《化学药品创新药Ⅲ期临床试验前会议药学共性问题及相关技术要求(试行)》

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目 录

I. Introduction

In order to encourage innovation and accelerate the research and development of new drugs, the "Measures for the Administration of Drug Registration" stipulates

Drug registration applicants (hereinafter referred to as "applicants") are key in drug clinical trials.

stage, you can discuss major issues with professional technical institutions such as the Drug Evaluation Center

Communicate.

End of Phase II clinical trials of innovative drugs (EOPÿ)/Phase III clinical trials of prodrugs

The scientific communication meeting (hereinafter referred to as the Pre-Phase III pharmaceutical meeting) is during the clinical trial

important communication meeting. The applicant is submitting an application for the Pre-ÿ phase pharmacy conference

When meeting, it is necessary to clarify the purpose of the meeting, raise specific communication issues, and prepare detailed

information and research data to identify and resolve key pharmaceutical issues for follow-up research as early as possible.

question. This technical requirement mainly explains the Pre-Phase III pharmaceutical innovative drugs.

Discuss common issues and general requirements to improve communication between applicants and drug review agencies

Quality and efficiency of communication.

The scope of application of this technical requirement includes chemical innovative drugs and improved new drugs.

When applying this technical requirement, it is recommended that the applicant also refer to the relevant guidelines and follow the

The research and development of new drugs is carried out according to general rules.

This technical requirement only represents the current views and understanding of the drug regulatory authorities and does not

It is legally binding. With the progress of scientific research, this technology will

The relevant content in Qiuzhong will be continuously improved and updated.

2. Overall considerations

The applicant is the person responsible for the research and development and registration application of innovative drugs.

Applicants should accompany the development of phase I/II clinical trials and combine the characteristics of the drug with

Point and the knowledge and production experience accumulated during the phase I/II clinical trial research phase, as soon as possible

In view of the remaining pharmaceutical-related issues in the clinical trial notification, and in accordance with the "Innovative Drugs

(Chemical Drugs) Phase III Clinical Trial Pharmaceutical Research Information Guidelines" and other technical requirements have been completed

Good related research. Applicants need to sort out the existing pharmaceutical research content and clarify the need to communicate

Prepare detailed information and research data through communication issues.

For APIs with complex processes and difficult quality control (such as peptides, small fractions

Sub-nucleic acids, polymer products, containing multiple chiral centers, containing fermentation processes or natural

drugs from natural sources), complex preparations (such as microspheres/microemulsions/liposomes, micelles,

Transdermal preparations, inhalation preparations, suspension injections, etc.) and complex drug and device combinations

Products, etc., the Pre-ÿ phase pharmaceutical meeting is particularly important. Applicants are requested to participate in the Phase ÿ clinical trials.

Consult with drug review agencies on key technical issues in pharmaceutical research before testing.

Discuss separately.

For drugs to be adopted, accelerated marketing registration procedures (such as conditional approval procedures

etc.), communication before key clinical trials (such as before phase II clinical trials)

Communication can be carried out with reference to this technical requirement. The pharmaceutical research plan should be consistent with the clinical trial.

The research plan is unified, and applicants are recommended to communicate with the drug review agency in a timely manner. this

Applications for marketing of similar drugs must meet the technical requirements for marketing applications.

3. Common issues

(1) API

1. Selection of starting raw materials

Common problems: unreasonable selection of starting raw materials; insufficient basis for selection.

General requirements: Applicants should refer to ICH Q11 and its Q&A

Reasonably select starting materials and discuss with the drug review agency the appropriate selection of starting materials.

Rational, provide relevant supporting research information for the selection of starting materials, and cooperate with drug review

The evaluation agency reached a consensus.

If there are multiple manufacturers of the same starting material, the manufacturing methods used by the manufacturers must be combined.

Establish corresponding quality control requirements for the preparation process.

For microbial fermentation involved in the production of proposed starting materials, the applicant needs to

Evaluate the rationality of starting material selection with reference to ICH Q11 guidance, if necessary

The process route should be extended and the microbial fermentation step should be included in drug production quality management.

Standardize management.

2. Process impurities and degradation products

Common problems: Insufficient analysis of potential impurities in raw materials; impurity inspection methods

The detection capability is insufficient.

General requirements: During the clinical research of innovative drugs, applicants should continue to improve

Impurity profile analysis and impurity control strategies for APIs.

Applicants should provide relevant material methodology research stage summary materials, based on

According to the research needs, it is emphasized that different analysis methods (separation principle, stationary phase

selection, elution procedure, detector, detection wavelength, etc.)

