appendix

Pharmaceutical Research Information Guide for Phase III Clinical Trials of Innovative Drugs (Chemical Drugs)

As research and development progress continues, innovative pharmaceutical research has different research purposes at different stages. During the clinical research of innovative drugs, the pharmaceutical research information provided should focus on the parts of the clinical trial related to the safety of the subjects. The depth and breadth of the research and the amount of information provided need to comprehensively consider a variety of factors, including the characteristics of the drug itself. , dosage form and route of administration, research and development stage, target population, disease characteristics and severity, clinical trial cycle, etc. Generally speaking, phase III clinical research has a longer research cycle, more subjects, and a greater demand for clinical samples. At the same time, the pharmaceutical information obtained with the progress of the research is gradually enriched, which determines the required information to enter phase III clinical trials. Pharmaceutical research information is different from Phase I/II clinical trials.

Due to the complexity and diversity of drugs, this guideline aims to elaborate on the general requirements for pharmaceutical research information to support innovative drugs (chemical drugs) entering phase III clinical trials. If clinical samples are prepared using unconventional production processes, more detailed research information may be required. API

S.1 Basic information S.1.1

Drug name Provide information

related to the naming of raw materials: INN (if it has been drafted), Chinese general name (if one has been drawn up), Chinese and English chemical names, code names, other names, etc.

S.1.2 Structure

Provide clarified structural information of the API, such as structural formula (salt formation and solubility should be included)

Compound ratio, chirality/stereochemistry), molecular formula, molecular weight.

S.1.3 Basic Properties List

the key physical and chemical properties and biopharmaceutical properties of the API, such as solubility, Permeability, BCS classification (if determined), hygroscopicity, dissociation constant (pka), partition coefficient (LogP/ LogD), crystal form, isoelectric point, etc.

S.2 ProductionS.2.1

Manufacturer

List the names and complete addresses of all manufacturers involved in the production of APIs (including production, inspection and release). If multiple production plants are involved, the specific responsibilities of each production plant must also be listed.

S.2.2 Production technology and process control

Provide synthesis route, process flow diagram and process description. Suggestions for process description include: (1) Batch size (range); (2) Material input ratio, synthesis operation and post-processing operation, indicating operating conditions/parameters (such as time, temperature) and process control (brief description of analysis method), List the solvents, reagents, catalysts, etc. used.

For example, if the API preparation process includes fermentation process, extraction process, peptide synthesis process, small molecule nucleic acid preparation process, etc., detailed information proving that the process is stable and controllable must be provided.

For sterile raw materials, sterilization processes and sterility assurance measures need to be provided.

S.2.3 Material Control:

According to the procedures in the process flow chart, list all materials used in production (such as starting materials, reaction reagents, solvents, catalysts, etc.), and describe their quality control information and usage steps. Impurities introduced into the final product from the materials used, including isomers (if applicable), toxic organic solvents/catalysts, potentially genotoxic impurities and biological xenobiotics (if applicable), etc., need to be controlled or combined with transformation in subsequent steps , and explain the clearing situation.

It is recommended to explain the rationality of the selection of starting materials, provide starting material suppliers, preparation routes and brief process descriptions, as well as control standards (including inspection items, description of analytical methods and tentative limits). For fermentation-derived raw materials or natural extracts as starting materials, detailed information must also be provided to prove other exogenous substances that may cause safety concerns (such as TSE/BSE and other viruses, bacteria, mycoplasma, fungi and allergenic substances). etc.) are controlled or eliminated in subsequent process steps.

S.2.4 Control of key steps and intermediates

If the key steps of production have been determined, the key steps and their process parameter control ranges need to be

listed. Provide control criteria for isolated intermediates (including inspection items, brief description of analytical methods and tentative limits). When necessary, preliminary validation information for the analytical method must be provided.

S.2.5 Process validation and evaluation

not applicable.

