etc., you also need to pay attention to changes

Possible impact on other safety-related indicators of the preparation, such as sterility and bacterial endotoxicity

Factors (or pyrogens), insoluble particles, visible foreign matter, osmotic pressure molar concentration, etc.

It is necessary to ensure that the relevant indicators of the changed product still meet the safety requirements.

2. Examples and research on classification of preparation changes

2.1 Change of preparation production site

Change of preparation production site refers to the production and packaging of preparations for clinical trials

Change of venue address.

Changes in preparation production sites require attention to the prescriptions, production processes,

Differences in production equipment, batch sizes, etc. If it occurs simultaneously with the change of production site

These changes need to be comprehensively evaluated on the performance of the formulation, impurity behavior and other

influence other safety-related indicators, select appropriate preparation performance-related indicators,

Safety-related indicators conduct a comprehensive quality comparison of products before and after the site change, and

Conduct stability studies as appropriate. If multiple production sites are used to produce formulation intermediates

Or the final product of the preparation, attention needs to be paid to the consistency of sample quality between different sites.

In principle, changes to the production site of sterile preparations must not reduce the sterility protection of the product.

certification level.

2.1.1Major changes

including but not limited to:

• Add or replace manufacturing sites (early clinical stage, use routine treatment

Ordinary oral preparations using prescription technology may be excluded).

2.1.2 General changes

including but not limited to:

• Change the name and address of the preparation manufacturing site, but the actual address does not

Change.

• Deletion of production sites for non-security reasons.

• Without changing the quality standards, packaging and storage conditions of the preparation,

Add/replace/delete packaging sites.

2.2 Prescription changes

Changes to preparation prescriptions (including prescriptions with special solvents) generally include:

Changes in excipient supplier/model/level, excipient type, and excipient dosage.

Such changes may affect excipient functionality or the acceptability of materials in the formulation process.

Processability affects the performance of the preparation and may also introduce new impurities or other safety issues.

Sexual hazards further affect the safety of subjects. Taking oral solid preparations as an example, if

Changing the particle size of the filler may affect the fluidity and uniform mixing of the mixed materials.

properties, and even cause stratification of mixed materials, thus affecting product content uniformity;

Change the model of some functional excipients (such as polysorbate and other surfactants) or

Dosage may change the dissolution behavior of the preparation, thereby changing the in vivo behavior of the drug.

Affecting subject safety or the scientific validity of clinical trial results; for prescription changes

Involving the use of new excipients, new uses of common excipients, and extraordinary uses of common excipients

When measuring, attention should also be paid to the safety of the type/amount of excipients, impurities introduced by excipients or

Safety of Other Factors.

After such changes occur, it is necessary to combine the nature of the drug, the characteristics of the dosage form and whether

Involving changes in key excipients (which play a key role in dissolution, release or body absorption, etc.

excipients) to evaluate the impact of changes on the preparation, and re-carry out the raw material and excipient phase if necessary.

Capacitive research. Select appropriate performance-related indicators and safety-related indicators of preparations

Conduct a comprehensive quality comparison of products before and after the prescription change, and conduct stability studies as appropriate

If necessary, corresponding compatibility and stability studies need to be carried out in conjunction with the clinical trial plan.

research (if applicable). Comparative study results in pharmaceuticals show that there are significant differences in the quality of preparations

differences, or the potential impact of changes on the quality of the preparation cannot be assessed solely through pharmaceutical comparative studies.

When influencing, formulations need to be considered in light of the current clinical stage and clinical trial protocols.

In vivo bridging studies and/or non-clinical safety studies.

For prescription changes that come with special solvents, they need to be combined with the changes in the formulated preparations.

The impact of quality will be investigated accordingly.

2.2.1 Major changes

including but not limited to:

• Changes in the formulation that may have a significant impact on the quality or in vivo behavior of the drug product

(such as significant changes in the type/model/amount of key excipients, etc.). • Changes (including

substitutions or additions) to the special solvent prescription set that comes with the injection

become.

2.2.2 General changes

including but not limited to:

• Add, delete, and replace without adversely affecting stability

Type of coloring agent or flavoring agent, or change the amount.

• Addition of non-functional tablet coatings.

