appendix

Clinical trials of topical drugs with local action

Technical Guidelines

Drug Evaluation Center

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Technical Guiding Principles for Clinical Trials of Locally Administered and Locally Acting Drugs

1. Background and purpose

Locally applied, locally acting

products, LALAP), refers to products that are applied locally and work at the application site

drug. Such drugs are considered unintended if they cause systemic effects

effect.

Topical administration Topically acting drugs involve a variety of dosage forms and are mainly used for skin,

Indications in facial features, respiratory, digestive, surgical, gynecological and other fields, including: skin

External preparations (such as creams, ointments, gels, etc.), ophthalmic preparations (such as eye drops,

Intraocular injections, eye implants, etc.), ear drops, nasal preparations (such as sprays

etc.), inhalation preparations for respiratory system (such as powder mist, aerosol, etc.), gynecological preparations

(such as vaginal suppositories, vaginal tablets, etc.), administered orally or rectally and in the digestive tract

Preparations that act locally, etc.

Compared with systemically administered drugs, topical administration of locally acting drugs has a higher

It has special characteristics in terms of composition, dosage form characteristics, route of administration, etc., therefore, it should be targeted

Clinical trial design and evaluation, including local and systemic effects after topical administration

Tolerability, safety, local and systemic pharmacokinetics, local pharmacodynamics,

Dose exploration, etc.

The clinical development of local-acting drugs for local administration should follow the clinical trials of drugs.

general principles for clinical trials, including technical guidelines related to domestic drug clinical trials and

Relevant technical guidelines of the International Conference on Harmonization of Technology for the Registration of Pharmaceuticals for Human Use (ICH).

This guideline is intended to provide guidance based on the characteristics of topical administration of locally acting drugs.

Scientific research and evaluation of such drugs provide targeted guidance and recommendations. For with

The development of medical science and technology has led to the emergence of more scientific, reasonable and recognized tools and

method may also be considered, but supporting and confirming evidence must be provided and consistent with

Regulatory agency communications.

2. Scope of application

This technical guiding principle is applicable to the research and development of local-acting drugs for local administration.

and evaluation, including innovative drugs, known active ingredients developed into topical administration topical

New and improved drugs that work, as well as chemical generics.

3. Characteristics of local administration of local-acting drugs

Topical administration Topically acting drugs often require special formulations to remain in place

For application topically (e.g., creams, gels), or in specific dosage forms and devices (e.g., powders

aerosols and corresponding devices) so that they can reach specific parts and remain in the application area.

exert local therapeutic effect.

In addition to the main active ingredients, these drugs often require more excipients to form

Corresponding dosage forms, the selection and changes of their prescriptions and dosage forms can directly affect the effectiveness of the drug.

efficacy and/or safety, for example, by changing the physicochemical properties of the drug or by changing

It is possible that the inactive ingredients in the drug change the penetration of the active substance

Affect the safety and/or effectiveness of the drug; in addition, the new excipients in the drug themselves

Safety and potential interactions between excipients and active ingredients are important to assess

The safety profile of a drug is of great importance. Oral inhalation for treating asthma

formulations, inhaler devices that require drug delivery, particularly drug flow dependence

Particle size distribution, etc., which will directly affect the site where the drug reaches and thus the effective

performance and/or safety.

Due to the above characteristics, the clinical development of topical administration of locally acting drugs

Clinical trials should be carried out in a targeted manner, and the trial design should be combined with the prescription composition of the drug,

Dosage form, administration device, administration site, nonclinical pharmacokinetics, nonclinical drugs

Characteristics such as efficacy and toxicity shall be comprehensively considered.

4. Overall principles of clinical trial design

1. Innovative drugs

For innovative drugs that are locally administered and locally effective, in addition to those developed in accordance with the

In addition to the general idea, the drug dosage and drug concentration of topical administration preparations should be considered.

