appendix

Clinical trial drugs (trial)

Chapter 1 Scope

Article 1 This appendix applies to the preparation of clinical trial drugs (including experimental drugs and placebos). When a marketed drug is used as a control drug or an experimental drug, this appendix also applies to changes in packaging, labeling, etc.

Chapter 2 Principles

Article 2 The preparation and quality control of drugs for clinical trials shall comply with the relevant basic principles of the Good Manufacturing Practice and data reliability requirements, minimize the risks of contamination, cross-contamination, confusion and errors in the preparation process, and ensure that clinical trials Use drug quality to ensure the safety of subjects. Article 3

The preparation and quality control of drugs for clinical trials have the following special requirements: sex:

(1) In the early clinical trial stage of a new drug, a mature preparation process has usually not yet been formed, and the conditions for full confirmation and verification are not yet available;

(2) The characteristics, potential effects and toxicity of the new drug are not fully understood, and the critical quality of the experimental drug is not fully understood. Identification of attributes, further in-depth research on quality control indicators and

methods is needed; (3) The preparation process of drugs for clinical trials may involve different activities such as preparation of experimental drugs, preparation of placebos, change of packaging labels of control drugs and experimental drugs, etc. Randomly and blinding requirements also increase confusion and differences in the preparation process of clinical trial d

Risk of being wrong.

It should be based on the above particularities, as well as its characteristics and clinical characteristics at different stages of development.

Trial design requirements, etc., and carry out corresponding controls on drugs for clinical trials.

Article 4 On the premise of ensuring the safety of subjects and not affecting the quality of clinical trials, the quality risk management strategy of clinical trial drugs can be adjusted accordingly according to research and development rules. The research and development of drugs urgently needed to prevent and control public health emergencies shall be based on emergency needs and the preparation of drugs for clinical trials in accordance with the principles of safety, reliability, science and feasibility.

Chapter 3 Quality Management

Article 5 Clinical trial drug preparation units shall establish a quality management system based on risks. The system shall cover the necessary factors that affect the quality of clinical trial drugs and establish a documentation system to ensure the effective operation of the quality management system.

Article 6 The applicant shall be responsible for the quality of the drugs used in clinical trials. If the preparation of drugs for clinical trials is entrusted, the applicant should audit and confirm the quality management system of the entrusted unit, sign an entrustment agreement and a quality agreement, clearly stipulate the responsibilities of each party, and ensure that the drugs for clinical trials meet the intended use and quality requirements.

Article 7 When the preparation site, prescription process, batch size, quality standards, key raw materials and excipients, packaging materials, etc. of clinical trial drugs are changed, or when technology transfer is carried out, changes that may affect the safety of clinical trial drugs should be evaluated. Changes and assessments should be recorded to ensure that relevant activities can be traced. Deviations from the preparation process and quality standards, as well as other deviations that may affect the quality of clinical trial drugs, should be investigated and evaluated, and corresponding records should be kept.

Chapter 4 Personnel

Article 8 Personnel involved in the preparation of clinical trial drugs shall have appropriate qualifications and training, and have the ability to perform corresponding duties. Personnel responsible for preparation and quality control shall not serve concurrently with each

other. Article 9 The applicant shall have a release responsible person responsible for the release of clinical trial drugs. (1)

Qualifications:

The person responsible for release should have at least a bachelor's degree in pharmacy or related majors (or an intermediate professional technical title or a licensed pharmacist qualification), and have at least five years of practical experience in drug research and development or drug production quality management, including at least one year of drug quality management experience. . The person responsible for release shall have necessary professional theoretical knowledge and undergo release-

related training. (2) Main responsibilities:

The person responsible for release shall be responsible for the release of clinical trial drugs, ensure that the preparation of each batch of released clinical trial drugs complies with relevant regulations and quality standards, and issue release audit records.

Chapter 5 Plant, Facilities and Equipment

Article 10 The factories, facilities and equipment for preparing drugs for clinical trials shall comply with the basic requirements of the Good Manufacturing Practice for Drugs and relevant appendices. Factory buildings, facilities, The qualification scope of equipment should be determined based on risk

assessment. Article 11 Clinical trial drugs and other clinical trials shall be conducted based on the toxicity, pharmacological activity, potential allergenicity and other characteristics of the clinical trial drugs, combined with factors such as the applicable population of the variety, route of administration, risk of the subjects and other factors. Drugs may be on the market

Feasibility assessment of collinear production of pharmaceuticals, etc. When producing on the same line, appropriate control measures (such as staged production methods, etc.) should be taken to minimize the risk of contamination and cross-contamination during the preparation process. In the early clinical trial stage, such as the

recognition of the toxicity and pharmacological activity of the experimental drug, etc.