S.2.6 The development of the production

process provides major process changes that may affect the quality of the drug relative to Phase I/II clinical samples, and provides specific changes, relevant research information before and after the changes, and necessary safety risk assessments. For

sterile APIs, if the sterile production process of the API is changed, the reason for the change and the content of the change must be described in detail, change research information must be provided, and the rationale for the change must be explained.

S.3 Characterization S.3.1

Structure and other characteristics Provide

research information to confirm the structure of the API, such as elemental analysis, high-resolution mass spectrometry, infrared, nuclear magnetic field, ultraviolet, mass spectrometry, single crystal X-ray diffraction (if applicable), etc. For peptide drugs/nucleic acid drugs, sequence determination, amino acid/nucleic acid ratio,

High-level structure determination and other information. Sample information for structure confirmation, specific data, spectra and analysis process must be provided. If

applicable, provide salt form, stereoconfiguration, crystal form, particle size and distribution research information.

S.3.2 The impurity

list describes the analysis of impurities, including impurity name and/or code, structure, source, whether it is included in standards, safety support limits, etc. For impurities whose structures have not yet been elucidated and exceed the identification limit, information such as relative retention time, whether they are controlled as specific impurities in standards, and safety support limits must also be provided.

For solvents/catalysts used in the process but not routinely controlled, it is necessary to

Line analysis instructions.

For potentially genotoxic impurities, relevant research information (such as source, structure, control strategy, etc.) needs to be provided. If the preparation process of

the API includes fermentation or extraction steps, it is also necessary to provide analysis, identification and sources of other exogenous substances that may cause safety concerns in the process, such as viruses (TSE/BSE, etc.), bacteria, mycoplasma, fungi and Allergenic substances, etc.

S.4 Quality Control S.4.1

Quality Standards Provide the

quality standards of raw materials in table form, including test items and methods (can be

Only the method type (such as HPLC method) and tentative limits are listed.

APIs used in sterile process preparations require microbial control.

S.4.2 Analysis method Provide

specific analysis method (if chromatography method is used, chromatography conditions need to be specified).

S.4.3 Validation of analytical methods

Summarize the methodology validation results in the form of a table, and provide typical spectra. If a pharmacopoeial method is selected, information confirming the applicability of the pharmacopoeial method must be provided.

S.4.4 Batch analysis

Updated batch analysis summary, including non-clinical safety study batches, Phase I/II clinical sample batches, stability batches, and batches that can represent Phase III clinical samples. It is necessary to indicate the batch number, batch size, production process (can be represented by code), production location, production date, use, analysis method (can be represented by serial number or version number), control limits and actual measurement results. Provide inspection

reports that can represent batches of Phase III clinical samples.

S.4.5 The basis for setting quality standards

describes the basis for setting the items in the quality standards and the basis for setting limits for key items (such as impurities, quality characteristics that may affect the performance

of the preparation). Provide the content of changes to the quality standards for phase III clinical samples compared to the quality standards for phase I/II clinical samples. If quality standards are relaxed (such as deleting inspection items, relaxing limit requirements), the reason for the change and the basis for the change must be provided. If there is a major change in the impurity analysis method, research information supporting the change must be provided to evaluate the rationality of the method change. If necessary, retest the safety study batches using the pre- and post-change methods to evaluate the rationality of the impurity limits.

S.5 Control

For homemade reference standards, it is recommended to provide the source, preparation or purification method, necessary structural identification, standardization method and standardization results. For purchased reference materials, the source must be stated and instructions and batch numbers must be provided.

S.6 The packaging system

provides the current packaging materials and containers. If there are any major changes compared with the previous period, Need detailed explanation.

S.7 Stability

Provides in table form the stability of support received to date for conducting phase III clinical trials.

The stability study results should be listed with the batch number, batch size, production location, production date, process used (which can be represented by a code number) of the stability batch, and the analytical method used in each stability study (which can be represented by a number or version number). Provide representative maps of key projects (such as related substances, etc.) (such as the starting point, the longest time point completed, the time point when quality changes significantly, etc.).