The size of the drug delivery area is closely related, so it should be based on the target disease and treatment target site.

and drug action characteristics, and explore the following contents in the early stage of clinical development:

(1) Local absorption and distribution of drugs after local administration. Pay attention to different drugs.

drug concentration, local and systemic exposure under different administration areas to evaluate its

Whether local administration can reach the target site and whether the dose or concentration of the drug at the target site is sufficient

to exert its pharmacological effect, as well as the potential safety risks that systemic absorption may bring

risk; (2) Based on the size of the target disease lesion, consider designing a sufficient drug delivery area

ongoing tolerability and safety studies. These exploratory studies can provide guidance for subsequent clinical

Design and provision of study dosage, concentration, dosage area, dosage interval, etc.

Sufficient supporting evidence.

Although the purpose of applying this type of drug is to exert its drug effect locally,

However, there may still be safety risks caused by drug absorption into the bloodstream. Apply

People should combine the non-clinical pharmacokinetic characteristics of the study drug with systemic exposure-related

Toxicity and other data to initially evaluate whether there is systemic absorption and potential after local administration

The security risks brought by the absorption of existing systems. If non-clinical research data suggest that research

The investigational drug may cause insufficiency in the whole body or certain tissues and organs due to systemic absorption.

Good reactions should be included in early exploratory clinical trials and confirmatory clinical trial designs

Pay special attention to the impact of systemic absorption on safety after local administration, and set corresponding

Observation indicators or end points.

Confirmatory clinical trials of innovative drugs should usually be carried out through well-designed clinical trials.

The test proves that the drug is safe and effective for the proposed indications and target population, and can

Provide sufficient evidence for marketing authorization and provide complete package inserts for the proposed drug.

Complete and comprehensive information.

2. Improved new drugs

Preparation on the basis of drugs with the same known active ingredients that have been approved for marketing

Developed new dosage forms and new administration methods that are locally effective and have not been marketed at home or abroad.

Pathway drugs are all improved new drugs. These improved new drugs have the same activity as

Compared with preparations for absorption of sexual ingredients through systemic drug delivery, the composition of drugs and

Dosage forms often contain factors that directly affect the effectiveness and/or safety of the drug.

Big difference. According to the current "Chemical Drug Registration Classification and Application Document Requirements",

Such improved new drugs should have obvious clinical advantages. Play with systemic drug delivery systems

Topical administration of topical-acting drugs should generally result in significantly improved

local efficacy; or significantly reduce current medication without reducing local efficacy

The patient's adverse reactions or medication-related risks may significantly increase the patient's medication

Compliance. When the results of pharmaceutical and nonclinical studies suggest that systemic administration of preparations be

Modification of the same active ingredients into topical formulations may provide patients with better potential clinical

When beneficial, the development of local-acting formulations for topical administration may be considered.

If it is intended to be used for the same indication as the original dosage form, the same active ingredient has been

PK, PD, dose-exposure-effect relationship, safety of systemic drug delivery system absorption preparations

Research data such as safety and effectiveness can be used as a reference, so it is usually not necessary to conduct further research.

Conduct complete non-clinical and clinical trials. Applicants can based on existing research data,

Conduct relevant clinical trials and/or bridging trials to support its marketing.

If an improved new drug is intended to be used for a completely new indication, reference should be made to the research and development of innovative drugs.

requirements, conduct comprehensive and systematic clinical trials, and provide safety data for the original preparations

It can provide reference information for risk management measures in the development of improved new drugs.

2.1 There are already systemic drugs on the market, and topical drugs with the same active ingredient are developed.

drug

Drugs with known active ingredients that have not been used topically but have been administered systemically

preparations are on the market, newly developed local-acting preparations for local administration should be targeted at the route of administration,

Administration site and topical formulation characteristics, influence dose-exposure-response relationships of topical medications

comprehensive studies on the relationship, safety and efficacy characteristics of

and systemic tolerability testing, pharmacokinetic testing, dose finding, and confirmatory

A series of tests such as clinical trials to ensure the systematicness and comprehensiveness of the trial design,

And provide experimental data support for the finalized indications, usage, dosage, specifications, etc.

hold. Local pharmacokinetic characteristics should be explored whenever possible in pharmacokinetic studies.

