已上市化学药品和生物制品临床变更技术指导原则

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目录

I. Overview

Clinical changes to already-marketed drugs refer to changes to the market after the drug is approved for marketing.
The license holder is required to use the medicine safely and effectively in clinical practice.
Indications, applicable population range, usage and dosage, drug instructions and safety information,
changes to pharmacovigilance plans and other matters. Post-market clinical change management of drugs
It is an important part of the full life cycle management of drugs.

This guideline clarifies the clinical changes to drugs after they are approved for marketing in China.
matters, and based on the size of the change and its possible impact on the safe and effective clinical use of the drug.
The impact and risk level of the production are classified, and the applications corresponding to different classifications are refined.
reporting procedures and technical requirements, etc., aiming to provide drug marketing authorization holders with drug
Post-marketing clinical change research, drug regulatory authorities conduct change classification management
etc. to provide useful technical guidance and reference.

This guidance applies to chemicals, prophylactic biological products and therapeutic
Biological Products. Adding new indications and modifications to already-marketed drugs that have not been approved in the country
Changing the route of administration, etc., must be carried out according to the drug clinical trial and marketing authorization application channels.
Application and review and approval.

2. Classification of clinical changes

Based on changes to drug safety, effectiveness and safe and effective clinical use
Based on the degree of impact and risk, clinically relevant changes are classified as major changes.
There are three types of updates, medium changes and minor changes, as follows:

(1) Major changes

Changes to drug safety and effectiveness information, and drug package insert safety

Changes to sex-related information are clinically significant changes. Reply based on major changes

Based on the degree of complexity and the research required, major changes are divided into categories A and B.

kind.

1. Major changes Category A

Changes to drug safety and effectiveness information fall into Category A of major changes.

Refers to the drug's population, effectiveness, safety, dosage and method of administration.

Relevant changes, such as: changes in the population taking the drug, dosage exceeding or lower than the approved

Accurate usage and dosage range, changes in drug interaction information, etc.

Such changes mainly involve expansion of the population or dosage range of the drug or

Changes in effectiveness information such as narrowing will directly affect the clinical use of drugs and should

Supported by clinical trial data and/or relevant non-clinical research data, submission is required

The supplementary application will be implemented after review and approval. Such changes should also be made to the drug

Instructions and/or packaging labels are revised accordingly.

Category A major changes mainly include the following situations:

(1) Changes in approved indications

ÿ Changes in the applicable population, for example: extending to children on the basis of adults

etc. as the age range of the applicable population expands.

ÿ There is insufficient evidence to prove effectiveness based on clinical studies or the risks outweigh the benefits.

, the indications need to be limited or deleted, etc.

(2) Changes in usage and dosage, including recommended dosage and/or prescription

Changes in the dosage form, etc., the dosage after the change is higher or lower than the approved usage.

quantity range.

(3) Changes in medication information for special groups, such as pregnant and lactating women

Changes in information on medications for women, medications for children, and medications for the elderly; increased liver function impairment,

Medication information for patients with renal impairment; additional medication information for patients with immunocompromised

wait.

(4) Changes in drug interaction information. For combined drug treatment of certain

The disease situation should be managed according to the new indication.

(5) Add new specifications, the drug content of the new specifications is not in the approved instructions

within the usage and dosage range. Adding new specifications is usually accompanied by changes in usage and dosage.

propose.

(6) Changes in existing risk management measures, for example: ÿ Due to safety reasons

Delete a certain route of administration or specification that has been approved; ÿ Delete contraindications

(For example: use by pregnant women, etc.); ÿ Change taboos to precautions.

(7) Add approved indications for the same domestic variety or delete approved indications

Indications.

(8) Others: other major changes related to the safe and effective clinical use of drugs

More class A.

2. Major changes Category B

Changes to safety-related information in drug instructions belong to Category B of major changes.

It refers to changes in drug risk management-related content in drug instructions. This class

The changes do not change the approved indications, usage and dosage. Such changes have an impact on clinical safety

Fully effective use has some impact, usually requiring large-scale pharmacovigilance (marketing

Post-safety alert) data support, a drug information change supplement needs to be submitted

Apply for recharge and execute after review and approval.

For changes that require clinical trial data or non-clinical research data to support

The situation should be classified as major change Category A, rather than safety-related information in the drug package insert.

Information changes.

Category B major changes mainly include the following situations:

(1) Standardize the written expression of approved indications to avoid misunderstandings.

Changes should not involve broadening or narrowing the scope of the indication population.

(2) Revise adverse reactions. For example: add or delete adverse reaction information;

Revise the frequency of known adverse reactions, etc.

(3) Add taboos or warnings. For example: Define a feature that is at high risk

Defined subgroups of people (for example: patients with certain diseases, people taking combined medications, or

patients of certain age groups). These changes also include clear risk management measures (e.g.

e.g. ensuring the patient is aware of certain risks).

(4) Revise the precautions, drug overdose, pharmacology and toxicology, etc. to guide

Guide safe clinical medication use.