The stability data are summarized and possible degradation pathways can be discussed in conjunction with the forced degradation test. Based on the results of the stability study, describe the proposed shelf life/retest period and storage conditions. If the validity period/retest period is not specified, a commitment should be made to retest the API before preparation production. To ensure sufficient stability data is obtained during the NDA phase, it is recommended to provide formal stability

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preparation

P.1 Dosage forms and product composition: Provide the prescription composition of the unit dose of phase III clinical samples in a list, and clarify the name, dosage, function and implementation standards of excipients. If premixed excipients are used, their composition must be clear, and the composition of coating materials and capsule shells must be as clear as possible. Ingredients used in the formulation but ultimately removed must also be listed. If a special solvent is included, its composition must be provided in accordance with the above requirements. For special preparations (such as inhalation preparations, nasal sprays, etc. that use specific delivery devices), the Phase III clinical sample prescriptions and delivery devices should remain similar to commercial products.

P.2 Product development Briefly describe the dosage form, specifications, prescription, and process development process. For preparations with a high risk of drug packaging material interactions (such as inhalation preparations, injections, ophthalmic preparations, oral solutions, etc.), necessary compatibility study information needs to be provided

(Such as extractables, leachables, etc.).

For products that need to be prepared for immediate use, relevant dilution and compatibility stability must be provided. Research information and preparation methods.

For use in a specific population (e.g., children), the drug ingredients, dosage form, and delivery device (if available) should be safe and suitable for that specific population.

Compared with phase I/II clinical samples, if there are major changes in dosage forms, prescriptions, and specifications that may affect product quality characteristics (such as causing changes in impurity profiles, affecting in vivo behavior, etc.), the specific content of the changes and reasons for the changes must be explained. , and pay attention to risk assessment, and conduct appropriate in vitro and/or in vivo bridging studies on samples before and after the change depending on the degree of risk.

Compared with phase I/II clinical samples, if the production process has undergone major changes that may affect the quality characteristics of the product, the specific content of the change and the reason for the change need to be explained, and attention should be paid to risk assessment. Depending on the degree of risk, appropriate in vitro testing should be carried out on the samples before and after the

change. and/or in vivo bridging studies. For sterile preparations, if the sterilization process is changed, the rationale for the change needs to be explained.

P.3 ProductionP.3.1

Manufacturer

List the names and complete addresses of all manufacturers related to the production of Phase III clinical samples (including production, packaging, inspection and release). If multiple production plants are involved, the responsibilities of each production plant must also be listed.

P.3.2 Batch prescription

Provide phase III clinical sample batch prescriptions (indicate the batch size or batch range if possible), and list the names and dosages of each ingredient. If there is excessive addition, please provide explanation. Solvents used in the formulation but ultimately removed should also be listed.

P.3.3 Production technology and process control

Provide the production process flow chart and production process description of Phase III clinical samples, as well as related process control. If

unconventional production processes are used, a detailed description is required.

For sterile preparations, more detailed sterilization technology and process control need to be provided.

P.3.4 Control of key steps and intermediates

If the key steps of production have been determined, process parameter control of the key steps needs to be provided Scope; if the preparation intermediates have been controlled, their standards need to be provided.

For preparation intermediates, if storage is required, the storage conditions and storage time must be clarified. Provide supporting research results where necessary.

P.3.5 Process Validation/Evaluation

Process validation information is generally not required. If an unconventional production process is used, sufficient information must be provided to evaluate the stability and controllability of the process. Among them, if an unconventional sterilization process is used, sufficient information needs to be provided to evaluate the sterility assurance level of the product.

P.4 Excipient control

If the excipients used comply with pharmacopoeia standards, the manufacturer, basic information (such as model, source, components, etc.) and the specific pharmacopoeia standards (such as Chinese Pharmacopoeia Ch.P, United States Pharmacopoeia USP, European Pharmacopoeia Ph.Eur, Japan) must be listed. Pharmacopoeia JP, etc.). If the excipients used comply with other industry standards or corporate standards, the specific standards must be listed and the methods used in the main projects must be

described. For brand-new excipients that have not been used in domestic and foreign preparations, relevant information should be provided in accordance with the related declaration requirements

or a related declaration should be made. For excipients of human origin/animal origin, it should be declared that there are no safety risks (such as TSE/BSE and other viruses, etc.).