This type of drugs should focus on evaluating the safety of local administration after changing the route of administration.

resistance and tolerability, as well as whether local absorption and exposure after administration can produce prognostic

period treatment effect. At the same time, due to clinical trials of its systemic drug delivery system

The data can indicate the safety and effectiveness of local administration to a certain extent, and applicants can use this to

Carry out corresponding bridging research, exploratory research and/or confirmatory research to further

A further step is to develop it as a topical delivery, topical acting formulation for proposed adaptations.

efficacy and safety.

2.2 Locally administered and locally effective drugs are already on the market, and the development of the same active ingredient

topical medication

If the preparation to be developed already has a known active ingredient that can be administered locally,

For effective preparations to be launched on the market, applicants should consider the comparison of the preparations to be developed with those already on the market for local drug administration.

The differences and research and development purposes of partial-acting preparations are analyzed, and clinical trials related to preparation changes are carried out.

test and determine whether it has obvious clinical advantages.

3. Generic drugs

For topical administration of locally acting generic drugs, applicants should fully understand what has been marketed

The research and development background, pharmacokinetics, and pharmacodynamics data of proposed generic drugs, and

Efficacy and safety data, post-marketing adverse reaction monitoring data, etc., evaluate and clarify

Determine the clinical needs and value of proposed generic drugs, and follow the guidelines issued by the State Food and Drug Administration

"Procedure for Selection and Determination of Reference Preparations for Chemical Generic Drugs" selects reference preparations.

Applicants should conduct step-by-step comparative studies based on drug characteristics.

Conduct pharmaceutical, non-clinical and/or necessary clinical comparative studies to support generic

Evaluation of equivalence between drug and reference preparation. For special preparations such as creams and emulsions,

For example, due to pharmaceutical and other reasons, it is difficult to evaluate generics through pharmaceutical and non-clinical comparative studies.

The consistency between the pharmaceutical preparation and the reference preparation should be basically consistent in the pharmaceutical comparison.

(high similarity), further carry out necessary non-clinical and clinical

Comparative Study. Comparative clinical studies can include biological products with PK and PD parameters as endpoints.

Equivalence studies, and equivalence studies with clinical endpoints as endpoints. for medicine

If scientific research indicates that the generic drug is inconsistent with the reference preparation, the applicant should conduct further

Only after the pharmaceutical research is further improved can subsequent research be considered.

Applicants may request a clinical trial exemption if certain conditions are met

application and provide corresponding reasons and supporting research evidence. Applicants can apply for

Consider the relevant technical guidance principles for generic drug research issued domestically and/or advanced foreign technologies.

Bioequivalence guidance from regulatory agencies for a specific variety, etc.

5. Special considerations for clinical trials

1. Prerequisites for entering clinical trials

Applicants should conduct comprehensive research on innovative drugs that are locally administered and have local effects.

Quality research, including properties, melting time, dissolution (release), related substances

Quality, content, microbial limits, bacteriostatic and antioxidant content and other relevant key qualities

Quantitative indicators.

Due to the particularity of topical pharmaceutical preparations, human pharmacokinetic studies may have

It is difficult, therefore, in non-clinical studies, in addition to conventional toxicology, pharmacology and pharmacokinetics

In addition to kinetic studies, applicants must also study the drug's mechanism of action based on the characteristics of pharmaceutical preparation.

fully explore the preparation, local pharmacokinetics and pharmacodynamic characteristics, etc., in order to

Provide information for determining dosing concentration, dose, dosing interval, etc. in subsequent human clinical trials.

Provide sufficient supporting data.

In addition, innovative drugs administered through local routes such as skin, mucous membranes, and oral cavity,

Before conducting clinical trials, the effects of using the preparation at the administration site should be studied.

Local (e.g. irritation, local allergy, etc.) and/or systemic toxicity (e.g. systemic

allergic) to indicate possible toxic reactions and toxic targets during clinical application

Officer and security range.

2.Clinical pharmacology research

2.1 Overall consideration

Early exploration of locally administered innovative drugs and improved new drugs

The general idea of clinical research is the same as that of other drugs, but special attention should be paid to local tolerance

Design for research on safety, local pharmacokinetics, local pharmacodynamics, etc.

planning and evaluation.