• Adjustment of coating composition for non-functional tablets.

2.3 Excipient process and control changes

Such changes include: changes in excipient preparation processes (for new excipients), quality

Quantity standards change.

When the preparation process of new excipients is changed, please refer to the evaluation of changes in raw materials and

Research principles and conduct change-supportive research.

2.3.1 Major changes

including but not limited to:

• Changes in internal control standards for excipients that may affect formulation performance (such as excipient particle size and particle size distribution affects the in vitro dissolution of the preparation).

• Relevant changes in the preparation process and quality standards of new excipients (please refer to Examples of major changes to corresponding parts of APIs).

2.3.2 General changes

including but not limited to:

• Relevant changes in the preparation process and quality standards of new excipients (please refer to Examples of general changes to corresponding parts of APIs).

2.4 Changes in production process

Changes in the preparation production process generally include: changes in the preparation production process (such as industrial process principles, process operations, process parameters, etc.), change preparation production process control Methods and limits (such as: intermediate quality standards, process inspection items, etc.), variables Update production equipment, change production scale, etc.

Such changes may affect product formulation performance, impurity behavior and other safety have an impact on sexual indicators, and the degree of impact depends on the complexity and variability of the preparation production process. Whether it involves key steps and processes related to product quality. by injection Taking the mixing steps of the drug as an example, for a true solution with stable physical and chemical properties of the drug, the production The order of adding raw materials and auxiliary materials and the mixing parameters (speed, time and temperature) during the process have a significant impact on The impact on drug quality is small, and the quality risks introduced by changing relevant parameters are low; However, for special injection preparations, such as fat emulsion, micelles, liposomes, etc., raw and excipients The order of addition and mixing parameters may be related to the formation of the microstructure of the formulation, Performance and stability are closely related, and changing relevant process parameters introduces quality risks.

higher.

When such changes occur, changes must be made based on the nature of the drug and the characteristics of the dosage form (variety specific

point) and whether the change involves key links or important parameters of the preparation production process,

Select appropriate indicators to comprehensively compare and evaluate the impact of process changes on formulation performance.

If necessary, it is also necessary to consider conducting in vivo bridging studies on the preparation before and after the change. such as production workers

Changes in the impurity behavior of preparations caused by process changes need to be analyzed and evaluated

analyze the applicability of the method, evaluate and update the safety basis of impurities, and conduct

Stability studies, and when necessary, corresponding compatibility needs to be carried out in conjunction with the clinical trial plan

Stability studies.

2.4.1 Major changes

including but not limited to:

• Change of process principles (e.g. replacement of dry and wet granulation).

• Process operations that may have a significant impact on drug product quality or in vivo behavior

operation or parameter changes.

2.4.2 General changes

including but not limited to:

• Adjust process parameters without affecting formulation quality.

• Batch changes that do not affect formulation quality.

• Provided there is no potential impact on in vivo behavior (e.g. before and after product changes)

similar to the dissolution profile), changing the shape of ordinary tablets (such as round to

Oval).

2.5 Changes in preparation quality standards

Changes to preparation quality standards generally include inspection items, analytical methods and

Acceptance of changes in limits that may result in quality-related

Changes in performance, security risk identification capabilities or detection capabilities. Usually with preparation

Deletion and inspection of test items related to performance, impurity behavior and other safety indicators

Changes in testing methods and relaxation of limits will have a greater impact on the quality control of preparations.

When the analysis method is changed, it is necessary to conduct a comparative study on the detection capabilities before and after the method change.

If necessary, new and old methods need to be used to test samples for animal safety testing and/or

Samples used in clinical trials are tested and compared, and the safety basis for impurities is re-evaluated.

Whether it is sufficient or not, in principle, the detection capability after the change of the analytical method should not be lower than before the change.

In the early stages of innovative drug research, the understanding and knowledge of the varieties being developed is limited.

It is necessary to pay attention to the accumulation of inspection data. Without sufficient data support, do not establish

It is recommended to delete the inspection items or relax the limits beyond the security support.

2.5.1 Major changes

including but not limited to:

• Eliminate key inspection items.