P.5 Quality Control P.5.1

Quality standards provide the

release standards and shelf life standards (if applicable) of the preparation in table form, including test items, methods (only the type of method can be listed, such as HPLC method), and tentative limits. Usually, the test items should at least include

identification, degradation products and content determination. In addition, specific inspection items and limit requirements for dosage forms should also be included (such as dissolution/disintegration time limit of oral solid preparations, content uniformity inspection, etc.; pH value, bacterial endotoxin and sterility inspection of injections, etc.). If a special solvent is included, the quality standards of the special solvent must be provided.

P.5.2 Analysis method Provide

specific analysis method (if chromatography method is used, chromatography conditions need to be specified).

P.5.3 Validation of analytical methods

Summarize the methodology validation results in the form of tables, and provide typical spectra. If a pharmacopoeial method is selected, information confirming the applicability of the pharmacopoeial method must be provided.

P.5.4 Batch analysis

Update the batch analysis summary to include non-clinical safety study batches (when necessary), Phase I/II clinical sample batches, stability batches, and batches representative of Phase III clinical samples. It is necessary to indicate the batch number, batch size, prescription process (can be provided in the form of code number), production location, production date, use, analysis method (can be provided in the form of serial number or version number), control limits and actual measurement results. Provide inspection reports that can represent batches of phase

III clinical samples.

P.5.5 Impurities

Provide information on impurities that exist in the preparation but are not covered under S.3.2, including impurity names and/or codes, structures, degradation pathways, safety support limits, etc. for knot

For impurities that exceed the identification limit and have not yet been clarified by the structure, information such as relative retention time, whether it is controlled as a specific impurity in the standard, and safety support limits must also be provided.

P.5.6 The basis for setting quality standards

describes the testing items that may affect effectiveness and safety and the basis for setting acceptable limits. If routine inspection items for

dosage forms are not formulated, their rationality must be explained. Explain the changes to the phase III clinical

quality standards compared to the phase I/II clinical standards. If quality standards are relaxed (such as deleting inspection items, relaxing limit requirements), the reason for the change and the basis for the change need to be provided. If the research process involves major changes in methods, necessary supporting research information before and after the changes must be provided.

P.6 Reference substance

For homemade reference standards, it is recommended to provide the source, preparation or purification method, necessary structural identification, standardization method and standardization results. For purchased reference materials, the source must be stated and instructions and batch numbers must be provided. If it is already covered in S.5, it does not need to be provided repeatedly.

P.7 Packaging system

Provides the packaging system used for phase III clinical samples (including inner packaging that directly contacts the drug and functional outer packaging) and implementation standards. For high-risk preparations

(such as inhalation preparations, injections and ophthalmic preparations, etc.)

For packaging systems, manufacturers and implementation standards of all components must be provided.

For pharmaceutical packaging materials with new materials, new structures, and new uses, relevant research information must be provided or related declarations must be made in accordance with the requirements for related declarations.

P.8 Stability

Provide the stability study results obtained so far to support the conduct of phase III clinical trials in the form of a table, listing the batch number, batch size, production location, production date, prescription process (can be represented by code) of the stability batch, and the data used in each stability study. Analytical method

(Can be represented by number). Provide representative maps of key projects (such as related substances, etc.) (such as the starting point, the longest time point completed, the time point when quality changes significantly, etc.). Based on the characteristics of the drug, it may be necessary to provide high temperature, high humidity, light, oxidation and Stability information under low temperature/freeze-thaw test conditions.

