已上市化学药品药学变更研究技术指导原则（试行）

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I. Overview

This guideline applies to research on changes to already marketed chemical raw materials and chemical preparations.

Drug marketing authorization holder/API registration enterprise (hereinafter referred to as the holder/registration enterprise)

Reference when conducting change studies.

Based on the risk of the change affecting the safety, effectiveness and quality controllability of the drug,

The changes described in this guideline are divided into three categories: major changes, moderate changes, and minor changes.

Even. The potential for significant impact on the safety, effectiveness or quality controllability of the drug

The change is a major change; it has an impact on the safety, effectiveness or quality controllability of the drug.

Changes with a moderate probability of

Changes that are likely to have a slight impact on quantity controllability are considered minor changes.

Post-market change management of drugs is part of the full life cycle management of drugs. changes and

The change research work should be based on the research and development during the previous drug registration stage and the actual production process.

Based on data accumulation. The more systematic and in-depth the research work in the registration stage is, the more active it is in the production process.

The more complete the data, the more helpful it will be for post-market change research.

Holders/registrants may refer to these guidelines to research and classify changes.

It can also be adopted based on the continuous and in-depth understanding of drugs, their processes, quality control, etc.

Various change management tools in ICH guidelines (such as ICH Q12, etc.) to manage changes

Research and classification, which will be more conducive to proactive continuous improvement and innovation of already marketed drugs.

Changes covered by this guideline include: changes in excipients, raw materials, etc.

Changes in the production process of drugs and preparations, changes in production sites, changes in production batches, and changes in raw materials used in preparations

Changes in suppliers of raw materials, changes in registration standards, changes in packaging materials and containers, expiration dates and

Storage conditions are changed, specifications are added, and major changes and intermediate changes are listed under each change situation.

and other changes, minor changes, and required research and verification work. listed in this guideline

The above contents are general technical requirements. When conducting change studies, the holder/registered enterprise should

Research should be carried out based on variety characteristics and changes, and should not be limited to those listed in this guideline.

content. At the same time, this guideline cannot cover all changes to already marketed chemicals.

For unlisted changes, the holder/registered enterprise can refer to this guideline and make changes based on the changes.

Conduct research on more specific situations. After the holder/registered enterprise completes the research work, it shall

Administration Law", "Measures for the Administration of Drug Registration", "Measures for the Supervision and Administration of Drug Production", "Measures for the Supervision and Administration of Drug Production", "Measures for the Administration of Drug Registration"

According to the provisions of the Measures for the Management of Post-market Changes of Products (Trial), through supplementary application, filing or

Various changes were implemented in the annual report.

This guidance reflects the current understanding of change classification and change research.

As the situation continues to deepen, this guiding principle will also be continuously improved.

2. Basic principles for research on pharmaceutical changes to already-marketed chemicals

(1) The holder/registered enterprise is the subject of change research

1. Design and carry out change research work

The holder/registered enterprise should deal with the research and development and production of drugs, quality control, and the nature of the product.

etc. have a comprehensive and accurate understanding. When changes occur, the holder/registrant should be aware

The reason for the change, the circumstances of the change and the impact on the drug, design and carry out corresponding changes in response to the change

research work.

This guideline lists each type of change according to major changes, medium changes, and minor changes.

Change Category Study Validation Work Requirements. Considering that each change category includes a variety of specific changes

The research work required for each change situation may be different, so this guide

The research validation work listed in the guidelines may sometimes not cover what is needed in certain change scenarios.

All research work is required, and sometimes some research work may not be applicable to certain change situations.

form, so the holder/registered enterprise needs to determine the type of change, the specific circumstances of the change, and the original

Design and carry out comprehensive consideration of the nature of the drug substance and/or preparation, the impact of changes on the drug, etc.

Related research work. When in vitro study results cannot accurately determine the impact of changes on the safety and effectiveness of the drug

When considering the impact on efficacy and quality controllability, in vivo equivalence studies need to be considered.

2. Comprehensive assessment of the impact of changes on drugs

Possible changes in drug prescriptions, production processes, batch quantities, quality standards, etc.

It has a comprehensive impact on drug safety, effectiveness and quality controllability.

The holder/registered enterprise needs to fully conduct a thorough review of the research results based on the change research.

Analyze, comprehensively evaluate and verify the impact of changes on drug safety, effectiveness and quality controllability

effects, including chemistry, physics, microbiology, biology, bioequivalence, stability

and other aspects to determine the feasibility of change implementation. Strictly speaking, there is no difference between before and after the change.

It must be completely consistent, but it must be equal and equivalent, that is, the quality of the drug must be comparable,

clinically equivalent.

(2) Related changes

A change in a drug often does not occur independently. For example, batch changes often occur simultaneously

Along with changes in production equipment and production processes, changes in prescriptions may accompany or trigger drug registration.

Standard changes, increased specifications may lead to adjustments to prescriptions, etc. This guidance will be accompanied by a change

Or causing other changes are called associated changes.

For related changes, the research work can be carried out in accordance with the research work on each change in this guideline.

The basic ideas can be carried out separately, or they can be combined taking into account the requirements of various change research work.

conduct. Since these changes may have an impact on drug safety, effectiveness and quality controllability,

can be different, that is, these changes may fall into different categories of changes in this guidance.

When carrying out research work according to the corresponding technical requirements for different categories of changes, the research work is generally

It should be carried out according to the change category with higher technical requirements. It is also recommended to pay attention to multiple related changes.

The additive impact on drug safety, effectiveness and quality controllability.

(3) Considerations about samples for research

Pharmaceutical changes to already-marketed chemicals occur during the production stage after the drug is approved for marketing.

More research and verification recommends using commercial production scale samples. If pilot scale samples are used,

Provide sufficient basis.

When conducting studies on changed drugs, various studies (such as formulation studies, process studies

and verification, compatibility studies, sealing studies, dissolution comparative studies, impurity profile comparative studies

Research (including mutagenic impurities, elemental impurities, etc.), detection methodology verification, stability research

etc.) should comply with the requirements of relevant guidelines (including ICH guidelines that have been implemented in China).

When conducting pharmaceutical comparative studies, if the medicine before the change is compared with the reference medicine according to the quality and efficacy

If the preparation is approved for marketing with consistent technical requirements, pharmaceutical comparison with the drug before the change may be considered.

than research. For those requiring in vivo equivalence studies, it is usually recommended to select a reference preparation

Conduct comparative studies. The reference preparation should comply with the relevant requirements of the State Drug Administration.

(4) Considerations for stability studies

When conducting stability studies in accordance with the relevant requirements set out in this guideline, sufficient

Consider whether the research work and research results can fully reflect the stability changes of the drug after the change.

If necessary, it is necessary to increase the number of research batches or extend the research time. For some changes,

On the basis of adequate evaluation, a stability study may not be required for the change.

While providing stability study data in accordance with this guideline, you should also commit to

The sexual research program examines long-term stability and is reported in the annual report.

(5) Pay attention to the impact of changes in raw and auxiliary packages on preparations

Various changes in original and auxiliary packages, such as changes in production processes, batch changes, and quality standards

Changes, etc., may have an impact on the quality of the original and auxiliary packages, which in turn will have an impact on the preparation. drum

Drug marketing authorization holders are encouraged to sign quality agreements with each material supplier and/or manufacturer, and promptly

Master relevant information. When various changes occur to the original and auxiliary packages, the preparations will be adjusted according to the changes in the original and auxiliary packages.