As a result, samples can be prepared from impurities, crude products or crude mother liquors, and rationally designed

Degradation test samples, influencing factors test samples, accelerated and long-term storage end samples

Select from samples such as products as needed, and optimize potential impurities based on research results.

Analytical methods for related substances with good quality and accurate detection.

Applicants are encouraged to refer to guidance such as ICH Q3A during clinical trials

Process impurities exceeding identification limits and degradation products in accelerated and long-term testing

Carry out attribution identification and combine with theoretical analysis to accumulate knowledge about the impurity spectrum of raw materials.

It is recommended that the transfer of impurities in the API process be carried out in a timely manner based on research progress.

Chemicalization and removal studies, and formulation of impurity control for starting materials, intermediates and APIs

Strategy. If the production process of raw materials is changed, possible new impurities need to be analyzed.

If necessary, the inspection methods for relevant substances should be optimized.

Levels of impurities (including new impurities) in raw materials used in phase III clinical trials

If it exceeds the level supported by existing animal safety tests, it is recommended to improve the process to reduce

Low impurity levels in clinical samples, or provide safety that supports corresponding impurity levels

in accordance with.

3. Mutagenic impurities

Common problem: Insufficient research and control of mutagenic impurities.

General requirements: Applicants are recommended to follow ICH M7 and S9 for mutagenic

Impurity studies are evaluated and supplemented, including process impurities (starting materials and

The impurities, intermediates, reaction by-products, solvents and reagents introduced by it) and degradation

The comprehensiveness of the decomposition product evaluation research, etc.

For class 1, class 2 and concern queue impurities in ICH M7, it should usually be established

Establish a proprietary and sensitive detection method, refer to ICH M7 and Q&A documents for such complex

Conduct research on relevant requirements during quality clinical trials and formulate reasonable control strategies.

For changes in the production process of APIs, ICH M7 and Q&A should be referred to.

Answer document et al. [6,7] carried out research on the mutagenicity of new impurities. It is recommended that applicants base their

For certain research results on mutagenic impurities, follow-up research plans and control strategies are formulated, and

Discuss with drug review agencies.

Nitrosamine impurities need to be determined according to the relevant technical requirements for nitrosamine impurities [11-13,21]

Conduct risk assessment and necessary research to formulate reasonable control strategies.

4. Control of crystal form

Common problem: Insufficient research and control on the crystal form of APIs.

General requirements:

It is recommended that applicants provide research information on crystal forms of APIs, including crystal form screening,

Crystal form solubility and dissolution rate, crystallization process development, crystal form stability, etc.

Thermodynamically stable crystal forms are usually used for drug development, and mixed crystals are avoided.

If a metastable crystal form is selected as the development crystal form, special attention should be paid to the stability of the drug crystal form.

Qualitative, and take appropriate measures to avoid crystalline transformation during storage.

It is recommended that applicants refer to ICH Q11 and other guiding principles based on research progress,

Strengthen research and process control on crystallization processes for the production of raw materials, and pay attention to batch amplification

The influence of the process on the crystallization process is maintained to maintain the consistency of the crystal form of the API between batches.

5. Quality control of raw materials

Common problems: API quality standards and quality control projects are not comprehensive; change research

insufficient.

General requirements: According to research needs, the quality of raw materials for phase III clinical trials

The quality control items that the standards need to focus on include related substances, isomer impurities, residues

Retention solvent, crystal form, particle size and particle size distribution, content determination (or potency), etc.,

APIs used for injections, etc. should also pay attention to microbial limits and bacterial endotoxins.

Applicants need to summarize the changes in API quality standards during phase I/II clinical trials.

status (including items, methods and limits), pay attention to the difference between phase III clinical trials and phase I/II
The convergence of quality standards for clinical trial raw materials. If the quality standards change, they should be
Refer to the "Technical Guidelines for Pharmaceutical Changes During Clinical Trials of Innovative Drugs (Chemical Drugs)"
(Trial Implementation)" to carry out change research. Need to continue to accumulate during phase III clinical trials
Study data and improve quality standards.

It is recommended that applicants control the particle size and particle size classification of raw materials according to research needs.
cloth, using reliable inspection methods to determine the particle size and
Particle size distribution, accumulated data.

(2) Preparations

1. Prescription process

Common problems: Insufficient research on prescription process changes; prescription process changes are harmful to
Insufficient assessment of impact on clinical trial sample quality.

