创新药人体生物利用度和生物等效性研究

技术指导原则

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I. Overview

Bioavailability (BA) and bioequivalence

(Bioequivalence, BE) are important indicators for the evaluation of innovative pharmaceutical preparations.

BA research is the process of selecting appropriate administration routes and determining medication during the research process of innovative drugs.

One of the important basis for the regimen (such as dosage and dosage interval). BE research rules

It is a comparative study based on a predetermined equivalence standard and is guaranteed to contain the same drug.

The consistency of the in vivo behavior of the two preparations of the active ingredients and whether they can be substituted for each other

basis.

During clinical trials of innovative drugs and after they are launched, as clinical trial data

and the continuous accumulation of clinical medication experience, the biopharmaceutical properties, safety and

The understanding of the safety and effectiveness of drugs is also deepening, and drugs are used in raw materials, preparations and

There may be changes to varying degrees in aspects such as dosing regimens, and these changes may

Affects the pharmacokinetic behavior of drugs, thereby affecting safety and effectiveness, so

If necessary, research including BA or BE needs to be carried out to carry out the above changes.

evaluate.

This guideline is mainly applicable to situations where systemic exposure indicators can be used to evaluate BA

and BE's chemically innovative drug oral preparations, non-oral preparations (such as transdermal absorption preparations)

formulations, some preparations for rectal administration and nasal administration, etc.) can also refer to this guideline

but.

(1) Bioavailability

Bioavailability refers to the release and absorption of drug active ingredients from the preparation into the whole body.

The speed and extent of body circulation. Generally divided into absolute bioavailability and relative bioavailability

Utilization.

1.Absolute bioavailability

Absolute bioavailability is based on intravenous preparations (usually considered intravenous preparations bioavailability

Utilization (100%) is the absorption of active pharmaceutical ingredients into the body obtained from the control preparation.

The relative amount of the inner loop.

2. Relative bioavailability

Relative bioavailability is a measure of the relative bioavailability of preparations administered by other non-intravenous routes (such as tablets

dosage and oral solution) for the control preparation to obtain the absorption of the active pharmaceutical ingredient into the body

The relative amount of the cycle.

During the development of innovative drugs, BA studies are usually used to evaluate both before and after changes.

Changes in the formulation, and the drug content of the changed formulation can also be obtained through BA research.

Dynamic information. Generally, the pharmacokinetics of the two preparations before and after the change should be provided.

Parameters, plasma concentration-time curve, main pharmacokinetic parameters AUC and Cmax geometry

Mean ratio and its 90% confidence interval, etc.

Pharmacokinetic properties such as absorption rate or extent of the preparation before and after the change

Differences may affect the benefits and benefits of the changed formulation or new administration method

Risk assessment. For example, the bioavailability of the modified preparation is significantly higher than or

Lower than before the change, the researcher needs to consider adjusting the dosage based on the degree of change;

When the variation in pharmacokinetic parameters of the preparation after the change is significantly greater than before the change, the

may affect the safety and effectiveness of the drug, indicating that the two preparations before and after the change are not

Comparable.

In some cases, based on peak drug concentration (Cmax) and exposure (AUC)

BA's similar conclusions may not be sufficient to demonstrate the safety of both formulations before and after the change

There was no difference in performance or effectiveness. For example, the time to reach peak drug concentration (Tmax) is expressed as

and the difference in blood drug concentration-time curves often indicates that the preparation before the change and the preparation after the change

The clinical effects of preparations vary. In this case, it may be necessary to submit additional

Data analysis, such as partial exposure (partial AUC), exposure-effect relationship

Or clinical study results to evaluate the BA of two formulations.

(2) Bioequivalence

Bioequivalence (with PK as the end point) refers to the

After the same dose of the test drug is administered one or more times, the dosage of the drug in the preparation is changed.

The difference in absorption speed and degree from the preparation before the change is within the acceptable range.

Generally speaking, the equivalence standard for BE studies is the main drug of the two preparations before and after the change.