Do the necessary research.

3. Changes in the production process of APIs

Changes in the production process of APIs covered in this guideline mainly refer to chemical synthesis raw materials

The pharmaceutical production process or the chemical synthesis of semi-synthetic APIs and subsequent changes in the production process, generally

Including changes to the synthesis route (such as extending/shortening the synthesis route, changing starting materials, etc.), changes

Production conditions, changes in material control/process control and other possible changes. Production process changes

It is more likely to involve changes in only one of the above situations, or it may involve changes in multiple situations above.

Even. For changes in the synthesis route, the selection of starting materials in the changed synthesis route should comply with

Relevant requirements of ICH Q11.

In this guideline, comparative study results can be considered miscellaneous when they meet the following conditions:

The mass spectra are consistent: ÿ The newly added impurities are not higher than the "Technical Guiding Principles for Research on Impurities in Chemical Drugs"

and the identification limits specified by ICH Q3A; ÿ Existing impurities (including stereoisomers) and impurities

The total quality is within the limits specified in the quality standards. If there is no stipulation in the standard, it should be produced in the original process.

Within the measurement range of multiple batches of products produced; ÿ The residual amount of newly used solvents complies with the "Chemical Drugs

"Technical Guiding Principles for Research on Residual Content of Organic Solvents" and relevant regulations of ICH Q3C; ÿNew

The inorganic impurities comply with the "Technical Guiding Principles for Research on Impurities in Chemical Drugs" and ICH Q3D, etc.

relevant requirements. ÿThe mutagenic impurities should be investigated with reference to ICH M7, and if necessary

control.

(1) Minor changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Add new production process control methods or formulate stricter process control limits,

To better control drug production and ensure drug quality.

If the above changes are due to process defects or instability found during the production of raw materials,

If it is carried out based on qualitative issues, it should be reported as a major change.

(2) Improve the quality standards of starting materials and intermediates.

(3) Change the quality standards of reagents and solvents used in the production process of raw materials or

level, but does not reduce the quality of reaction reagents and solvents.

(4) Change the production equipment used in the process step before the last reaction, or

Change the production equipment used in the final reaction and subsequent process steps and the materials, design and

The working principle remains unchanged, and the impurity spectrum or key physical and chemical properties (such as particle size, crystal form, etc.) of the raw material drug remain unchanged.

Change.

(5) Change the supplier of starting raw materials (referring to the actual manufacturer, the same below), the starting raw materials

The synthetic route of the material remains unchanged, and the quality of the starting raw materials does not decrease.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed process.

(2) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(3) Report the long-term stability test data of the first batch of samples in the annual report.

(2) Medium changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Extend the process route based on the approved process route and use the original starting raw materials as

Intermediates where the extended process route is consistent with the original starting material.

(2) Change the synthesis route of the starting materials without reducing the quality of the starting materials.

(3) Change the reaction reagents and solvent types in the process steps before the last reaction 1

category, production conditions, etc. (except for major changes (4)), but the impurity spectrum of the API remains consistent.

If the above-mentioned added or changed solvent types have been used in the synthesis process of raw materials before the change,

It can be managed according to minor changes.

(4) Caused by incorporating the rework process into the registered production process as a fixed production step

Register production process changes.

(5) Change the quality standards of starting materials and intermediates (except for minor changes (2)),

The quality control level of starting materials and intermediates shall not be reduced after the change.

(6) Change the production equipment and materials used in the final reaction and subsequent process steps

Changes in quality, design and working principle, impurity spectrum of raw materials or key physical and chemical properties (such as granules

Degree, crystal form, etc.) remain unchanged.

(7) The following situations for sterile raw materials:

ÿ Change the filtration parameters of the sterilization filtration process (including flow rate, pressure, time, or volume

area, but the hole diameter remains unchanged) and exceeds the original approved range.

ÿ The sterilization process filter is changed from a single filter to two sterile grade filters in series.

[1] The last reaction step in this guideline is limited to chemical reactions that form covalent bonds, and reactions such as salt formation are not included.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research and analysis on the changed process.

/or verify.

For sterile raw materials, if changes in the production process may affect the level of sterility assurance, it is also necessary to

Perform aseptic/sterilization process validation.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on proving the quality of the samples before and after the change

The impurity spectrum and key physical and chemical properties of the samples are consistent and meet the requirements of relevant guidelines.

(4) Inspect the 1-3 batches of samples produced after the change and they should meet the quality standards.

Regulation.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability study data for no less than 3 months, and compare it with the stability of the product before the change.

For comparison, the stability of the sample after the change should not be lower than before the change.

(3) Major changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change the synthesis route of the API (except for medium changes (1)).

(2) Change the synthesis route of the starting materials, and the quality of the starting materials will change.

(3) Change the last step of the reaction and subsequent production processes (such as changing the type of crystallization solvent)

class, etc.).

(4) Change process parameters that may affect the critical quality attributes of APIs.

(5) Add reprocessing technology to the registered production technology.

(6) Relax or delete the quality control and production process of approved starting materials and intermediates.

Process control may lead to changes in the impurity spectrum and key physical and chemical properties of raw materials.

(7) Changing the equipment in the API production process may result in the impurity spectrum of the API or

Key physical and chemical properties change.

(8) Changes in the production process of sterile APIs may affect the level of sterility assurance in the following situations:

shape:

ÿChange the sterilization/sterile process of raw materials, such as from sterilization filtration, dry heat sterilization,

Change of one process in radiation sterilization to another process.

ÿ Change the pore size of the sterilizing filter used in the aseptic production process.

(9) Others may cause the impurity spectrum and key physical and chemical properties of the API to be different from those before the change.

resulting changes.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research and analysis on the changed process.

/or verify.

For sterile raw materials, if changes in the production process may affect the level of sterility assurance, it is also necessary to

Perform aseptic/sterilization process validation.

(2) For changes that affect the product structure, the changed API or the changed

Intermediates were used for structural confirmation.

(3) Provide batch production records of the changed batch of samples.

(4) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change

The impurity spectrum and key physical and chemical properties of the sample should comply with the requirements of relevant guidelines.

(5) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards

Provisions.

(6) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

4. Change of excipients in preparation prescriptions

Changing the excipients in the preparation prescription includes changing the type, dosage, supplier, and technology of the excipients

Level etc.

Generally speaking, changes in the type of excipients are major changes, and changes in colorants and flavorings

More exceptions. Change the formula of coating material for ordinary oral solid preparations, if it is already used in other drugs

It is a minor change that is approved for use and does not affect the dissolution behavior, quality and stability of the preparation.

Changes in the dosage of each excipient in the prescription should be based on the original approved prescription (such as pivotal clinical trials

batch, BE batch) as the comparison target, rather than using the prescription after minor changes or moderate changes.

for comparison purposes. Changes in preservative dosage in non-sterile semi-solid dosage forms are considered separately and are not listed

If the total amount of changes is entered, significant changes may be considered exempt from bioequivalence studies. This guideline

Changes in dosage of excipients that are not covered by the dosage form will be managed as major changes.

This guideline does not cover changes in excipient suppliers and technical levels of dosage forms, please refer to them.

other dosage forms.

Changes to excipients included in registration management, such as the changed excipients have not yet been registered or the registration status

For I, follow major change management.

(1) Minor changes

1. Ordinary oral solid preparations

1.1. Changes

Such changes include but are not limited to the following situations:

(1) Change the supplier of excipients, but the technical level of excipients remains unchanged and the quality of excipients

The quantity does not decrease.