If the knowledge is insufficient, dedicated or independent facilities and equipment should be used for the preparation of experimental drugs.

Chapter 6 Materials Management

Article 12 Quality standards for raw materials and excipients and packaging materials should be established, and the level of detail in the content should be appropriate to the stage of drug research and development, and should be re-evaluated and updated in a timely manner. The

preparation unit shall conduct corresponding inspections and inspections on the raw materials, excipients and packaging materials used in the preparation of clinical trial drugs, and can release them for use only after they pass the test. Excipients and packaging materials for drugs used in early clinical trials can be released based on the supplier's inspection report, but at least they should be ensured to be correct through identification or verification. If the drugs for clinical trials are sterile drugs, the excipients used in their preparation and the packaging materials in direct contact with the drugs should also be tested for safety aspects such as microorganisms and bacterial endotoxins. Article 13 Operating procedures should be established to manage material sample retention. Samples of each batch of raw materials and excipients used in the preparation of clinical

trial drugs and packaging materials in direct contact with the drugs should be retained. The number of retained samples should at least meet the needs for identification. The sample retention time should not be shorter than the sample retention time of the corresponding clinical trial drugs (except for raw materials and excipients with poor stability). For packaging materials that are in direct contact with drugs (such as infusion bottles), if samples of the finished product have been retained, there is no need to retain separate samples.

Chapter 7 Document Management

Article 14 Prescription processes and operations for the preparation of drugs for clinical trials should be formulated.

procedures, as well as documents such as quality standards and inspection operating procedures for raw materials and packaging materials, intermediate products and finished products. The content of the document should reflect the mastered product knowledge as comprehensively as possible, and at least cover the critical quality attributes and key process parameters of known or potential clinical trial drugs in the current research and development stage.

Documents such as prescription processes, quality standards, operating procedures, etc. should be evaluated at different stages of drug development and updated if necessary. Updated documents should take into account the latest acquired data, applicable technical requirements and regulatory requirements, and should be able to trace the document revision history. Article 15 During the preparation process of clinical

trial drugs, if the prescription process is adjusted or changed, different prescription processes should be uniquely identified and numbered, and can be traced back to the corresponding preparation process. Article 16 The applicant shall formulate procedures to clarify the requirements for the

generation, confidentiality, distribution, processing and storage of drug codes in clinical trial drug packaging. If a blinded trial is involved, procedures and documents for emergency unblinding should also be developed. Article 17 Applicants should establish clinical trial drug files and continuously update them with the progress of drug research and

development to ensure traceability.

(1) The file should at least include the following content: 1. An overview

of the research status of clinical trial drugs, including chemical structure, physical and chemical properties, biological properties, pharmacological and toxicological properties, proposed clinical indications and characteristics of the population taking the drug, etc.;

2. Original information Manufacturer information of excipients, packaging materials in direct contact with drugs;

3. Quality standards and analysis methods of raw materials, excipients, packaging materials in direct contact with drugs, intermediate products, raw solutions, semi-finished products and finished

products; 4. Prescription

process; 5. Intermediate products Control Method;

6. Previous finished product

labels; 7. Previous clinical trial protocols and drug codes (if applicable); 8. Quality

agreements related to the trustee (if applicable); 9. Stability data; 10.

Storage and transportation

conditions; 11. Batch Production

records, batch packaging records and inspection reports; 12. Instructions for

control drugs (if applicable); 13. If the drugs for clinical trials

are traditional Chinese medicine preparations, the base of the medicinal materials used, medicinal parts, place of origin, and harvest period must also be included. Preparation methods for prepared pieces, quality standards for medicinal materials

and prepared pieces, etc.; 14. If the drugs for clinical trials are biological products, they should include preparation and testing materials. Information about bacterial (virus) species and cell lines/strains. (2)

The archives should be used as the basis for evaluation of the release of clinical trial drugs. (3) When

clinical trial drugs undergo different preparation steps at different sites, the applicant must collect and save the above-mentioned relevant documents or certified copies of all sites in the archives. Article 18 Clinical trial drug files shall be kept for at

least 2 years after the drug is withdrawn from the market. If the drug is not approved for marketing, it should be kept until 2 years after the termination of the clinical trial or the termination of the registration application.

Chapter 8 Preparation Management

Section 1 Preparation

Article 19 When preparing drugs for clinical trials, measures should be taken to prevent contamination, cross-contamination, confusion, and errors as much as possible. Cleaning operating procedures should be formulated to clarify the cleaning methods, and necessary confirmation or verification should be carried out to confirm the cleaning effect.