For innovative drugs or improved new drugs, if the systemic exposure is not yet clear, systematic

Traditional pharmacokinetic studies. For some special indications or special preparations, such as

Pharmacokinetic profiles and tolerability may differ in healthy subjects and patients

When doing so, clinical research and development should be considered on the basis of obtaining relevant data on healthy subjects.

Conduct early patient pharmacokinetic, tolerability and safety studies to support

Follow-up exploratory and confirmatory clinical trials.

2.2 Study on local pharmacokinetics

Local pharmacokinetic studies, development of locally administered and locally acting drugs

It is of great significance and evaluation, aiming to study the role of locally acting drugs and their metabolites in drug

The dynamic changes in absorption, distribution, metabolism and excretion of substances at their action sites can be

Used to evaluate whether the drug can reach the target site, the concentration of the drug reaching the target site, or

Dosage, metabolic characteristics of the drug at the target site, establishment of drug dose-exposure-effect

corresponding relationship, and provide information for the design of dosing regimens in subsequent clinical exploration and confirmatory trials.

Important supporting evidence.

However, pharmacokinetic studies of such drugs are limited by biological sample sampling,

Test technology methods, drug clinical trial ethics and other issues, local pharmacokinetics

Research and evaluation of medicine are faced with many difficulties and challenges. It is difficult to obtain whether drugs

Data on reaching the target site, drug concentration at the target site, and metabolic processes.

This guiding principle encourages and supports drug research and development companies or institutions to develop and

Apply advanced technologies, methods, tools, etc. to carry out local pharmacokinetics in clinical trials

Science and local pharmacodynamics research, the advanced technologies, tools, methodologies used, etc.

Should be fully verified.

At present, for drugs for external use on the skin, pharmacokinetic testing is commonly used in my country.

The main methods include in vitro skin transdermal absorption testing and systemic pharmacokinetic testing.

However, there are differences in active transport processes and physiological states between skin in vitro and skin in vivo.

However, systemic pharmacokinetic parameters cannot reflect the actual process of the drug at the target site.

Currently, there are many sampling methods to directly obtain skin tissue, such as needle biopsy,

Scrape biopsies and skin surface biopsies can be used to study skin pharmacokinetics, but this

These methods are all invasive and are carried out on healthy people and some subjects with skin diseases.

There is a certain degree of difficulty, therefore, applicants are encouraged to actively explore advanced non-invasive sampling and

/or detection techniques and methods for local pharmacokinetic studies.

2.3 Local pharmacodynamic studies

Pharmacodynamic studies on topical administration of locally acting drugs should be based on the development of drugs

characteristic design. Pharmacodynamic studies, local and plasma concentration-effect studies can be done in

Conducted in healthy volunteers or patients. If suitable measurement methods are available, the test

Based on pharmacodynamic data, drug activity and potential effectiveness can be estimated early

not only for early assessment, but also for subsequent studies in target indication populations.

Provide basis for determining dosage and dosage regimen.

3. Exploratory clinical trials and confirmatory clinical trials

When conducting exploratory clinical research, applicants should combine the characteristics of indications,

The dosage forms, specifications, and routes of administration of drugs are determined based on research purposes for different sub-categories.

Group population, administration route, administration dose, administration interval, treatment course, evaluation index

Fully explore other aspects to obtain preliminary information on the effectiveness and safety of the drug.

information to determine whether subsequent confirmatory testing can be conducted. For example, it is proposed to develop

For topical creams for atopic dermatitis, applicants should be as clear as possible about the labeling of the drug.

distribution and metabolism in target sites such as skin and dermis, early exploratory research should

Consider conducting experiments with different application areas, different drug concentrations, different dosing intervals, etc.

Fully study to provide a basis for the selection of dosing regimen for subsequent confirmatory studies;

If eye drops are to be developed, the absorption path and target of the drug in the eye should be clarified.

site, and adequate dosing concentration and dosing frequency should be considered in early exploration

Research.