(2) Improve the quality standards of excipients (such as tightening quality control limits) or change the pharmacopoeia version

Changes in quality standards caused by updates or additions.

(3) Remove or partially remove coloring agents and flavoring agents.

(4) Change the ingredient of printing ink to another ingredient used in approved drugs.

point.

(5) Change the dosage of excipients.

Changes in the dosage of excipients are calculated based on the total weight of the original approved prescription (referring to the total weight of the tablet core or gum).

Calculated as a percentage (w/w) of the total weight of the capsule contents (the same below), it should be less than or equal to the following

The percentage range in the table.

Table 4-1 Changes in the dosage of excipients for ordinary oral solid preparations (minor changes)

		Percentage of excipients in total weight of original approved prescription (w/w)
Excipients and fillers		±5
disintegrant	Starch	±3
	other	±1
Adhesive		±0.5
Lubricant	Calcium stearate or magnesium stearate	±0.25
	Other	±1
glidant	talc powder	±1
	other	±0.1

The raw material drug is calculated at 100% of the labeled amount, and the total amount of changes in all excipients shall not exceed

5% (for example: a product formulation includes active ingredient A, lactose, microcrystalline cellulose and hard

If the amounts of magnesium fatty acid, lactose and microcrystalline cellulose are changed, the total change should not exceed 5%.

For example, if lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%, the total change is 5%).

The total weight of the single-dose prescription should be the same as the original approved total weight or total weight range, otherwise it should be

Conduct research on moderate or major changes.

Just as an excipient plays different roles in a formulation, it is recommended that the most stringent changes

Classification, such as starch paste as a binder, starch also acts as a disintegrant, recommended

The limit for minor changes is 0.5%.

1.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(3) Supply of excipients that may affect dissolution behavior (such as SDS, polysorbate 80, etc.)

For changes in suppliers, comparative studies should be conducted on samples before and after the change to prove that the drugs before and after the change

The dissolution curves are consistent.

(4) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

2. Oral sustained-release/controlled-release preparations and enteric-coated preparations

For such preparations, appropriate demonstration means (such as drug release mechanism and preparation

Preparation method), prove which excipients have a significant impact on drug release, that is, drug release control

Excipients, which are excipients that have little effect on drug release, that is, non-drug release controlled excipients,

The function of each excipient in the formula should be clear. Taking film-controlled sustained-release tablets as an example, sustained-release coating materials

(such as ethylcellulose), plasticizers, and porogens can all be classified as drug release controlled excipients, and tablets

Excipients such as core fillers (such as microcrystalline cellulose) are non-drug release controlled excipients. Two types of excipients

The calculation methods for usage changes are different, and the allowable limits for changes are also different.

2.1. Changes

2.1.1. Changes in non-drug-releasing controlled excipients

Such changes include but are not limited to the following situations:

(1) Change the supplier of excipients, but the technical level of excipients remains unchanged and the quality of excipients

The quantity does not decrease.

(2) Improve the quality standards of excipients (such as tightening quality control limits) or change the pharmacopoeia version

Changes in quality standards caused by updates or additions.

(3) Remove or partially remove colorants, flavoring agents, or components of printing ink

Change to another ingredient used in an approved drug.

(4) Change the dosage of excipients.

Changes in the dosage of non-drug-releasing controlled excipients, as a percentage of the total weight of the original approved prescription

Ratio (w/w) calculation, should be less than or equal to the percentage range in the table below.

Table 4-2 Changes in the dosage of non-release controlled excipients in oral sustained-release/controlled-release preparations and enteric-coated preparations (micro

small changes)

		Percentage of excipients in total weight of original approved prescription (w/w)
Excipients and fillers		±5
disintegrant	Starch	±3
	other	±1
Adhesive		±0.5
Lubricant	Calcium stearate or stearin	±0.25
		±1
glidant	Magnesium	±1
	acidate other talc powder other	±0.1

The raw material drug is calculated at 100% of the labeled amount, and the total amount of changes in all excipients shall not exceed

5%ÿ

The total weight of the single-dose prescription should be the same as the original approved total weight or total weight range, otherwise it should be

Conduct research on moderate or major changes.

2.1.2. Changes in controlled drug release excipients

Such changes include but are not limited to the following situations:

(1) Change the supplier of excipients, but the technical level of excipients remains unchanged and the quality of excipients

The quantity does not decrease.

(2) Improve the quality standards of excipients (such as tightening quality control limits) or change the pharmacopoeia version

Changes in quality standards caused by updates or additions.

(3) Change the dosage of excipients.

Changes in controlled-release excipients are calculated based on their proportion of all controlled-release excipients in the original approved prescription.

Calculated as a percentage of the total weight of the material (w/w), it should not exceed 5%. The main drug is 100% of the labeled amount

Feeding. The total change in the dosage of all drug release controlled excipients should not exceed 5%. Total product weight

The weight should be the same as the original approved weight, otherwise the study should be conducted as a moderate or major change.

For example: a prescription consists of active ingredient A, sustained-release coating material and plasticizer

dosage form, if the change complies with the minor change requirements, the extended-release coating material and plasticizer

The total amount of change in the total weight percentage of the sustained-release coating material and plasticizer should not exceed

5%, if the sustained-release coating material increases by 2.5% and the plasticizer decreases by 2.5%, the total change is

5%ÿ

2.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(3) When changing the supplier of controlled release excipients, a comparison of samples before and after the change should be made.

Comparative studies have proven that the drug dissolution curves before and after the change are consistent.

(4) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

3. Non-sterile semi-solid preparations

3.1. Changes

Such changes include but are not limited to the following situations:

(1) Remove or partially remove coloring agents and flavoring agents.

(2) Improve the quality standards of excipients (such as tightening quality control limits) or change the pharmacopoeia version

Changes in quality standards caused by updates or additions.

(3) Change the dosage of excipients.

The change in the dosage of each excipient shall not exceed 5% of the original approved dosage of the excipient. The dosage of all excipients

The total number of changes should not exceed 5%. However, due to changes in the prescription, diluents (such as water) are used

The amount of change is allowed to exceed this range.

(4) The change in preservative dosage shall not exceed 10% of the original approved dosage.

(5) Changes in matrix suppliers whose structure is a single chemical entity (purity ÿ95%),

Or changes in other excipient suppliers or technical levels.

3.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(3) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

(4) If the preservative is changed, a test with the lowest concentration of bacteriostatic agent within the specified range should be carried out.

Antibacterial efficacy test.

(2) Medium changes

1. Ordinary oral solid preparations

1.1. Changes

Such changes include but are not limited to the following situations:

(1) Change the type of colorants and flavoring agents or increase their dosage. The dosage is generally less than 2% (w/w) of the total weight of the prescription. The colorants and flavoring agents used should comply with relevant regulations and standards. This change does not affect the differences between specifications or the taste compliance of children's medicines. safety, will not cause potential safety issues, etc.

(2) Change the technical grade of excipients, such as replacing microcrystalline fiber with microcrystalline cellulose PH200 PH101). The technical grade of excipients is mainly related to the quality standards, uses, and impurity status of excipients. Conditions etc. related.

(3) Change the quality standards of excipients (except for minor changes (2)), quality control standards Flat does not decrease.

(4) Change the dosage of excipients.

