# 生物类似药临床药理学研究

# 技术指导原则

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# 生物类似药临床药理学研究技术指导原则

I. Introduction

In recent years, the development and application of biosimilar drugs have been increasing. Domestic and foreign Some drugs have been approved for marketing as biosimilars to better meet patients' clinical drug needs. Find sum accessibility. Clinical pharmacology research is an important part of biosimilar drug comparison research. Important content, relevant information supporting the effectiveness and safety of biosimilars and reference drugs Similarity evaluation is very important. To further standardize and guide the research and development of biosimilar drugs and evaluation, this guiding principle is contained in the Technical Guidelines for the Development and Evaluation of Biosimilar Drugs. Rules (Trial)" and "Biosimilar Similarity Evaluation and Indications Extrapolation Technology Under the framework of the Guiding Principles, it is further proposed that clinical pharmacology research on biosimilar drugs The guiding recommendations of the research are intended to provide technical reference for the research and development of biosimilar drugs.

Biosimilar drugs mentioned in this guideline refer to: in terms of quality, safety and effectiveness Biological agents for therapeutic use that are similar in efficacy to registered reference drugs products.

This guidance applies to recombinant proteins with well-defined structure and function for therapeutic use. quality products. For modified products such as polyethylene glycol and antibody-conjugated drug products, Careful consideration should be given when developing biosimilar drugs.

2. Purpose of Clinical Pharmacology Research

The research and development of biosimilar drugs is based on comparative experimental studies to prove that the candidate drug and the reference drug Based on the similarity of the medicine, it supports its safety, effectiveness and controllable quality. biological Clinical pharmacology studies on similar drugs should also follow the principle of comparison and prove that candidate

There is no clinically significant difference between the drug and the reference drug, thus proving that it is different from the reference drug.

Similarity is one of the key steps in biosimilar research. clinical pharmacology research

The study mainly provides pharmacokinetics (Pharmacokinetics,

Similarity data in terms of PK) can also be obtained through pharmacodynamics

(Pharmacodynamics, PD) research (including both efficacy and toxicity)

and quantitative pharmacology analysis to assess whether drug candidates and reference drugs have clinical

difference in meaning. Clinical pharmacology research can address issues that remain after preliminary analysis and evaluation

The partial uncertainty that exists increases the overall evidence of the similarity assessment and can

Guide the research and design of subsequent clinical trials. Clinical pharmacology study results may also be

It can indicate the clinically significant differences between the candidate drug and the reference drug, thereby guiding further

step research design to assess these potential differences. Based on the degree of potential differences

Can evaluate whether to continue development of the drug candidate or what additional studies should be conducted. Pro

Clinical pharmacology research data is also an important scientific basis to support data extrapolation. biology

The types of clinical pharmacology studies to be conducted on similar drugs should depend on the availability of the corresponding studies.

Resolve uncertainties and thereby increase the overall evidence base for biosimilar development.

3. Research content

(1) Pharmacokinetics and pharmacodynamics studies

This guideline proposes general principles for comparative PK and PD studies of biosimilars.

Sexual requirements, for some special situations, such as the elimination mechanism of drugs in the body is not clear or

Involving obvious target-mediated elimination mechanisms and variation in the exposure-effect relationship of the reference drug

Larger, etc., it may be necessary to carry out multiple clinical pharmacology studies or adopt special designs,

In such cases, it is recommended to communicate with the regulatory agency in advance based on specific drug characteristics.

1. Overall research design

Clinical pharmacology studies of biosimilars can be designed using crossover designs

or parallel design.

Crossover design: Single-dose, randomized, crossover

Research design. For drugs with short half-life (e.g., less than 5 days) and rapid PD response (e.g.,

The onset of action, maximum effect and subsidence time are basically synchronized with the exposure of the drug),

For products where the incidence of immunogenicity is expected to be low, a crossover design is recommended. The study

The design is most sensitive to the assessment of PK similarity and can use the smallest number of subjects

number to provide a reliable estimate of differences in drug exposure. When the PD effect is delayed more or is related to

When the PK behavior of a single dose is not parallel, multiple doses may be needed to assess PD similarity.

Quantitative research design. The crossover design needs to fully consider the occurrence and disappearance of immunogenicity.

time and its relationship with the cleaning period.

Parallel design: Some biological products have long half-lives and can cause

immune response. Parallel designs are suitable for applications with long half-lives or where repeated exposure may result in

Drugs that increase immune response thereby affecting PK and/or PD similarity assessment. Should

The design is also suitable when the study population is patients whose drug exposure changes over time over the course of the disease.

about changing circumstances.