The 90% confidence interval of the geometric mean ratio of the kinetic parameters (AUC and Cmax) falls within

Within the range of 80.00%~125.00%.

When the two preparations before and after the change are not bioequivalent, the sponsor should base

Available dose-response or exposure-response data illustrate differences in the rate and extent of absorption

It will not have a significant impact on the safety and effectiveness of the drug. When there is no sufficient evidence

When doing so, consideration should be given to adjusting the prescription, changing the production process, or adding new safety and

Effectiveness data.

(3) Application of BA/BE research in different stages

1. Early stage of clinical trials

In the early stages of clinical trials of innovative drugs, BA studies can be chosen to reflect

quality of the drug product, elucidating the absolute bioavailability of the drug, and establishing next steps

Dosing regimen provides reference basis. For example, when innovative drugs are developed simultaneously for intravenous and non-intravenous

When dosing dosage forms, non-intravenous routes of administration may be determined through absolute bioavailability studies.

Absolute absorption percentage of diameter.

2. Pre-launch changes

During drug clinical trials, when changes occur, changes should be made in accordance with the "Innovative Drugs

(Chemical Drugs) Technical Guiding Principles for Pharmaceutical Changes During Clinical Trials (Trial)"

and other guiding principles, combined with the pharmacokinetic characteristics, safety,

Effectiveness and other possible impacts, comprehensively evaluate whether BA/BE research is needed

Research, such as:

(1) When the preparations for early-stage and late-stage clinical trials are different;

(2) When specifications are different;

(3) When the preparation to be marketed is different from the preparation in the pivotal clinical trial (should be

BE research).

3. Post-market changes

When changes occur after drug approval and marketing, is it necessary to conduct BE studies?

You should refer to the "Technical Guiding Principles for Pharmaceutical Change Research on Marketed Chemical Drugs (Trial)"

and other guiding principles, and conduct a comprehensive evaluation based on the actual situation of the drug.

2. Methods of human BA/BE research

In general, recommended BA/BE research methods include in vivo and in vitro

method. Evaluate potency according to study methods, with priority given to pharmacokinetics

(PK) studies, pharmacodynamic (PD) studies, clinical studies, and in vitro

Research.

(1) Pharmacokinetic studies

By measuring drugs in biological matrices (such as blood, plasma, serum, etc.)

concentration to obtain PK parameters that reflect drug release from the formulation and absorption into the circulation

The speed and extent of the ring system. Usually the PK endpoint indicators Cmax and AUC are used.

evaluate.

The overall design, sample size, and subjects involved in the BA/BE study of innovative drugs

Selection, selection of single dose/multiple dose (steady state) studies, biological sample analysis

Analysis, PK parameters used for evaluation, test implementation process and data statistical analysis tools

For physical requirements, etc., please refer to "Clinical Single and Multiple Administration Dose Delivery of Innovative Chemical Drugs"

"Technical Guiding Principles for Pharmacokinetic Research", "Taking pharmacokinetic parameters as endpoints"

Technical guidance for human bioequivalence research on chemical drug generics based on evaluation indicators

Principles", "Statistical Guiding Principles for Bioequivalence Studies", "High Variability

"Technical Guiding Principles for Drug Bioequivalence Studies" and "Narrow Therapeutic Index Drug Development"

"Technical Guiding Principles for Physical Equivalence Studies" and other related guiding principles. this guideline

This article mainly explains the special considerations for BA/BE research on innovative drugs.

1. Preliminary test/formal test

Sponsors may conduct studies in a small number of subjects before conducting formal BA/BE studies.

Conduct a pilot test. The pilot test was designed to: (1) initially evaluate the variability of PK parameters;

(2) Determine the sample size that can obtain sufficient power to conduct formal BA/BE

Study; (3) optimize sample collection time; (4) determine cleaning period between cycles.

In some cases, if the design and conduct of the pilot experiment are scientifically standardized,

And a sufficient number of subjects are included and evaluable PK data are obtained, in the protocol

If pre-specified, the preliminary test results can be used to confirm the preparation BA/BE.

in accordance with.