Change in dosage of excipients, calculated as a percentage (w/w) of the total weight of the original approved prescription calculated, exceeds the range of minor changes, but is less than or equal to the percentage range in the table below (treatment Drugs with narrow windows and drugs with low solubility and low permeability (except BCS Class IV).

Table 4-3 Changes in excipient dosage of common oral solid preparations (moderate change)

		Percentage of excipients in total weight of original approved prescription (w/w)
Excipients and fillers		±10
disintegrant	Starch	±6
	other	±2
Adhesive		±1
Lubricant	calcium stearate or hard Magnesium	±0.5
	fatty acid	±2
glidant	other Talc	±2
	powder other	±0.2

The raw material drug is calculated at 100% of the labeled amount, and the total amount of changes in all excipients shall not exceed 10%, and the change in the total weight of a single dose prescription shall not exceed 10% of the original approved total weight.

1.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and analyze the dissolution of the samples before and after the change.

The output curve, impurity spectrum, key physical and chemical properties, etc. should be consistent and comply with relevant guidelines.

requirements.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability study data for no less than 3 months, and compare it with the stability of the product before the change.

After comparison, the stability of the sample after the change is not lower than before the change.

(6) If the product before the change was exempted from bioequivalence based on the biopharmaceutical classification system

Marketed drugs must still comply with relevant exemption principles (such as ICH M9) after changes, otherwise they should

Conduct bioequivalence studies and make supplementary applications in accordance with major changes.

2. Oral sustained-release/controlled-release preparations and enteric-coated preparations

2.1. Changes

2.1.1. Changes in non-drug-releasing controlled excipients

Such changes include but are not limited to the following situations:

(1) Change the type of colorants and flavoring agents or increase their dosage. The dosage is generally less than

2% (w/w). The colorants and flavoring agents used should comply with relevant regulations and standards. This change

It will not affect the differences between specifications, will not affect the taste compliance of children's medicines, and will not cause

Potential security issues.

(2) Change the technical grade of excipients.

(3) Change the quality standards of excipients (except for minor changes (2)), quality control standards

Flat does not decrease.

(4) Change the dosage of excipients.

Changes in the dosage of non-drug-releasing controlled excipients shall be calculated as a percentage of the total weight of the original approved prescription

Ratio (W/W) calculation, beyond the range of minor changes, but less than or equal to the percentage in the table below

ratio range.

Table 4-4 Changes in the dosage of non-release controlled excipients in oral sustained-release/controlled-release preparations and enteric-coated preparations (medium

etc.)

		Percentage of excipients in total weight of original approved prescription (w/w)
Excipients and fillers		±10
disintegrant	Starch	±6
	other	±2
Adhesive		±1
Lubricant	calcium stearate or hard Magnesium	±0.5
	fatty acid	±2
glidant	other Talc	±2
	powder other	±0.2

The raw material drug is calculated based on 100% of the labeled amount, and the changes in the dosage of all non-drug release controlled excipients are

The total amount of changes does not exceed 10%, and the change in the total weight of a single dose prescription does not exceed the original approved total weight.

10%ÿ

2.1.2. Changes in controlled drug release excipients

Such changes include but are not limited to the following situations:

(1) Change the technical grade of controlled drug release excipients.

(2) Change the quality standards of controlled release excipients (except for minor changes (2)),

The level of quality control is not reduced.

(3) Change the dosage of controlled drug release excipients.

The main drug is fed 100% according to the labeled amount. Changes in the dosage of drug release controlled excipients are calculated according to their proportion

Calculation of the percentage (w/w) of the total weight of all drug release controlled excipients in the original approved prescription, exceeding

The scope of minor changes, but not more than 10%. The total weight of a single dose prescription does not vary by more than

10% of the original approved total weight.

2.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and review the changed prescription

Research.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and analyze the dissolution of the samples before and after the change.

The output curve, impurity spectrum, key physical and chemical properties, etc. should be consistent and comply with relevant guidelines.

the requirements of the rules.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability research data for no less than 3 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

3. Non-sterile semi-solid preparations

3.1. Changes

Including but not limited to the following situations:

(1) Change the dosage of excipients.

The change in the dosage of each excipient exceeds the scope of minor changes, but does not exceed the original approved dosage.

10%. The total amount of changes in all excipients shall not exceed 10%. dilution due to change in prescription

The dosage of release agent (such as water) is allowed to change beyond this range.

(2) The change in the amount of preservatives is greater than 10% of the original approved amount, but not more than 20%

(3) Changes in substrate suppliers not covered by minor changes.

(4) Change the technical level of the substrate.

(5) Changes in quality standards for excipients (except for minor changes (2)), quality control levels

Not lowered.

3.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and analyze the dissolution of the samples before and after the change.

The output curve, impurity spectrum, key physical and chemical properties, etc. should be consistent and comply with relevant guidelines.

requirements.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability research data for no less than 3 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

(6) If the preservative is changed, the bacteriostasis should be carried out with the lowest concentration of bacteriostatic agent within the specified range.

Efficacy testing.

(3) Major changes

1. Ordinary oral solid preparations

1.1. Changes

Such changes include but are not limited to the following situations:

(1) The change in excipient dosage exceeds the range of medium change.

(2) The changes in excipient dosage of drugs with narrow therapeutic windows exceed the scope of minor changes.

(3) The excipient dosage of low-solubility and low-permeability drugs (BCS Class IV) changes by more than

range of minor changes.

1.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and review the changed prescription

Research.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change

The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the sample should comply with relevant guidelines.

Require.

(4) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards.

Provisions.

(5) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

(6) Bioequivalence studies generally need to be considered. If applying for a bioequivalence exemption

Research requires adequate research and analysis.

2. Oral sustained-release/controlled-release preparations and enteric-coated preparations

2.1. Changes

(1) The change in the dosage of non-drug-releasing controlled excipients exceeds the range of moderate changes.

(2) The change in the dosage of drug release controlled excipients exceeds the range of moderate changes.

(3) The changes in the dosage of excipients for drugs with narrow therapeutic windows exceed the scope of minor changes.

2.2. Research and verification work

(1) Explain the specific changes and reasons, and conduct research on the changed prescription.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change

The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the sample should comply with relevant guidelines.

Require.

(4) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards.

Provisions.

(5) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

(6) Bioequivalence studies generally need to be considered. If applying for a bioequivalence exemption

Research requires adequate research and analysis.

3. Non-sterile semi-solid preparations

3.1. Changes

Such changes include but are not limited to the following situations:

(1) The change in excipient dosage exceeds the range of medium change.

(2) The change in the amount of preservatives exceeds 20% of the original approved amount (including deletion of preservatives

agent).

3.2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed prescription.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change

The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the sample should comply with relevant guidelines.

Require.

(4) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards.

Provisions.

(5) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

(6) If the preservative is changed, the bacteriostasis should be carried out with the lowest concentration of bacteriostatic agent within the specified range.

Efficacy testing. For new preservatives, new content determination methods should be established and relevant

Verification to prove that preservatives do not interfere with the testing of other items.

(7) Bioequivalence studies generally need to be considered. If applying for a bioequivalence exemption

Research requires adequate research and analysis.

5. Change of preparation production process

Changes in the preparation production process mainly include changes in the preparation production process and process parameters, changes

Internal control standards for raw materials/internal control standards for preparation intermediates or production process control, changes in preparation production

Production equipment, etc.

After the preparation production process is changed, corresponding research work needs to be carried out to evaluate the impact of the change.