Article 20 During the process development period, key quality attributes should be gradually identified, key process parameters should be determined, and appropriate intermediate controls should be carried out on the preparation process. With the in-depth understanding of quality attributes and the accumulation of preparation process data, process procedures are formulated and process parameters and control ranges are clarified.

The preparation and management of drugs for clinical trials should be continuously improved, optimized and enhanced to ensure Certify that drugs used in clinical trials meet quality requirements. Article

21 The key preparation processes of clinical trial drugs shall be evaluated and demonstrated in accordance with relevant technical requirements. In the early stage of clinical trials, if the preparation process of the experimental drug cannot be completely determined, necessary monitoring should be carried out to ensure that it meets the quality requirements and ensure the safety of the subjects.

If process verification is performed during the confirmatory clinical trial phase, its scope and extent should be determined based on risk assessment. If the drugs for clinical trials are sterile drugs, the verification of the sterilization process or sterile production process should follow the current relevant technical requirements to ensure that the sterility assurance level meets the requirements; if the drugs for clinical trials are biological products, the verification of viruses, etc. The inactivation/removal effect of pathogens or other exogenous factors ensures the safety of subjects.

Article 22 The preparation of drugs for clinical trials should be able to ensure uniform quality of products in the same batch. After determining the prescription process, the quality of clinical trial drugs should be consistent between batches.

Article 23 When drugs for clinical trials are prepared at different sites, comparability studies on drug quality between different sites should be conducted.

Section 2 Comparative Drugs

Article 24 When conducting controlled trials using already marketed drugs, the quality of the control drugs should be ensured. In a blind trial, the packaging and labeling of the control drug need to be changed.

When performing labeling and other operations, it should be fully evaluated and data (such as stability, dissolution, etc.) should be available to prove that the operations performed did not have a significant impact

on the quality of the original product. Article 25 When the control drug is repackaged with different packaging materials due to the need for blind testing, the use period of the repackaged control drug should not exceed the validity period of the original product.

When the use period of the test drug and the control drug in the blind trial are inconsistent, the validity period The labeling should be based on the latest usage period.

Article 26 When using a placebo to conduct a controlled trial, the prescription process of the placebo should be determined to avoid breaking the blind due to the appearance and properties of the placebo. Materials used to prepare placebos should meet appropriate quality requirements. Quality standards for placebos should be established, and only those that pass the test can be released for clinical trials. Storage conditions and shelf life of placebo should be determined based on stability studies.

Section 3 Packaging and Labeling

Article 27 Clinical trial drugs are usually provided to subjects in clinical trials in individually packaged form. Full consideration should be given to the sample size of the clinical trial protocol design and the quantity of clinical trial drugs required for quality inspection, sample retention and change research, etc., and sufficient quantities should be prepared, purchased or imported/exported according to the clinical trial progress plan. To ensure that the quantities of each product are accurate at all stages of operation, material balance calculations should be performed and deviations from the material balance should be explained or investigated.

Article 28 In order to ensure the accuracy of packaging and labeling of clinical trial drugs, operating procedures should be established to clearly define measures to prevent mislabeling, such as label quantity balance calculations, site clearance, and intermediate control inspections by trained personnel. wait. If a blind trial is involved, effective measures should also be taken to prevent the trial drug and the control drug (including

Placebo) had a labeling error. For operations that require the removal of original product labels and packaging, corresponding measures should be taken to prevent contamination, cross-contamination, confusion, and errors between the experimental drug and the control drug (including placebo).

Article 29 The packaging of clinical trial drugs should be able to prevent and avoid deterioration, contamination, damage and confusion during storage and transportation, and any opening or modification of the packaging should be able to be identified.

Article 30 Test drugs and control drugs are usually not allowed to be packaged at the same time on the same packaging line. If clinical trials require simultaneous packaging on the same packaging line, appropriate operating procedures and equipment should be in place, and relevant operators should be trained to avoid confusion and errors. Article 31 The labels of drugs for clinical

trial use should be clear and legible and usually include

Contains the following

content: (1) The name of the clinical trial applicant, clinical trial drugs, etc.; (2) The batch number

and/or serial number that identifies the product and packaging operation (used for blind trials)

The label information of clinical trial drugs tested should be able to remain blinded);

(3) Clinical trial number or other unique code corresponding to the clinical trial; (4) "Only for clinical trials"

or similar instructions; (5) Validity period, in XXXX (year)/XX (month)/XX (day) or