(5) Revise the instructions for drug use, including medication preparation, dispensing methods, etc.

to optimize the safe use of medicines.

(6) Others: Other major changes related to the safe clinical use of drugs B

kind.

(2) Medium changes

According to the National Medical Products Administration announcement or approval information change instructions

Security information, moderate change. In most cases, such changes are to pharmaceuticals

Marketing authorization holders refer to the announcement or approval information from the National Medical Products Administration

Safety information or packaging for chemical generics or biosimilars

Changes to label information. Such changes usually require simultaneous changes to the packaging label

Revised accordingly. Such changes may be submitted to the relevant management department for filing.

Medium changes mainly include the following situations:

1. Revise the instructions uniformly according to the requirements announced by the State Food and Drug Administration.

2. Refer to the innovative drugs and improved drugs that have been approved for marketing by the National Medical Products Administration

The new drug may be included in the "Chemical Generic Drug Reference Preparation Catalog" and has been launched in my country

The latest version of the package insert for the reference preparation, for generic or biosimilar chemical drugs

Changes to safety information in drug package inserts. Security information change package

include:

(1) Revise adverse reactions.

(2) Revise taboos or warnings.

(3) Revision precautions, drug interactions, drug overdose, pharmacological toxicity

content, etc.

(4) Revise the instructions for drug use, including medication preparation, dispensing methods, etc.

to optimize the safe use of medicines.

3. Modify the packaging label according to the approved drug package insert.

(3) Minor changes

Changes to the administrative information in the drug instructions are minor changes and are

Refers to changes that do not change information about the safety and effectiveness of a drug. such changes

Packaging labels usually need to be revised accordingly. Such changes do not need to go through

For review, approval or filing, the drug marketing authorization holder shall conduct the review and approval in the annual report.

line report.

Minor changes mainly include the following situations:

1. Changes made based on the approval documents of the National Medical Products Administration, such as

Change the drug name or product name, etc.

2. Change the name or location of the drug marketing authorization holder and/or manufacturer

address name without the actual subject or address changing (e.g. name change due to a merger)

name, the subject has not changed).

3. Update the contact information of the drug marketing authorization holder (e.g. phone number

code, URL).

3. Clinical Change Procedure

For clinical changes to already marketed drugs, the drug marketing authorization holder should

Determine the classification of the change based on the changed matters, and declare and file according to the corresponding procedures.

or annual report. When applying, the classification of changes and major changes should be clearly stated in the application form.

matter.

(1) Supplementary application

For major clinical changes to already marketed drugs, drug marketing authorization holders

Before implementing the change, a supplementary application must be submitted to the State Food and Drug Administration.

Explain the changes and the basis. Corresponding changes can be made only after approval is obtained.

Drug marketing authorization holders should carry out corresponding changes according to different circumstances.

Research. Generally, the research content used to support Category A and B major changes is not

However, different reporting procedures are required. Specifically include:

1. Category A major changes, the impact and risks on the safe and effective use of drugs

are more risky and usually require rigorously designed and conducted clinical trial data and/or

Supported by non-clinical research data. Drug marketing authorization holders are conducting clinical trials

Before proceeding, a supplementary application should be submitted first, and clinical trials can only be carried out after approval.

The drug marketing authorization holder completes clinical trials and evaluates the trial data

When corresponding changes can be supported, a supplementary application can be submitted to the National Medical Products Administration

please.

2. Major changes to Category B will have a certain impact on the safe and effective use of drugs,

Post-marketing pharmacovigilance (safety vigilance) data support of the drug is usually required. medicine

The holder of the product marketing authorization should submit the pharmacovigilance data after fully evaluating and demonstrating

Submit supplementary application.

(2) Filing management

Medium changes, because the basis for the changes have been approved by the National Medical Products Administration

Review and approval, so such changes can be managed according to filing. Pharmaceutical marketing authorization holder

Relevant information to support the filing should be provided at the same time as the filing.

(3) Annual report

Minor changes, which usually do not affect the safe and effective use of the drug, can be made on an annual basis

Report management. Pharmaceutical marketing authorization holders should provide information to support annual reporting

Supporting documents and other information for the item.

(4) Others

When multiple clinical changes are reported at the same time, the highest type of change should be reported.

The procedure requires a supplemental application or filing.

4. Technical requirements for clinical changes

Before applying for post-market clinical changes to the drug marketing authorization holder, the drug marketing authorization holder should

First, evaluate the impact of changes on drug safety, effectiveness, and safe and effective clinical use.

potential impacts in all aspects. For those with potential impacts, relevant measures should be carried out in a targeted manner

Relevant research, before research data is obtained and evaluated to support relevant changes

Please submit an application and submit supporting technical information. potential impact on

However, changes are made with reference to announcements or approval information from the National Medical Products Administration.

You can file directly and submit relevant supporting information. For those that have no impact,

Can conduct annual reports and submit relevant supporting information.