Impact on drug safety, effectiveness and quality controllability. Research work should be based on the following aspects

Comprehensive process: ÿ The degree of impact of the change on the preparation. ÿThe complexity and difficulty of the preparation production process.

ÿPreparation dosage forms, etc.

(1) Minor changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Add new production process control methods and formulate stricter quality control standards (including

Including internal control standards for raw materials/internal control standards for preparation intermediates or production process controls) to better

to control drug production and ensure drug quality.

If the above changes are due to process defects or stability problems during the production of the preparation,

If it is carried out on a certain topic, it should be reported as a major change.

(2) Change the mixing time of general oral solid preparations (powder mixing, granule mixing)

and drying time; change the mixing time of solution-type preparations.

(3) The hardness of the tablet is changed, but the drug dissolution behavior before and after the change does not change.

(4) Change solution-type preparations or solutions used in unit operations (such as granulation solutions)

The order in which the components (except raw materials) are added, the aqueous phase preparation of non-sterile semi-solid preparations, or

The order in which excipients are added when preparing the oil phase.

(5) Add a sieving step to material pretreatment under non-sterile conditions to remove agglomerations.

(6) Eliminate or reduce the number of preparation production batches previously used to compensate for production losses.

Prescription overdosing.

(7) For sterile preparations produced by terminal sterilization process, the process of changing the filtration step

parameter.

(8) Minor changes in the shape and size of ordinary oral tablets, capsules or suppositories, but

The drug dissolution behavior before and after the change did not change. For example, the slight curvature of a tablet edge or surface

Fine adjustments.

(9) Change the markings of ordinary oral solid preparations and suppositories. This change is included in the film

Add, delete or modify printing, markings, etc. on the surface of pharmaceuticals, capsules or suppositories, but functional inscriptions

Except for marks.

(10) Production equipment of the same design and working principle replaces another equipment.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research on the changed process.

(2) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(3) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

(2) Medium changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change process parameters that do not affect the critical quality attributes of the preparation.

(2) Change quality control standards (including internal control standards for raw materials/internal control standards for preparation intermediates)

or production process control) analytical method, but does not reduce the quality control level of the preparation.

(3) Significant changes in the shape and size of ordinary oral tablets, capsules or suppositories, but

The drug dissolution behavior before and after the change did not change. For example, change a circle into a special shape, etc.

(4) Production equipment of different design and working principle replaces another equipment.

(5) The organic solvent in the coating solution for ordinary oral solid preparations is changed to water.

(6) For sterile preparations, the following situations include:

ÿ Sterile preparations produced by terminal sterilization process, eliminating the filtration loop in the intermediate process

section, or change the material and pore size of the filter;

ÿ Change the filtration parameters of the sterilization filtration process (including flow rate, pressure, time, or volume

area, but the hole diameter remains unchanged) and exceeds the original approved range.

ÿ Change from a single filter to two sterile grade filters in series.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research and/or research on the changed process or verify.

For sterile preparations, if changes may affect the level of sterility assurance, sterility testing is also required. /Sterilization process validation.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and analyze the dissolution of the samples before and after the change. The output curve, impurity spectrum, and key physical and chemical properties should be consistent and comply with relevant guidelines. Require.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying. Provide stability study data for no less than 3 months, and compare it with the stability of the product before the change. Line comparison. The stability of the sample after the change should not be lower than before the change.

(3) Major changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Fundamental changes occur in the preparation production process or production technology, such as oral solid The preparation is changed from wet granulation to dry granulation, or vice versa; such as drying method in the production process Change from oven drying to fluidized bed drying or vice versa.

(2) Changes in the preparation production process that may affect the controlled-release or sustained-release properties of the preparation may Affects the in vivo absorption of the preparation (such as inhaled preparations), or affects other critical quality attributes of the preparation of.

(3) Relax or delete approved quality control standards (including internal control standards for raw materials/preparations)

Intermediate internal control standards or production process control).

(4) Change the type of solvent used in unit operations during the preparation production process (moderate change

(Except 5)). For example, the granulation solvent was changed from water to ethanol.

(5) Change the shape, size and marking of sustained- and controlled-release preparations.

(6) Add or delete functional notches on the tablet.

(7) Situations in which changes in the production process of sterile preparations may affect the sterility assurance level of drugs:

ÿ Change the product sterilization process from sterilization filtration sterilization process to terminal sterilization process

Or the opposite change; the terminal sterilization process is changed from the residual probability method to the overkill method or

Opposite change; changing from one sterilization process of dry heat sterilization or radiation sterilization to another

Sterilization process, etc.

ÿ Change the pore size of the sterilizing filter used in the aseptic production process.

2. Research and verification work

(1) Explain the specific circumstances and reasons for the change, and conduct research and/or research on the changed process

or verify.

For sterile preparations, if changes may affect the level of sterility assurance, sterility testing is also required.

/Sterilization process validation.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change

The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the sample should comply with relevant guidelines.

Require.

(4) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards.

Provisions.

(5) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change.

(6) Ordinary oral solid preparations for drugs with narrow therapeutic windows or poorly water-soluble drugs

and sustained-release preparations. Such changes may affect drug safety, effectiveness and quality controllability.

If there is a significant impact, bioequivalence studies generally need to be considered. Other preparations should be

Consider whether it is necessary based on the complexity of the process, drug characteristics, changes, etc.

Bioequivalence testing is required. If applying for exemption from bioequivalence studies, sufficient

Research and analysis.

6. Change the supplier of raw materials used in preparations

Suppliers who change the raw materials used in preparations shall not be responsible for the safety, effectiveness and quality of the drug.

Controllability has a negative impact.

To reduce the number of API suppliers or change the name of the API supplier (the main body remains unchanged), click on the micro button

Small change management, no research and verification required.

The changed API is an approved API and is generally managed as a medium change.

If the changed API has not yet been approved, it will be managed as a major change. All need to be carried out

The following research and verification work:

1. Explain the specific circumstances and reasons for the change.

2. Provide quality standards for raw materials before and after changes.

3. Conduct a comprehensive quality comparative study on the raw materials before and after the change, and compare the quality with the preparations

Relevant key physical and chemical properties (such as crystal form, particle size, etc.) should remain consistent. After the change, the API

Impurity control should comply with the requirements of relevant guidelines.

4. Conduct a comparative study on the quality of preparations prepared using raw materials before and after the change,

The dissolution curves and key physical and chemical properties of the samples before and after the change should be consistent, and the impurity control should comply with

In line with the requirements of relevant guidelines, the quality of preparations should be consistent.

5. Inspection of three batches of preparations produced continuously using the changed API shall comply with

stipulations of quality standards.

6. Accelerate and long-term stability of three batches of preparations produced using the changed API

During the inspection, provide 3-6 months of stability research data when applying, and compare it with the stability of the product before the change.

Compare the qualitative situation and the stability of the product after the change is not lower than before the change.

7. If there are differences in the dissolution curve and key physical and chemical properties of the preparation before and after the change, one

Generally, it is necessary to consider conducting bioequivalence studies. If applying for exemption from bioequivalence studies, it is necessary to conduct

Fully researched and analyzed. This situation should be managed as a major change.

7. Change the production batch size

Production batch changes refer to changes in the original approved batches (such as critical clinical trial batches, BE batches, etc.)