Based on the above research results, the storage conditions of clinical samples, the proposed validity period and the validity extension plan are proposed. For products that require dilution and compatibility for clinical use, stability study information on dilution compatibility must be provided; for multi-dose packaging (except oral solid preparations), necessary stability study information after package opening must be provided. The information in this section should support usage in clinical protocols. To ensure sufficient stability data is obtained during the NDA phase, it is recommended to provide formal stability

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placebo

If the clinical trial plan involves the use of placebos, the placebo manufacturer, prescription, production process (pay attention to the difference from sample preparation for clinical trials), and quality control (the quality standards should include at least one clearly identifiable item) must be provided in accordance with the above requirements. Test items that distinguish clinical trial drugs from placebo), packaging systems, and necessary stability study information. Propose placebo storage conditions, shelf life, and shelf life extension plans (if applicable). If a marketed product is directly used as a placebo (such as 0.9% sodium chloride injection), no additional information is required.

control drug

If the clinical trial plan involves the use of control drugs, and the marketed product needs to be further processed (such as repackaging) according to the requirements of the clinical plan, the necessary processing information, quality research and stability information must be provided. In principle, it should be ensured that the processing has no impact on product quality. negative impact

ring. If a marketed product is directly used as a control drug, no additional information is required.

Glossary 1. Major

changes: changes that occur during the research process that may affect safety or in vivo behavior. Examples are as follows: (1) Changes in the production method of raw materials, such as

from fermentation and extraction to chemical synthesis.

become.

(2) For chemically synthesized drugs, changes in the API synthesis route or key purification processes (such as changes in materials involved in bonding reactions, changes in the solvent used in the last reaction and/or crystallization step, changes in impurity profiles) (3) For the preparation of drugs by fermentation and extraction processes, changes in the fermentation process and

extraction process that may affect the quality of the raw materials, such as changes in bacterial strains and changes that affect the removal of impurities.

(4) Changes in sterilization methods of raw materials or preparations. (5) Changes

in the preparation process that affect the quality of the preparation, such as dry granulation changing to wet granulation.

(6) Prescription changes that affect the quality of preparations. (7) Change in

dosage form. (8) Quality standard

limits have been relaxed, inspection items have been deleted, and analysis methods for key quality control items have been significantly changed, etc.

(9) Changes in the packaging system that affect the quality of the dosage form (such as quantitative accuracy, delivered dose). 2. Unconventional production process:

it should be combined with the properties of raw materials, properties of preparations and

The characteristics of the process itself are used to determine whether it is an unconventional production process. Examples are as follows:

(1) Production of special preparations, such as: ÿ aerosols and powder sprays that are inhaled into the lungs in a measured amount; ÿ heterogeneous sterile preparations; ÿ sustained-release preparations; ÿ drug loading less than 2%

of solid preparations.

(2) Introduce certain new technologies into conventional processes.

(3) Special processes and complex processes, such as microtablet preparation and dry pressing coating.

(4) Unconventional sterilization processes, such as: ÿ Using moist heat terminals that are not included in pharmacopoeias Terminal sterilization conditions; ÿ Use radiation terminal sterilization with a radiation dose lower than 25 KGy.

references

1. EMAÿ2016ÿGuideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials ÿdraftÿ.

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3. FDAÿ1995ÿGuidance for Industry Content and Format of Investigational New Drug ApplicationsÿINDsÿfor Phase 1 Studies of DrugsÿIncluding Well-CharacterizedÿTherapeuticÿBiotechnology-derived Products.

4. FDAÿ2008ÿGuidance for Industry CGMP for Phase 1 Investigational Drugs.

5. EMAÿ2014ÿGuideline on process validation for finished products information and data to be provided in regulatory submissions.

6. ICHÿ2014ÿM7 Assessment and Control Of DNA Reactive ÿMutagenicÿImpurities in Pharmaceuticals to Limit Potential Carcinogenic Risk 7.

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8. State Food and Drug Administration, "About the Release of Pharmaceutical Excipients for Pharmaceutical Packaging Materials"

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9. State Food and Drug Administration, "About the Release of Pharmaceutical Excipients for Pharmaceutical Packaging Materials"

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