XXXX

(Year)/XX (Month) and other methods that can clearly indicate the year, month and day;

(6) Specifications and instructions for use (instructions for use or other information may be provided to the subjects)

A written explanation from the investigator, the content should comply with the requirements of the clinical trial protocol);

(7) Packaging specifications;

(8) Storage conditions; (9) If

the clinical trial drug is allowed to be taken home by subjects, it must be

Special markings to avoid misuse. Article

32 All label contents in Article 31 of this Appendix shall be included on both the inner and outer packaging. If the size of the inner packaging label is too small to indicate all the above contents, at least items (1) to (4) of the label contents in Article 31 of this Appendix should be marked. Article 33 If the validity period needs to be changed, the drug for clinical trial use

shall be affixed with an additional label, and the new validity period shall be marked on the additional label while covering the original validity period. When affixing additional labels, the original batch number or drug code must not be covered. After evaluation by the applicant, the additional labeling operation for changing the validity period

can be affixed at the institution conducting clinical trials. The operation of pasting additional labels shall be carried out in accordance with the operating procedures

approved by the applicant. The operators must be trained and approved, and there must be personnel at the operation site for review and confirmation. The attachment of additional labels should be correctly recorded in clinical trial-related documents or batch records and ensure traceability. Applicants should conduct quality audits on clinical trial drugs with additional labeling operations.

Article 34 The appearance similarity and similarity of other characteristics of drug packaging for clinical trials shall be inspected and recorded according to the blinding requirements of the clinical trial plan to ensure the effectiveness of blinding.

Chapter 9 Quality Control

Article 35 Quality control activities shall be organized and implemented in accordance with quality standards, relevant operating procedures, etc. Each batch of clinical trial drugs must be inspected to confirm that they meet quality standards. Investigation and evaluation should be carried out if the inspection results exceed the standard.

Article 36 Samples should be retained for each batch of clinical trial drugs:

(1) The retained sample should include the experimental drug and placebo, and the packaging form of the retained sample should be

When the packaging form is the same as that of clinical trial drugs, the number of retained samples should generally be at least sufficient to ensure that two full inspections are completed in accordance with the corresponding quality standards, and at least one finished product in the smallest package should be retained.

(2) The number of retained samples of marketed control drugs can be determined based on the risk principle. The number of retained samples should meet the possible quality investigation needs of the control drugs, and at least one finished product in the smallest package should be retained.

(3) If the packaging of clinical trial drugs is changed, the packaging before and after the change should be Keep samples for each form, and keep at least one finished product with the smallest package for each packaging form.

(4) The retained samples should include blinded clinical trial drugs, and at least one complete package of the trial drug and control drug (including placebo) should be kept to prepare for verification of product information when necessary.

(5) The sample retention period of clinical trial drugs shall be based on the longer of the following circumstances: 1. Two years after the approval of the drug marketing authorization application or two years after the termination of the clinical trial; 2. After the expiration of the validity period of the clinical trial drug Two years. Article 37 A stability study plan should be formulated, and the packaging of samples for stability studies should be consistent with the packaging form of drugs for clinical trials. For clinical trial drugs whose packaging materials have been changed, the stability of the samples after the packaging changes should be examined.

Chapter 10 Release

Article 38 The release of drugs for clinical trial use shall at least meet the following requirements: beg:

(1) Before approval for release, the person responsible for release shall conduct a quality evaluation on each batch of clinical trial drugs to ensure that they comply with laws, regulations and technical requirements, including:

1. Batch records, including batch production records, batch packaging records, batch inspection records, etc.;

2. All deviations and changes, subsequent investigations and evaluations have been completed;

3. The packaging of drugs used in clinical trials meets the requirements, and the labels are

correct; 4 .Production conditions meet

the requirements; 5. Confirmation status of facilities and equipment, verification status of preparation processes

and inspection methods; 6. Release status of raw materials and excipients, and

inspection results of intermediate products and finished products; 7. Relevant inspection results of

control drugs (including placebo) (if applicable); 8. Stability study

data and trends (if

applicable); 9. Storage conditions; 10. Certificate of conformity of reference/

standard products (if applicable); 11. Audit report of the quality management system of the

entrusted unit (if applicable) applicable); 12. Proof of legal source of

control drugs (if applicable); 13. Other requirements related to the quality of this batch of clinical trial drugs.

(2) The quality evaluation of clinical trial drugs should have clear conclusions, such as approval

Approval of release, non-release or other decisions shall be signed by the person responsible for

release. (3) Clinical trial drug release review records should be issued.