For drugs that can be used both as monotherapy and in combination therapy, such as

When immunosuppressants or chemotherapy drugs are used in combination, monotherapy can minimize variation,

Therefore PK may be more sensitive than studies using monotherapy. In some cases,

If combined treatment is required, it is recommended to choose a chemotherapy regimen that introduces less variation factors

and subjects, such as first-line treatment (the patient's clinical status is relatively stable) or early

Adjuvant therapy for patients with advanced stage tumors (low tumor burden).

If a drug is in a different therapeutic area (such as autoimmunity and oncology)

When different targets mediate elimination, separate PK studies may be required.

2. Reference drug

Should be in accordance with the "Technical Guiding Principles for R&D and Evaluation of Biosimilar Drugs (Trial)"

Other relevant policies and regulations require the selection of reference drugs.

3. Study population

Clinical pharmacology research must be based on medical ethical requirements and must be conducted in sensitive areas.

The selected drug is carried out in healthy volunteers or patient populations that are different from the reference drug. should be provided

Sufficient evidence to justify the selection of populations for clinical pharmacology studies. Subject-like

This amount should ensure sufficient statistical power for PK and/or PD similarity assessment.

It is generally believed that healthy volunteers have small variations in PK and PD, while patients often

There are often confounding factors, such as disease status, comorbidities, and concomitant medications. like

If the safety of the drug is better in healthy volunteers, or if healthy volunteers are associated with patients

For the same evaluable PD indicators, it is recommended that people in clinical PK and PD studies be given priority.

Use healthy volunteers.

For some drugs, due to safety and ethical considerations, or PD

Biomarkers are only relevant to patients with relevant symptoms or diseases. In this case, they need to be selected

Patients underwent clinical pharmacology studies. If a patient is not suitable for a single-dose study,

Multiple-dose studies should be conducted.

If the population and/or dose used in the PK comparison study is compared with clinical effectiveness

Different studies, it is recommended to conduct population PK assessment in clinical effectiveness comparison trials.

These data add to the overall evidence of drug similarity and can be used to explain clinically useful

The results of comparative studies on efficacy and safety.

4. Dose selection

Dosage selection should take into account whether the study population is healthy volunteers or patients, ranging from sensitive

Comprehensive assessment of sexual and ethical aspects. To evaluate drug candidates and reference drugs in

differences in PK and/or PD, the drug most likely to be elucidated should be selected.

sensitive dose with clinically significant data.

If the study uses healthy volunteers or detects PD indicators, the exposure-effect ratio is generally

Studies should be conducted at lower doses within the steeper range of the relationship curve.

If patient studies are conducted, doses approved for the corresponding indications of the reference drug are usually used.

To carry out clinical pharmacology studies in large quantities, it is generally recommended to use the lowest therapeutic dose. if

The approved dose of the reference drug is in the non-linear PK characteristic region or exceeds the maximum production

dose for PD effects, it would be better to use other dosing regimens, e.g. in patients with chronic disease

The single dose may be lower than the approved dose of the reference drug. Choice of dosage regimen

The choice depends on many factors, such as whether the lower dose is consistent with the approved reference drug.

doses have the same PD effect, if there is a difference in effect, the ethical aspect is

Is it feasible?

Sufficient evidence should be provided to justify dose selection.

5. Route of administration

In clinical pharmacology studies, candidate drugs and reference drugs should be administered in the same manner

way. If the reference drug is approved for administration by multiple routes, such as intravenous

administration and subcutaneous administration, etc., the administration that is most sensitive to detecting drug differences should be used

Pathways were evaluated for PK and PD similarity. In most cases, subcutaneous administration or

Other extravascular routes of administration are more sensitive because they can assess both

Differences in distribution and elimination phases can be estimated, as well as potential PK differences in the absorption phase.

In addition, the extravascular route of administration allows for a more sensitive assessment of the immunogenicity of drugs.

face differences.

6. Sampling design

6.1 PK study sampling design

In single-dose studies, the sampling time needs to be designed to characterize the entire PK process.

Including absorption phase, distribution phase and terminal elimination phase. Usually, AUC0-t /AUC0-ÿ

The ratio ÿ80% is acceptable, if the AUC0-t /AUC0-ÿ ratio is <80%

If the proportion of subjects is >20%, the reliability of the trial conclusions needs to be fully evaluated.