Expand or reduce production batches based on the requirements. Production batch size is reduced to relevant guidelines or technical requirements

It is not required to reduce the batch size below the specified batch size (for example, the batch size of oral solid preparations is reduced to less than 100,000 tablets).

within the scope of this guideline. If the production batch is changed, the process parameters, production

If equipment, etc. is changed, related change research must be conducted in accordance with the requirements of the relevant chapters of this guideline.

(1) Changes in batches of raw materials

1. Minor changes

1.1. Changes

The production batch size of the API is changed within 10 times (including 10 times) of the original approved batch size.

1.2. Research and verification work

(1) Explain the specific circumstances and reasons for the batch change, and describe the production process before and after the change

Conduct comparative analysis with the design and working principles of production equipment, and conduct research on the changed batches

research and/or verification. For sterile APIs, sterility/sterilization process verification is also required.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and determine the quality of the samples before and after the change.

Mass spectrometry, key physical and chemical properties, etc. should be consistent and comply with the requirements of relevant guidelines.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

2. Moderate changes

2.1. Changes

The production batch size of the API is changed to more than 10 times the original approved batch size.

2.2. Research and verification work

(1) Explain the specific circumstances and reasons for the batch change, and describe the production process before and after the change

Conduct comparative analysis with the design and working principles of production equipment, and conduct research on the changed batches

research and/or verification. For sterile APIs, sterility/sterilization process verification is also required.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and determine the quality of the samples before and after the change.

Mass spectrometry, key physical and chemical properties, etc. should be consistent and comply with the requirements of relevant guidelines.

(4) Inspect the three batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability research data for no less than 3 months, and compare it with the stability of the product before the change.

After comparison, the stability of the sample after the change is not lower than before the change.

(2) Changes in batches of preparations

1. Minor changes

1.1. Changes

Such changes include but are not limited to the following situations:

(1) The production batch size of ordinary oral solid preparations and non-sterile semi-solid preparations is changed in

Within 10 times (inclusive) of the critical clinical trial batch or BE batch.

(2) Changes in production batches of non-sterile liquid preparations.

(3) For preparations using terminal sterilization technology, under the premise that the microbial load level remains unchanged,

The solution storage time shall not be increased by more than 50% of the original approved time limit.

1.2. Research and verification work

(1) Explain the specific circumstances of the batch change and the reasons for the change, and analyze the production before and after the change.

Comparative analysis of the design and working principles of processes and production equipment, and batch batch changes after changes

Conduct research and/or verification.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the samples before and after the change, and determine the dissolution profiles of the samples before and after the change.

lines, impurity spectra, key physical and chemical properties, etc. should be consistent and comply with the requirements of relevant guidelines.

beg.

(4) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(5) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

2. Moderate changes

1.1. Changes

Such changes include but are not limited to the following situations:

(1) The production batch size of ordinary oral solid preparations and non-sterile semi-solid preparations is changed in

More than 10 times the volume of the pivotal clinical trial batch or BE batch.

(2) For preparations using terminal sterilization technology, under the premise that the microbial load level remains unchanged,

The solution storage time is increased by more than 50% of the original approved time limit.

(3) Batch changes of sterile preparations using aseptic production processes, while maintaining sterility

Production time of steps related to barrier level (including liquid preparation, liquid storage, filtration, filling, etc.)

Increase.

1.2. Research and verification work

(1) Explain the specific circumstances of the batch change and the reasons for the change, and describe the production before and after the change.

Conduct comparative analysis on the design and working principles of the production process and production equipment, and analyze the batch size after the change.

Conduct research and/or verification. For sterile preparations, aseptic/sterilization processes are required if necessary

verify.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a comparative study on the quality of the samples before and after the change, and analyze the dissolution of the samples before and after the change.

The output curve, impurity spectrum, key physical and chemical properties, etc. should be consistent and comply with relevant guidelines.

requirements.

(4) Inspect the three batches of samples after the change and they should comply with the quality standards.

(5) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability research data for no less than 3 months, and compare it with the stability of the product before the change.

After comparison, the stability of the sample after the change is not lower than before the change.

3. Major changes

3.1. Changes

Such changes include but are not limited to the following situations:

Special dosage form preparations (such as complex process sustained-release preparations and enteric-coated preparations, transdermal drug delivery preparations, liposomes, long-acting preparations, etc.).

3.2. Research and verification work

(1) Explain the specific circumstances and reasons for the batch change, and analyze the production process and production process before and after the change. Comparative analysis of the design and working principles of production equipment, and study of batches after changes and/or verification. For sterile preparations, aseptic/sterilization process verification is required when necessary.

(2) Provide batch production records of the batch of samples after the change.

(3) Conduct a quality comparative study on the samples before and after the change, focusing on comparing the quality before and after the change The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the sample should comply with relevant guidelines. Require.

(4) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards. Provisions.

(5) Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and submit them when applying. Provide stability research data for 3-6 months and compare with the stability of the product before the change Comparatively, the stability of the product after the change is not lower than before the change.

(6) Based on the changes, comprehensively evaluate whether bioequivalence studies are needed, If you apply for exemption from bioequivalence studies, you need to consider the complexity of the process, drug characteristics, batch Comprehensive consideration should be given to quantity changes, production equipment conditions and other aspects to provide sufficient basis.

8. Change of registration standards

Changes to drug registration standards generally include changes to the inspection standards in the registration standards for raw materials and preparations.

Inspection items, inspection methods, limits, etc. Changes in drug registration standards may only involve one of the above

Changes in one situation may also involve changes in many of the above situations.

Generally speaking, changes to the registration standards for raw materials and preparations should not cause changes in drug quality control levels.

flat reduction. It is still necessary to consider whether changes to drug registration standards will affect the validity period of the drug.

If the standards are improved (such as tightening limits, adding inspection items, optimizing testing methods

etc.), it is necessary to examine whether the drug meets the requirements of the revised quality standards during the original validity period.

beg.

For changes in registration standards caused by changes in national drug standards, please refer to relevant publications.

Implementation of reporting requirements (for example, the State Food and Drug Administration's Notice on the Implementation of the "Pharmaceuticals of the People's Republic of China")

Announcements on matters related to the Code).

(1) Moderate changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Add new inspection items.

The new inspection items should be able to control product quality more effectively. The method of adding new inspection items should be

Legal verification and proposed control limits should comply with the requirements of relevant guiding principles.

This change does not include additional inspection items due to safety or quality controllability reasons.

In addition, due to changes in the production process resulting in changes in pharmaceutical properties, the addition of

Inspection items also do not fall within the scope of such changes. For example, after the API is switched to micronization,

Added particle size distribution check to standard.

(2) Tighten the limits within the scope of the original standard

This type of change refers to tightening the control limits within the scope of the original standard. For example, API

Or the preparation has been verified through multiple batches of production, and the indicators such as moisture and related substances can achieve better results.

control levels, thereby tightening control limits.

The scope of the limit is reduced due to major changes in the production process and prescription of the drug.

Small does not fall within the scope of such changes. For example, adding micronization treatment in the production process of raw materials and

Causes changes with smaller granularity.

(3) Changes in the Chinese text description of the registration standard. Such changes should not involve inspection methods,

Changes in limits, etc.

2. Research and verification work

(1) Explain the specific changes and reasons, and provide the changed quality standards.

(2) Research the rationality of changes in quality standards.

If the limit revision is involved, a certain batch of samples (suggested to include samples with near-expiry date) need to be batched

The analysis results are summarized to provide basis for revision of limits. In addition, it is necessary to examine the validity of the original plan

During the period, whether the drugs meet the requirements of the revised quality standards.