(1) Technical considerations for change research

Whether a clinical change requires research and the complexity of the research will depend on

The potential impact of changes on drug safety, effectiveness and safe and effective clinical use

In response, specific issues should be analyzed in detail. on the clinical and/or

adequacy of non-clinical data, drug marketing authorization holders are encouraged to cooperate with national drug

Communicate with the Supervision and Administration Bureau.

Typically, for Major Change Category A, supporting non-clinical and/or clinical

The type and scope of safety and efficacy studies should be based on the benefits associated with the change/

Risk assessment, drug characteristics, approved indication characteristics (morbidity, mortality,

Acute or chronic disease, availability of current disease treatment, etc.), safety factors, etc.

Determined after comprehensive evaluation of aspects. For example: For an approved indication expanded by adults

For the pediatric population, necessary studies should be carried out in accordance with the relevant guidelines for pediatric drug research.

Non-clinical and/or clinical research, taking into account factors such as indication characteristics; for use

Changes in dosage should be made after evaluating existing dose-related safety and effectiveness data and confirming

On the basis of ensuring the safety of subjects, conduct corresponding research, such as using different methods before and after changes

Comparative study of safety and effectiveness under legal dosage; evaluation of existing risk management measures

Changes may require existing clinical trials, post-marketing observational studies, or large-scale

Post-marketing safety data to obtain supporting evidence, etc.

For major changes Category B, a pharmacovigilance report is usually required (such as

periodic safety update report) to support changes in safety information related to the instructions.

For medium changes, a release from the National Medical Products Administration is usually required.

Relevant announcements or supporting information such as approved instructions for the same variety.

For minor changes, it is usually necessary to provide relevant supporting evidence in the annual report.

Documentation, if unavailable, should be stated.

Drug marketing authorization holders should refer to the

Relevant pharmacology, toxicology and clinical technical guidelines issued by the national drug administration department

Guidelines for conducting targeted research. For example: the marketing authorization holder intends to change the drug

For drug interaction information, please refer to the "Guiding Principles for Drug Interaction Research"

Carry out targeted research, etc.

(2) Requirements for changing application materials

1.Major changes

(1) Major changes Category A

ÿChange content and reason for change.

ÿSummary of research related to changes. Should be provided for use in assessing the effectiveness of changes to the drug product

The main research methods and completed studies on the safety and/or safety effects.

ÿNon-clinical research materials and necessary domestic and foreign documents related to the change

material.

ÿ Drug clinical trial data related to the change, including review data, clinical

clinical trial plans and protocols, statistical analysis plans, clinical research reports, etc.; clinical

The clinical measurement methods and verification should be described in detail in the research report.

ÿ Sample instructions and packaging labels for application changes, and description of drug approval documents

Book and packaging label attachments, revision instructions, and comparison table before and after revision.

ÿPharmacovigilance plan, determine whether it is necessary to change the content and research data

Relevant pharmacovigilance plans should be developed and provided.

The relevant information for the above ÿ, ÿ and ÿ can be obtained in accordance with "M4: Application for Registration of Drugs for Human Use"

Please write according to the requirements of relevant modules in Common Technical Document (CTD).

(2) Major changes Category B

ÿChange content and reason for change.

ÿ Clinically relevant supporting data (pharmacovigilance reports, etc.) and statistical analysis

result.

ÿ Sample instructions and packaging labels for application changes, and description of drug approval documents

Book and packaging label attachments, revision instructions, and comparison table before and after revision.

2. Moderate changes

(1) Change content and reasons for change.

(2) Relevant documents supporting the change, including documents issued by the State Food and Drug Administration

Announcements issued by the State Food and Drug Administration, innovative drugs and improved drugs that have been approved for marketing by the State Food and Drug Administration

The new drug may be included in the "Chemical Generic Drug Reference Preparation Catalog" and has been launched in my country

The latest version of the instructions for the reference preparation, etc.

(3) Application instructions and packaging label samples for change, and domestic approved originals

Attachments to the latest version of the instruction manual of the research product or reference preparation, revision instructions, and comparison before and after revision

Comparison table.

3. Minor changes

(1) Change content and reasons for change.

(2) Supporting documents or relevant documents supporting the change.

(3) Sample instructions and packaging labels for application changes, and description of drug approval documents

Instructions and packaging label attachments, revision instructions, and comparison table before and after revision.

references

1. Guidelines on procedures and data requirements for changes to approved biotherapeutic products Proposed guidelines. WHO/PAC for BTPs_DRAFT/3, Oct 2016.

2. Guidance for Industry: Changes to an Approved NDA or ANDA. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), April 2004, CMC.

3. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of

variations to the terms of marketing authorizations for medicinal
products for human use and veterinary medicinal products and on
the documentation to be submitted pursuant to those procedures.
Official Journal of the European Union, 2013/C 223/01.

author

"Technical Guiding Principles for Clinical Changes of Marketed Chemical Drugs and Biological Products"

Research group