General requirements: Applicants need to summarize the prescription process during Phase I/II clinical period
Changes and related supporting studies will be discussed with the drug review agency for Phase III
Issues such as the formulation process and batch size of clinical trial samples.

For complex preparations, skin external preparations, etc., it is recommended to be used in phase III clinical trials.
The origin, prescription process and production batch size of the test sample should be consistent with the application for marketing authorization.
consistent. For inhaled preparations and drug-device combination products, it is appropriate to use
Use the same delivery device as in the Phase III clinical trial.

If the formulation process used for phase III clinical trial samples changes, please refer to
"Technical Guidance Principles for Pharmaceutical Changes During Clinical Trials of Innovative Drugs (Chemical Drugs)" (Trial
Conduct research on pharmaceutical changes according to relevant requirements such as "Pharmaceutical Industry" and fully evaluate changes in prescription processes

If necessary, consider the impact on the quality, safety and adaptability of preparations.

In vivo bridging studies.

2. Degradation products

Common problems: Incomplete analysis of degradation products of preparations; degradation product analysis methods

Insufficient legal testing capabilities.

General requirements: Combining research on degradation products of raw materials with preparation formulation processes

technology research, analyzing preparation production and stability investigation period, clinical sample preparation and

Use moderately likely to produce degradation products. Applicants should provide degradation product methods

Summarize the data in stages of scientific research, and highlight the use of different analysis methods according to research needs.

Analysis method (separation principle, stationary phase selection, elution procedure, detector, detection

wavelength, etc.), the sample can be prepared from the degradation products of directional preparation.

substances, reasonable design of degradation test samples, influencing factors test samples, acceleration and long-term

The samples at the end of the period of placement should be selected as needed, and the samples should be selected based on the research results.

Related substance analysis methods with good separation and accurate detection of potential degradation products

Law. At the same time, pay attention to the interference of blank excipients on the determination of degradation products. If necessary,

Reasonably determine the deduction method for the blank excipient peak.

Applicants are encouraged to refer to guidance such as ICH Q3B during clinical trials

For accelerated and long-term tests and clinical sample preparation and use that exceed the identification limit

Degradation products are identified and combined with degradation pathway analysis to accumulate preparation degradation products.

Understanding of decomposition pathways and degradation products. Such as changes in the formulation and/or production process of the preparation,

Possible new degradation products need to be analyzed, and relevant substance inspections should be optimized if necessary.

method.

If the levels of degradation products in preparations used in phase III clinical trials exceed existing

The level of support for animal safety testing is encouraged by optimizing prescriptions and strengthening work

Process control, adoption of appropriate packaging and storage conditions, etc., to avoid or reduce corresponding degradation

formation of degradation products, or provide safety evidence to support corresponding degradation product levels.

Nitrosamine impurities need to be determined according to the relevant technical requirements for nitrosamine impurities [11-13,21]

Conduct risk assessment and necessary research to formulate reasonable control strategies.

3. Dissolution and release studies

Common problems: Insufficient dissolution or release studies; lack of discrimination

Research.

General requirements: Applicants should base the drug pH-solubility curve and preparation

To meet the needs of pharmaceutical quality control, continue to improve dissolution or release method research, and

Dissolution or release studies are summarized and evaluated to provide rationale for method selection.

Based on the specificity, formulate a research plan for the discriminating power of the dissolution or release method.

If there are major changes in the type, dosage or production process of preparation excipients, it is necessary to

Re-evaluate the feasibility of confirming dissolution or release methods.

4. Preparation quality control

Common problems: preparation quality standards and quality control projects are not comprehensive; change research is not

full.

General requirements: According to research needs, the quality of phase III clinical trial preparations

The quality control items that the standards need to focus on include degradation products, dissolution or release,

Assay (or potency), pH, sterility, drug substance crystalline form, particle size and particle size

degree distribution, etc. Applicants need to summarize changes in quality standards for phase I/II clinical trials

(including items, methods and limits), pay attention to the quality of preparations for phase I/II clinical trials. The connection of quality standards. If the quality standards change, refer to the "Innovative Drugs (Chemical) "Technical Guiding Principles for Pharmaceutical Changes During Clinical Trials (Trial)" was launched Change research. During phase III clinical trials, research data will be accumulated and quality standards will be improved.

It is recommended to refer to ICH Q3D to formulate the evaluation and control of elemental impurities in preparations. research plan.

Not suitable for aqueous solutions for inhalation, oral, mucosal, dermal and nasal administration. For bacterial preparations, Burkholderia cepacia should generally be treated with reference to relevant technical requirements [14]. Conduct research and formulate corresponding control strategies.

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