If additional testing items are involved, methodological research on the testing methods (including methods

selection, verification) and provide the basis for setting limits. A certain batch of samples (recommended to contain approximately

Expiration date samples) batch analysis results are summarized to examine whether the drug is

Whether it meets the requirements of the revised quality standards.

(3) Inspect the three batches of samples according to the changed quality standards and they should comply with the regulations.

(2) Major changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change the inspection method.

(2) Relax control limits.

(3) Delete any items in the registration standards.

2. Research and verification work

(1) Explain the specific changes and reasons, and provide the changed quality standards.

(2) Research the rationality of changes in quality standards.

If there is a change in the inspection method, methodological research and verification of the new method must be carried out and the changes must be coordinated accordingly.

Compare with the previous method to ensure that the method change does not cause a decrease in the quality control level of the drug.

In addition, the batch analysis results of a certain batch of samples (recommended to include samples with near-expiration dates) need to be summarized.

To examine whether the drugs meet the requirements of the revised quality standards within the original validity period.

If it involves deleting any content in the standard, it must be combined with drug production process control, drug research and development

Comprehensive analysis of the development process and drug properties and prove that the change will not cause drug quality control

reduction in control levels.

If it involves relaxing the control limits, detailed research needs to be conducted and, if necessary, safety related

Supported by safety and/or effectiveness trial data or literature. Limit changes must also be based on certain

The test data of batch samples are in compliance with relevant technical guidelines.

(3) Inspect the three batches of samples according to the changed quality standards and they should comply with the regulations.

9. Change packaging materials and containers

Packaging materials and containers are integral parts of pharmaceutical products. The packaging materials covered by this guideline

and containers mainly refer to packaging that comes into direct contact with pharmaceuticals. Changes in packaging materials and containers may affect the drug's

It will affect the physical and chemical properties, impurity spectrum, content, stability, etc. of the product. The risk depends on the manufacturing process.

route of administration, performance of packaging materials and containers, and compatibility of packaging and formulations, etc.

Generally speaking, changes to the packaging materials and containers of drugs should be able to ensure the quality and stability of the drugs.

Play a beneficial role and must not affect the protection, functionality, safety and quality of the drug.

adverse effects.

Changes to the packaging materials and containers of drugs covered by this guideline include changes, additions

or removal circumstances.

(1) Minor changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change the packaging volume of raw materials and single-dose packaging preparations, such as grams per bag

number, the number of capsules per plate, the number of injections per box, etc.

(2) Packaging materials for raw materials and non-sterile solid preparations not specified in these guidelines

and changes in material and/or type of container. The changed packaging materials and containers have been

Used in marketed drugs with the same route of administration and have the same or better applicability.

(3) Suppliers, sizes and/or packaging materials and containers not specified in these guidelines

or change in shape.

2. Research and verification work:

(1) Explain the reasons for the change of packaging materials and containers, and describe in detail the changed packaging

Packing materials and containers. List the changed quality standards for packaging materials and containers.

(2) Comparative study on the related characteristics of packaging materials and containers before and after the change.

(3) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(4) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

(2) Medium changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change the packaging quantity of multi-dose packaging preparations, such as the number of tablets per bottle, the number of tablets per bottle Grams, milliliters per bottle, etc.

(2) Change of liquid/semi-solid preparations (except inhalation preparations, injections, ophthalmic preparations), Material and/or type of packaging materials and containers for sterile and/or liquid drug substances. For example, oral Liquid medicinal polypropylene bottles are changed to oral liquid medicinal polyester bottles, etc.

(3) Changing the material and/or type of packaging materials and containers for non-sterile solid preparations The following situations: For example, changes between blister packaging, bottles, bags, etc., changes in double aluminum blister packaging For aluminum-plastic blister, etc.

(4) Change the supplier, size and/or shape of packaging materials and containers for injections.

2. Research and verification work

(1) Explain the reasons for the change of packaging materials and containers, and describe in detail the changed packaging Packing materials and containers. List the changed quality standards for packaging materials and containers.

(2) Comparative study on the related characteristics of packaging materials and containers before and after the change, and conduct packaging materials equivalence/substitutability studies.

(3) Conduct packaging material compatibility research as appropriate. Changes to seals should also be packaged Installation sealing study.

(4) Carry out packaging process verification. For sterile products, perform sterilization/sterilization when necessary Process Validation.

(5) Inspect the 1-3 batches of samples after the change and they should comply with the quality standards.

(6) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability study data for no less than 3 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change. Depending on the changes, proceed as appropriate

Conduct in-use stability studies.

(3) Major changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change the packaging materials and container materials of inhalation preparations, injections, and ophthalmic preparations

quality and/or type. For example, the three-layer co-extruded infusion bag is changed to a five-layer co-extruded infusion bag, polypropylene

The infusion bottle was changed to an upright polypropylene infusion bag, and the soda-lime glass infusion bottle was changed to a five-layer

Squeeze the IV bag.

(2) Change the supplier, size and/or shape of the dosing device for inhaled preparations.

(3) Remove secondary packaging that provides additional protection to the drug product (e.g., high-barrier outer bags).

(4) Change to packaging with new materials, new structures, and new uses with increased risk

Materials and Containers.

(5) Changes in packaging materials and containers included in registration management, packaging materials after changes

and the container has not yet been registered or the registration status is I.

2. Research and verification work

(1) Explain the reasons for the change of packaging materials and containers, and describe in detail the changed packaging

Packing materials and containers. List the changed quality standards for packaging materials and containers.

(2) Comparative study on the related characteristics of packaging materials and containers before and after the change, and conduct packaging materials

equivalence/substitutability studies.

(3) Conduct packaging material compatibility research as appropriate. Changes to seals should also be packaged

Installation sealing study. For changes to the dosing device, the characteristics of the dosing device must be

Conduct corresponding studies to prove that the dosage accuracy after the change is not lower than before the change.

(4) Carry out packaging process verification. For sterile preparations, perform sterilization/sterilization when necessary

Process Validation.

(5) Inspect the three batches of samples produced continuously after the change and they should meet the quality standards

Provisions.

(6) Conduct accelerated and long-term stability studies on the three batches of samples after the change, and submit them when applying.

Provide stability study data for 3 to 6 months, and compare it with the stability of the product before the change.

By comparison, the stability of the product after the change is not lower than before the change. Depending on the changes, proceed as appropriate

In-use stability studies.

10. Change of validity period and storage conditions

Changes in the validity period and storage conditions of drugs may include the following situations: ÿ Extended validity

period; ÿ shorten the validity period; ÿ strict storage conditions; ÿ relax storage conditions. Changes may only

Changes involving one of the above circumstances may also involve changes in multiple of the above circumstances.

(1) Moderate changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Extend the validity period of drugs

The validity period change is mainly based on the long-term stability test results. Extending the validity period of medicines should not

The time after which long-term stability testing has been completed has exceeded.

(2) Shorten the validity period of drugs

Such changes do not include requests to shorten the duration of a drug due to problems with its production or stability.

Product expiry date.

2. Research and verification work

(1) Explain the validity period after the change and the reason for the change.

(2) Provide long-term stability investigation data of three batches of samples.

(2) Major changes

1. Changes

Such changes include but are not limited to the following situations:

(1) Change drug storage conditions.

(2) Due to the production process, prescription, quality standards, direct contact with drugs

Changes in validity due to changes in packaging materials, containers, etc.