For some drugs that require two or more doses, the first

Sampling is done after both the first and last dose, because both the first and last doses are taken.

Can be used for similarity assessment. Sampling after final dose administration can also assess differences in elimination phases.

There is a difference, and this part cannot be observed after the first dose.

If a multiple-dose study is used to evaluate the candidate drug versus the reference drug in patients,

similarity, or the inability to characterize elimination after final dose administration, the sampling design should be able to

Characterize the PK profile after the first dose and subsequent doses (preferably steady state). In participation

In cases where the drug exhibits nonlinear PK (e.g., many antibodies with cellular targets

Tumor mAbs exhibit dose- or time-dependent distribution and elimination kinetics

PK, or the presence of immunogenicity-related changes), characterizing the intact plasma drug at steady state

The concentration-time curve is particularly important.

6.2 PD study sampling design

The selection of PD biomarker sampling time points and sampling duration depends on PD

Characteristics of the indicator itself (eg: PD reaction time after administration). When starting dosing

When the post-PD response lags behind, studies on multiple doses of administration to steady state are very important, especially

Do not use drugs for long-term clinical treatment. PD changes may be related to PK

Changes are out of sync. The optimal sampling scheme for the PD indicator may be different from that of the PK indicator

Sampling plan, in this case the PD sampling plan should be fully justified. like

If a clinical pharmacology study collects both PK and PD data, the sampling plan

Optimization should be based on both PK and PD indicators.

7. Test substances

When conducting comparative studies on PK and PD, it may be necessary to examine a variety of different

Detection of substances. For example, the test substances in PK comparison studies may include free drugs,

The complex formed by binding to the drug target and the total drug. It is recommended to use the

The most sensitive test substance to evaluate the difference in pharmacological activity between candidate drugs and reference drugs

Perform quantitative analysis and use validated bioanalytical methods. should be in accordance with relevant

Technical requirements for testing.

8. Pharmacokinetic evaluation indicators

For single-dose studies, when administered intravenously, AUC0-ÿ is the main evaluation index;

When administered subcutaneously, Cmax and AUC0-ÿ are the main evaluation indicators. Cmax should be used

Actual measured data without extrapolation.

For cases where only multi-dose studies are conducted, the main evaluation index is the first dose

Intercepted AUC (AUC0-t) after the drug to before the second dose and two doses at steady state

AUC between intervals (AUC0-ÿ). The drug trough concentration (Cmin,ss) and/ or peak concentration (Cmax,ss) at steady state are secondary evaluation indicators.

9. Pharmacodynamics evaluation indicators

When the PD index has a relatively high value within the drug concentration range obtained from PK studies, When using a wide dynamic range, it should be based on biomarkers that can reflect the mechanism of drug action. The PD similarity evaluates the similarity of drugs. Even though humans in PK/PD studies PD data are insufficient to assess whether there is a clinically meaningful difference between the drug candidate and the reference drug However, human PD data can still inform the design and development of subsequent safety and efficacy trials. Data collection program provides support. Ratio of PD indicators between candidate drugs and reference drugs Correspondence was evaluated by the area under the effect curve (AUEC). If the PD mark When only one PD test result can be obtained based on the characteristics of the marker itself, the test result should Correlate with drug exposure tested at the same time, and drug exposure and PD standards should be The correlation between markers and substances serves as the basis for comparison between candidate drugs and reference drugs.

Conducting research using a single PD indicator or multiple related PD indicators can reduce Lowers uncertainty in similarity assessment between candidate drug and reference drug and significantly increases drug Overall evidence of similarity. It is recommended to use multiple PD markers (if present) Conduct evaluation. Using broader biomarkers that capture multiple pharmacological effects (e.g. Protein or mRNA chip analysis) for research, you can also add corresponding research value.

Where feasible and applicable, data related to clinical endpoints in clinical pharmacology studies It can also provide value in assessing whether there are clinically meaningful differences between drugs. Information.

10. Statistical analysis and acceptance criteria

Whether the candidate drug and the reference drug are similar in clinical pharmacology need to be based on Evaluated using statistical methods. Log-transformed exposures are generally recommended parameters for statistical analysis. Currently, comparison of PK and PD parameters generally recommends The average bioequivalence statistical method was used. Mean bioequivalence study methods require Calculate the 90% confidence area of the geometric mean ratio of the corresponding parameters of the candidate drug and the reference drug between. When evaluating similarity, the confidence interval should fall within the acceptance limits. Confidence The choice of intervals and acceptance limits can vary from drug to drug, and similarity zones need to be defined in advance. time and properly justify it. In general, the acceptance limits of a confidence interval Typically set to 80%-125%; if other acceptance limits are used, they should be Conduct adequate demonstration, including assessment of potential effects on clinical efficacy and safety.