• Relax the acceptance limits of testing items related to safety and key performance of preparations

degree (such as relaxing impurity limits and relaxing dissolution limits)

• Change the analysis method (different principles) of key inspection items (such as NIR

Instead of HPLC determination of content)

2.5.2 General changes

including but not limited to:

• Tightening of acceptance limits (non-safety reasons).

• Add inspection items (non-safety reasons).

• Adjustment of analytical methods (within the scope of existing methodological validation or new

Method validation yields equivalent or better validation results).

2.6 Changes to packaging container system

Changes to the preparation packaging container system include: changes in packaging type, source/

Material/specification (including size, shape) changes, etc.

The preparation packaging container system is an important part of the preparation and usually serves to protect the drug.

Functions of objects, such as protecting from light, moisture, and contamination (microbial invasion), etc.

The points also have the function of delivering drugs (such as packaging container systems for inhaled preparations, etc.).

Changes to the dosage form packaging container system may affect packaging system functionality and dosage form

stability. The degree of impact and the nature of the drug, the route of administration of the preparation, and the dosage form and prescription

Process characteristics, intended functions of pharmaceutical packaging container systems, and drug and packaging materials

the possibility of interaction between them. In principle, the preparation packaging container system

Changes should not adversely affect the formulation.

When the preparation packaging container system is changed, the changed packaging container must be fully evaluated

Functional changes in the system (protection of drug function and drug delivery function) and drug

Possibility of interaction between objects and packaging materials. Choose appropriate indicators for new

Examine the functionality of the packaging container system and stability of the formulation, such as drug delivery function

Evaluation indicators can be considered, such as delivery dose uniformity, aerodynamic particle size analysis, etc.

Cloth, extractable volume, etc. Multi-dose packaging products may be subject to in-use stability testing

Research. For sterile preparations (such as injections, inhalation solutions, etc.), it is also necessary to

Note that changing the packaging container system may cause packaging sealing and packaging material compatibility

Change risk.

2.6.1 Major changes

including but not limited to:

• Changed packaging container systems may affect the accuracy of administration or delivery of doses

accuracy (e.g. changes in metered dose inhaler valves or actuators).

• Changes to packaging container systems that protect degraded performance.

• Changed packaging may interact with the drug product.

Use better protective packaging container systems for safety reasons.

2.6.2 General changes

including but not limited to:

• A modified packaging container system that provides the same or better protection (not

security reasons).

2.7 Changes in storage conditions

Available formulation stability study data in the early development stages of innovative drugs

Very limited, more conservative storage conditions are usually chosen. With the stability number

With the accumulation of data and the continuous enrichment of knowledge about preparations, more appropriate

Appropriate storage conditions for preparations.

Changes in the storage conditions of the preparation may affect the stability of the preparation, so a

It is generally necessary to provide sufficient stability data to prove the impact of changes in storage conditions on the preparation.

The product has no negative side effects.

2.7.1 Major changes

including but not limited to:

• Changes in storage conditions due to safety reasons.

2.7.2 General changes

including but not limited to:

• Change storage conditions if supported by sufficient stability data

(Non-security reasons).

2.8 Other changes

Changes in dosage forms and specifications may have greater impact on product safety and quality.

Significant impact should generally be considered a major change. When dosage forms and specifications change,

Usually accompanied by changes in prescriptions and processes. Overall research on changes in dosage forms and specifications

The idea is similar to prescription process change. For special formulations (such as metered inhalation into the lungs

aerosols and powder sprays, heterogeneous sterile preparations, sustained-release preparations, etc.),

Pharmacy changes in special processes, complex processes, and unconventional sterilization processes have a negative impact on clinical

In vitro assessment of the potential effects of bed samples may be limited and will need to be done in compliance with this guidance.

Based on the guiding research ideas and combined with the characteristics of the product itself, a more comprehensive

Change research work to obtain more supporting data for changes.

Glossary

1. Early clinical trials: refers to exploring the applicable population and appropriate usage and dosage, and obtaining

An exploratory clinical trial to obtain safety and preliminary efficacy data.

2. Key clinical trials: refers to obtaining core safety and effectiveness to support marketing

confirmatory clinical trials.

3. Key inspection items: refers to those related to safety, effectiveness and quality controllability.

related inspection items.

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