Confirmatory clinical trials confirming local efficacy of topical administration should be based on data

Conduct a comprehensive review of the local and systemic safety of the study drugs, as well as the effectiveness of the drugs.

comprehensive benefit-risk assessment. Determination of key elements of confirmatory clinical trials usually

It needs to be supported by the results of multiple exploratory trials. Applicants should consider randomized, blinded

method, control design. Confirmatory clinical trials should accurately measure the efficacy of the experimental drug.

accurate estimate. The explanation of drug efficacy requires both demonstrating the statistical significance of the main hypothesis and

It is also necessary to evaluate whether the efficacy has clinical significance, and statistical comparisons can be superiority, etc.

effectiveness or non-inferiority.

If a drug with a known active ingredient is developed for topical administration and is used

For indications for which the original active ingredient has been approved for systemic administration, topical administration of drugs should

Improve efficacy, and/or improve safety, and/or improve compliance, and/or

Other clinically significant advantages. Applicants should generally choose to include approved

Drugs with the same active ingredient serve as positive controls. At the same time, since the placebo group

Be able to ensure that the trial is sufficiently sensitive to differences between treatment groups and takes into account expected

The placebo effect and the need for negative controls may be considered by the applicant in terms of ethical

Select improved new drugs, approved positive drugs and placebos based on requirements

A clinical trial comparing three groups was conducted.

In confirmatory clinical trials, the main efficacy indicators should be selected from recognized

Guidelines and standards, efficacy indicators that can efficiently and reliably reflect the true benefit to patients,

It should be as objective and quantifiable as possible. The design of safety indicators should be based on the investigational drug

Characteristics of the mechanism of action, route of administration (such as inhalation through the mouth, local application on the skin of the affected area)

Wipes, eye drops, intravitreal injections, sustained-release preparation implants, vaginal administration, etc.),

Local and systemic absorption, non-clinical safety information, known safety information of similar drugs

Determined after comprehensive assessment of safety information and potential risks. For example, targeting the skin locally

Medication may cause some specific local adverse reactions such as contact dermatitis. It is recommended to take

Use static scales to assess skin signs such as erythema, edema, and erosion; use patient

Use indicators such as patient-reported outcomes to assess symptoms such as itching or burning sensations; set safety assessments

time and frequency of assessment to determine expected adverse effects; through diagnostic patch testing

Hypersensitivity to drugs (active ingredients and excipients) by visual or photopatch testing

and photoallergic contact dermatitis are described and analyzed.

4. Bridging research

For improved new drugs, relevant clinical trials and/or bridging are usually required

Research. Among them, the bridging study design and evaluation requirements depend on the specific circumstances.

Requesters can communicate with the Center for Drug Evaluation on issues related to bridging study design.

4.1 There are already systemic drugs on the market, and topical drugs with the same active ingredient are developed.

drug

It is divided into two situations according to the indications to be developed: one is for use with known activity

A new indication for which the ingredient has not yet been approved, and the other is for a known active ingredient that has been approved

batch of indications.

If it is intended to be used for a completely new indication, it should be based on the characteristics of the proposed indication.

Conduct comprehensive and systematic clinical studies to confirm the topical administration of local-acting drugs

Efficacy and safety for newly proposed indications. Known active ingredients

The safety, tolerability, pharmacokinetics and pharmacodynamics data of systematic administration can

Consider as supporting data.

Ruxin develops therapeutic drug for topical delivery to be formulated with the same active ingredient

For approved indications for systemic administration of drugs, the applicant should conduct necessary clinical

Experiments have shown that topical administration of locally acting drugs is more effective than systemic administration of preparations.

Significantly improve local efficacy; or significantly reduce local efficacy without reducing local efficacy.

Adverse reactions or drug-related risks in patients who have previously taken the drug may significantly increase the risk of drug use.

Compliance etc. If an improved new drug aims to improve clinical efficacy, the applicant should

Among the approved target indications, randomization and positive controls are carried out (select domestically listed drugs).

(pharmaceuticals with the same active ingredients on the market) and superior efficacy designed confirmatory trials to confirm the efficacy.

Unless there are good reasons, equivalent or non-inferior designs are generally not accepted.