Chapter 11 Shipping

Article 39 Applicants should at least confirm the following content before shipping clinical trial drugs to clinical trial institutions and keep relevant records:

(1) The drug for clinical trial has been approved for release; (2)

The relevant requirements necessary for initiating clinical trials have been met, such as the ethics committee

Meeting and approval or consent of the drug regulatory department; (3)

Inspection and confirmation of transportation conditions.

Article 40 The shipment of clinical trial drugs shall be carried out in accordance with the applicant's shipping instructions and specific requirements.

Article 41 Applicants should select appropriate transportation methods based on the packaging, quality attributes and storage requirements of clinical trial drugs, take corresponding measures to prevent deterioration, damage, contamination, temperature control failure and other problems, and confirm that clinical trial drugs are used for clinical trials. Drugs are sent to

designated clinical trial facilities. Article 42 Clinical trial drugs transported to clinical trial institutions shall be accompanied by at least a certificate of conformity, a delivery list and a receipt confirmation form for use by research institution personnel.

Complete written records should be kept for the transportation of clinical trial drugs. The record content should usually include the name or code, dosage form, specification, batch number or drug code, quantity, validity period, applicant, preparation unit, packaging form, and storage requirements of the clinical trial drug. As well as the receiving unit and address, contact information, shipping date, transportation method, temperature monitoring measures during the process, etc. If transportation is entrusted, relevant information of the carrier should also be included. The content of the shipping record can be appropriately adjusted according to blinding needs.

Article 43 Clinical trial drugs are generally not allowed to be transferred directly from one clinical trial institution to another clinical trial institution. If necessary, the applicant and the clinical trial institutions of both parties should have complete quality assessment and operating procedures for transferring clinical trial drugs, which can only be implemented after full evaluation and approval by the applicant.

Chapter 12 Complaints and Recalls

Article 44: For complaints arising from quality issues of clinical trial drugs, the applicant shall jointly investigate with the preparation unit and clinical trial institution to assess the potential impact on subject safety, clinical trials and drug research and development. Release Responsible Person and Clinical Trial

Relevant responsible personnel should participate in the investigation. The investigation and handling process should be documented.

Article 45 When it is necessary to recall drugs for clinical trial use, the applicant shall organize the recall in a timely manner in accordance with the operating procedures. Clinical researchers and supervisors should perform corresponding duties during the recall process of clinical trial drugs.

Article 46 When the supplier of control drugs or other therapeutic drugs specified in the clinical trial plan initiates a drug recall, if product quality and safety issues are involved, the applicant should immediately recall all issued drugs after learning the recall information.

Chapter 13 Recall and Destruction Article

47 The applicant shall establish corresponding operating procedures to clarify the recall procedures and requirements for clinical trial drugs. Repossessions should be recorded. Recalled clinical trial drugs should be clearly labeled and stored in a controlled, dedicated area.

Article 48 Recalled clinical trial drugs shall generally not be used in clinical trials again. If necessary, the applicant should fully evaluate the quality of the withdrawn clinical trial drugs, have evidence to prove that the quality of the withdrawn clinical trial drugs has not been affected, and dispose of them in accordance with the corresponding operating procedures before they can be used again. Article 49 The applicant is responsible

for destroying unused and recovered clinical trial drugs. If a clinical trial institution or a third party is authorized to destroy, the authorization should be in writing and the applicant should conduct an inspection if necessary to prevent clinical trial drugs from being used for other purposes. Unused and withdrawn clinical trial drugs can be destroyed only after confirming

the balance between the issuance, use and withdrawal of clinical trial drugs. Destruction should be fully recorded, including at least the reason for destruction, time of destruction, batch number and/or drug code involved in destruction, actual quantity destroyed, destroyer, supervisor and other information. destruction record

The record shall be kept by the applicant.

Chapter 14 Supplementary Provisions

Article 50 The meanings of the following terms in this appendix are: (1) The person responsible for release refers to the person who has certain professional qualifications and experience in drug research and development and production quality management, and is responsible for the release of each batch of clinical trial drugs. (2) Clinical trial drug files include clinical trial drug development, preparation, packaging, quality inspection, release and A set of documents and records for shipping and other related activities.

(3) The drug code is assigned to the code of each independent package through random grouping.

(4) Early clinical trials It refers to clinical pharmacology and exploratory clinical trials, which in principle should include preliminary safety evaluation, pharmacokinetic studies, preliminary pharmacodynamic studies and dose exploration studies. Article 51 The raw materials used in clinical trial drugs shall be governed by this appendix.