2. Research design

A non-replicated crossover study design is generally recommended. For long half-life drugs

(If the elimination half-life is ÿ24 hours), a parallel study design can be chosen. bid

Investors can also use other research designs to conduct BA/BE research on innovative drugs and provide

Sufficient scientific basis.

3. Administer on an empty stomach or after meals

BA/BE studies of innovative drugs are usually carried out under fasting conditions. This is

Conditions most sensitive to evaluate potential differences between formulations, fasting conditions may be severe

If there are safety risks, BA/BE studies under postprandial conditions can be carried out. Is it necessary to open

For research on the food impact of modified preparations, please refer to "Food during the Development of New Drugs"

Technical Guiding Principles for Physical Impact Research.

When the intended use instructions for the modified preparation clearly indicate that it can only be taken with food or after meals

When dosing, in addition to conducting BA/BE studies under postprandial conditions with the preparation before change,

Food impact studies of the changed formulation should also be conducted.

4. Dosage

In general, one unit of the highest strength preparation (e.g. single tablet or

single pill) administration. If the highest strength formulation poses a safety risk to healthy subjects,

Patients may be included as subjects, or lower strength formulations may be used.

When the specifications of the preparation before and after the change are inconsistent, it is recommended to use the same or similar

Dosage administration (not exceeding the maximum dose intended for clinical use). If similar doses are used

drug, and the PK characteristics are linear within the dosage range, dose-corrected

Methods to Calculate Bioavailability.

5. Detection of substances

It is generally recommended to measure the original drug because the drug-time curve of the original drug is specific to the activity.

Sexual metabolites can more sensitively reflect differences between preparations.

For active metabolites, they are mainly produced before entering the systemic circulation (such as from

First-pass effect or intestinal metabolism, etc.) and affect effectiveness or safety,

The original drug and the active metabolite should be measured simultaneously.

For prototype drug concentrations that are too low to be reliably tested in biological matrices

In the case of measurement, only active metabolites can be measured.

(2) Other methods to support BA/BE

When pharmacokinetic methods are indeed not feasible, PD research can also be considered

research, clinical studies, in vitro studies, etc., but the methods used need to be fully confirmed

It is scientific and reasonable.

3. BA/BE research on common dosage forms

(1) Oral solution

For oral solution, syrup and other solution dosage forms, if the following conditions are met,

To be exempted from BA/BE studies:

(1) The preparation is in a true solution state;

(2) The solution does not contain excipients that affect drug absorption (such as sorbitol, vitamin B, etc.)

Vitamin E, etc.).

May occur when oral solutions are exposed to gastric contents or used diluted

precipitates (if the prescription contains latent solvents, buffers, etc.), the handling of such preparations

In vivo studies should be considered for changes in formulation.

(2) Sustained release preparations

Sudden-release preparations include tablets, capsules, lozenges, chewable tablets, orally disintegrating tablets and tongue

When taking tablets, etc., it is generally recommended to conduct single-dose fasting BA studies and food effect studies.

In some cases, multiple-dose BA studies are also required.

Unconventional dosage forms (such as lozenges, chewable tablets, orally disintegrating tablets, sublingual tablets, etc.) should

Administer according to intended labeling. Additionally, such products may need to be swallowed intact

oral BA studies to evaluate the effects of accidental swallowing of intact drug products.

During the development of new drugs, if specifications change, if the previous requirements are met at the same time,

BA/BE studies are exempted if the following conditions are met:

(1) The drug dosage form is the same, but the specifications are different;

(2) The prescription proportions of preparations of various specifications are similar;

(3) The in vitro dissolution curves of various specifications of preparations in different pH media are similar;

In addition, new strengths should be considered within the dose range where the PK characteristics are linear.

(3) Oral suspension

The research technical requirements for oral suspensions are the same as those for extended-release preparations.

(4) Modified release preparations

Modified release preparations include delayed release preparations and sustained release preparations. modified release preparation

For relevant requirements of BA/BE research, please refer to "Clinical Pharmacokinetics of Modified Release Preparations of Improved New Drugs".

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