2. Research and verification work

(1) Explain the storage conditions and/or validity period after the change, and study and explain the reasons for the change.

(2) According to the determined stability test plan, conduct stability inspections on three batches of samples,

Provide stability study data for 3 to 6 months.

11. Add specifications

The additional strengths covered by this guideline refer to single-dose pharmaceutical products such as tablets/capsules.

The amount of the main drug indicated in the single-dose prescription, the amount of the main drug indicated in the single-dose packaging of the injection/

Concentration, drug concentration in prescriptions for non-sterile semi-solid preparations/oral solutions/eye drops and other preparations

degree of change. The new specifications should be new specifications added to the original drug or new specifications added to the current original version of the generic drug.

The existing specifications of the investigational drug/reference preparation shall not be changed, and the original approved indications and uses of the drug shall not be changed.

Legal dosage or applicable population, etc. Adding specifications is considered a major change.

Increased specifications should follow the principle of convenient clinical use and should be based on reasonable and scientific basis.

Generally speaking, the increased specifications should generally be within the range of clinical usage and dosage, and should not be larger than

The maximum dose for a single dose in adults, or for adults, shall not be less than the maximum dose for a single dose in adults.

Low dose.

For multi-dose packaging of non-sterile semi-solid preparations/oral liquids/eye drops and other preparations

Changes to single-dose packaging are also reported as increased specifications.

Research verification work:

1. Explain the specific circumstances and reasons for the change.

2. Conduct prescription research, process research and/or verification on the new specifications, and communicate with them before the change

specifications for comparison. For sterile preparations, sterility/sterilization process validation is also required.

3. Provide batch production records of the changed batch of samples.

4. Conduct a comparative study on the quality of samples before and after the specification change, focusing on the comparison before the change.

The dissolution curve, impurity spectrum, key physical and chemical properties, etc. of the final sample should comply with relevant guidelines.

requirements.

5. Inspect the three batches of samples produced continuously after the change and they should meet the quality standards.

Regulation.

6. Conduct accelerated and long-term stability inspections on the three batches of samples after the change, and provide them when applying.

Stability research data for 3 to 6 months, and compare with the stability of the original specification product

Compare.

7. You should refer to the "Generic drug manufacturers using pharmacokinetic parameters as endpoint evaluation indicators".

"Technical Guiding Principles for In vivo Bioequivalence Studies" and other relevant guiding principles, consider adding new regulations

Whether bioequivalence studies are required.

12. Change of production site

Change of production site, including change or addition of production address, or within the same production address

New construction, reconstruction and expansion of production sites.

Changing the production site. Due to the production equipment and production environment (temperature and humidity) of the new production site,

degree), the quality of technical personnel, etc. are difficult to be completely consistent with the conditions of the original production site, which will affect the raw materials,

Preparation production and quality will have a certain impact, which generally requires more comprehensive research work.

Personnel who have worked at the same production address for a period of time and have sufficient experience in the production process,

It can usually be understood as having the same personnel qualities.

Generally speaking, the prescriptions, production processes, batch sizes, etc. of the new and old sites should be consistent, including the original

/Excipients, solvents, packaging materials and containers, quality process control of production, etc. If the venue is changed

At the same time, if its prescription, production process, batch size, etc. are changed, these guidelines must be followed

Relevant sections require associated change studies.

Changes to the production site need to be carried out in accordance with the "Measures for the Supervision and Administration of Drug Production" and the "Drug Listing

The relevant provisions of the Post-Change Management Measures (Trial) will be implemented. Research and verification of production site changes

The work needs to refer to the following content.

(1) Change of API production site

1. Change the non-sterile API or the non-sterile status of the sterile API within the same production address.

The production site of the production steps, as well as the production equipment, operating procedures, and environmental conditions before and after the change

conditions (such as temperature and humidity), quality control processes and personnel quality.

Research verification work includes:

(1) Explain the specific circumstances and reasons for the change, and conduct research on the relevant processes after the change

and/or verification.

(2) Compare the production process conditions of the old and new sites. Production equipment manufacturers before and after the change

Compare the models, models, materials, equipment principles, and key technical parameters, and explain the changes before

Matching of post-production equipment and production process.

(3) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(4) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

2. Change the production site of the sterile production steps of sterile APIs within the same production address,

Or the production address of the API is changed to a different production address.

Research verification work includes:

(1) Explain the specific circumstances and reasons for the change, and conduct research on the relevant processes after the change

and/or verification.

For sterile APIs, sterility/sterilization process verification is also required.

(2) Compare the production process conditions of the old and new sites. Production equipment manufacturers before and after the change

Compare the models, models, materials, equipment principles, and key technical parameters, and explain the changes before

Matching of post-production equipment and production process.

(3) Provide batch production records of the changed batch of samples.

(4) Conduct a comparative study on the quality of the raw materials before and after the change, and conduct a comparative study on the key physical and chemical properties and

Impurity profiles, etc. should be consistent and comply with relevant guidelines.

(5) Inspect the three batches of samples after the change and they should comply with the quality standards.

(6) Conduct accelerated and long-term stability inspections on the batch of samples after the change, and submit it when applying.

Provide stability study data for no less than 3 months, and compare it with the stability of the product before the change.

For comparison, the stability of the sample after the change should not be lower than before the change.

(2) Change of preparation production site

1. Change the location of the printing process of solid oral preparations, change the secondary packaging and outsourcing

The site for the packaging process and labeling process, and the sterilization site for changing packaging materials and containers should be in the same place.

Changes to the production and primary packaging site of non-sterile preparations, intermediates within the production address (change

Before and after production equipment, operating procedures, environmental conditions (such as temperature and humidity), quality control

The production process and personnel quality are consistent).

Research verification work includes:

(1) Explain the specific circumstances and reasons for the change, and conduct research on the relevant processes after the change

and/or verification.

(2) Compare the production technology and production process control of the new and old sites. Relatively new and old

Site production equipment conditions, including manufacturer, model, material, equipment principle, and key technologies

Technical parameters, etc., and explain the matching of production equipment and production process before and after the change.

(3) The batch of samples after the change shall be inspected and shall comply with the quality standards.

(4) Conduct long-term stability inspection on the first batch of samples after the change and report in the annual report

Long-term stability test data of this batch of samples.

2. Production sites and primary products of preparations and intermediates not otherwise specified in these guidelines

Change of packaging site.

Research verification work includes:

(1) Explain the specific circumstances and reasons for the change, and conduct research on the relevant processes after the change

and/or verification.

For sterile preparations, sterility/sterilization process validation is also required.

(2) Compare the prescriptions, production techniques, production process control, etc. of the old and new sites. Compare

The status of production equipment at newer and older sites, including manufacturer, model, material, equipment principle,

Key technical parameters, etc., and explain the matching of production equipment and production process before and after the change.

(3) Provide batch production records of the changed batch of samples.

(4) Conduct quality comparative studies on the samples before and after the change, focusing on proving the quality of the samples before and after the change

The dissolution curve, impurity spectrum, key physical and chemical properties of the sample should be consistent and comply with relevant

Guiding Principles Requirements.

(5) Inspect the 1-3 batches of samples produced after the change and they should comply with the quality standards.

Certainly.

(6) Conduct accelerated and long-term stability studies on the 1-3 batches of samples after the change, when reporting

Provide 3 to 6 months of stability study data and compare with the stability of the drug before the change

Compare. The stability of the sample after the change should not be lower than before the change.

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