Data analysis should be carried out in accordance with the predetermined analysis plan, and any subsequent statistics All analyzes are exploratory.

If a multicenter study is used, it is recommended that the same study protocol be used, e.g. There are differences in some aspects, and the impact of the above differences on PK, Impact of PD, safety, and immunogenicity similarities.

11. Application of modeling and simulation technology

The application of modeling and simulation techniques may help PK and/or PD research devices count. For example, it can help select the optimal dose for assessing PD similarity. Dangcai When comparing candidate drugs with reference drugs using biomarker data, it is best to choose Conduct studies at doses in the steep portion of the reference drug dose-response curve. Data should be provided Demonstrate that the chosen dose is on the steep part of the dose-response curve rather than on the

The plateau phase of the dose-response curve. Using model simulation method, it can be based on parameters

PK and/or PD studies based on known dose (or exposure)-response relationships

Justify the chosen dose.

If exposure-response data for the reference drug are not available, a

An exploratory study was conducted to determine this information to select the optimal dose (e.g., to achieve

A comparative study is conducted based on the dose at which the maximum effect of the reference drug is 50% [ED50]. exploratory

Studies can evaluate multiple dose levels (e.g., approved low, intermediate, and high doses)

PK/PD relationship under the reference drug to obtain the dose-effect or exposure-effect relationship of the reference drug

system data. In addition, it is also possible to use methods in which a clear dose-response relationship can be observed

Conduct evaluation of candidate drugs and reference drugs at low doses, intermediate doses, and the highest approved doses

PK/PD comparison study. If used to guide multiple dose studies, PK/PD parameters should be

Numbers such as EC50, maximum PD effect (Emax), and the slope of the concentration-effect relationship

Carry out similarity evaluation. Relationship between biomarkers and clinical endpoints and modeling and

Simulated data can also be used to define limits on PD similarity.

(2) Safety and immunogenicity considerations

When immunogenicity results in altered PK behavior of the drug, reduced PD effect, or

When the therapeutic effect is lost (such as neutralizing antibodies), or immune-mediated adverse reactions occur,

The frequency and intensity of associated reactions should be assessed. Provisional

safety and immunogenicity data from clinical pharmacology studies and integrate clinical pharmacology

Safety and immunogenicity data collected from the study are simultaneously submitted to the clinical

Safety and immunogenicity data were pooled for comprehensive evaluation.

When evaluating safety and immunogenicity data from clinical pharmacology studies,

Full consideration should be given to the known safety and immunogenicity information of the reference drug. For example, if

Reference drugs have potential immunogenicity, and it is recommended to develop them in advance to detect drug-resistant

Analytical methods for antibodies (or neutralizing antibodies) to ensure timely assessment of PK and PD

Immunogenicity samples under study.

Evaluate safety and immunogenicity data collected from clinical pharmacology studies

The timing of onset and resolution of safety signals or immune responses should be fully understood.

The PK characteristics of candidate drugs and the published PK data of reference drugs can be used to judge safety.

Safety and immunogenicity follow-up time.

4. Declaration information

In addition to the regular application information requirements, clinical pharmacology research information needs to be provided

Submit necessary documents such as research plan and research summary report. Similarity evaluation should be provided

scientific and reasonable basis for acceptance criteria.

Comprehensive PK parameters should be provided, including but not limited to AUC0-t, AUC0-ÿ,

AUC0-ÿÿAUC0-t /AUC0-ÿÿÿÿCmaxÿtmaxÿCmin,ssÿCmax,ssÿ table

Observe the volume of distribution, clearance rate and elimination half-life.

PD comparative study plans should detail key study designs such as study dose,

Sampling design, testing substances, etc. The correlation between PD indicators and clinical endpoints needs to be explained

nature and provide scientific basis. It is necessary to fully analyze the PK/PD relationship and analyze whether there is

In special cases such as delayed PD effects.

When using modeling and simulation methods to carry out the key design of the research plan, it is necessary to submit

For detailed information on modeling and simulation, please refer to "Model-Guided Drug Research and Development Technology"

"Technical Guiding Principles" and "Technical Guiding Principles for Population Pharmacokinetics Research", etc.

## 5. References

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