If an improved new drug aims to improve safety, the applicant should consider

Blind, equivalent/non-inferior, confirmatory trial designed to compare with the improved drug already on the market

Confirm that on the premise that the conclusion of equivalent effectiveness/non-inferiority is established, the improved new drug

Achieve clinically meaningful improvements in safety. If intended to provide compliance, apply

Applicants should consider conducting randomized controlled clinical trials based on preliminary research.

To prove that the improved new drug maintains effectiveness and safety no less than that of the improved drug.

Under the premise, the patient's medication compliance can be significantly improved.

4.2 There are already local-acting drugs on the market for local administration, and the development of the same active ingredient

topical medication

For applications for different indications or applications for different dosage regimens, the

Conduct relevant clinical trials on proposed indications or proposed different dosage regimens to

Confirm its safety and efficacy for this indication or adopt a new dosing regimen.

Historically demonstrated tolerability and pharmacokinetics of marketed topical formulations

Experimental data can serve as supporting evidence.

When the applied preparation is a different dosage form of an already marketed preparation, the applicant should

Provide sufficient evidence to clarify the obvious clinical advantages of the new dosage form. Applicants should carry out

Safety and efficacy studies and/or pharmacokinetic studies (applicants should prescribe as much as possible

carry out local pharmacokinetic studies). If necessary, drug absorption and

Study of penetration characteristics and local tolerance.

5. Equivalence studies

Evaluation of equivalence for topical, locally acting generic drugs should be based on the generic

The number of comprehensive comparative studies on pharmaceutical, non-clinical and clinical aspects of the product and the reference preparation

Conduct a comprehensive evaluation. The extent of comparative clinical studies should be based on topical drug formulations

The complexity, quality and non-clinical comparative study data and other specific conditions are carried out.

Corresponding clinical comparative trials to support its equivalence evaluation.

Bioequivalence studies with clinical indicators as endpoints (clinical efficacy and safety

Comparative study), which should be based on examining the clinical differences between the study drug and the reference preparation.

Research purposes. The experimental design of such comparative studies should be based on the clinical

bed characteristics, and determine the study population, administration route and dosage, effective

endpoints, effectiveness evaluation time points, research periods, safety indicators, equivalence

Key elements of clinical trials such as sexual boundary values.

It is important to note that topical administration of generic versions of locally acting drugs, such as difficult

To clarify the relationship between generic drugs and reference preparations from pharmaceutical and non-clinical comparative studies

for most locally administered, locally acting drugs, the local PK parameter is usually

Several sensitive methods for assessing bioequivalence. However, studies on local pharmacokinetics

The research is difficult and the research methods need to be improved. Since plasma drug levels are related to local

The correlation with efficacy is low, so the bioequivalence test with plasma PK parameters as the endpoint

testing is not a suitable method to show equivalence, but in this case bioequivalence testing can

It has certain reminders in terms of safety. This technical guideline encourages applications for issuance of

Development and application of scientifically sound and validated methods for topical pharmacokinetic studies

Method to conduct bioequivalence studies with PK and/or PD parameters as endpoints. For containing

External preparations of corticosteroids can achieve a high degree of consistency in comparative pharmaceutical studies.

Based on the similarity, a skin blanching test will be carried out subsequently.

study), an in vivo pharmacodynamic method that uses PD parameters as endpoints to evaluate generic drugs

Equivalence to reference preparation.

6. Conclusion

The development of locally administered, locally acting drugs should be based on clinical therapeutics

demand and value, combined with existing research data, pharmaceutical formulations (components,

Dosage form, specifications, administration device, administration site, etc.) characteristics, etc., carry out comprehensive and

Systematic clinical trials or bridging studies to confirm that it is compatible with already marketed drugs for the proposed

Therapeutic equivalence for indications. In clinical trials of topical administration of topical-acting drugs

Special attention should be paid to local drug metabolism, local drug efficacy, local safety, tolerability, etc.

fully discussed. Due to the complexity of the research and development of local-acting drugs for local administration, it should

Based on specific analysis of specific situations, this guideline encourages applicants to

Communicate and communicate on R&D and technical evaluation of topical-acting drugs for topical administration.

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