appendix

Drugs for Clinical Trial (Trial)

Chapter 1 Scope

Article 1 This appendix applies to the preparation of drugs for clinical trials (including trial drugs and placebo). When a marketed drug is used as a reference drug or an experimental drug, this appendix is also applicable to its changed packaging and labels.

Chapter 2 Principles

Article 2 The preparation and quality control of drugs for clinical trials shall follow the relevant basic principles and data reliability requirements of the Good Manufacturing Practice for Drugs, minimize the risks of contamination, cross-contamination, confusion and errors in the preparation process, and ensure clinical trials The quality of medicines is used to ensure the safety of subjects. Article 3 The preparation and quality control of drugs for clinical trials have the following special features

sex:

(1) In the early clinical trial stage of the new drug, the mature preparation process has not yet been formed, and the conditions for sufficient confirmation and verification are not yet available; The identification of attributes and the research on quality control indicators and methods need to be further in-depth; (3) The preparation process of clinical trial drugs may involve different activities such as the preparation of test drugs, the preparation of placebos, the change of packaging and labels of control drugs and test drugs, and random and blinding requirements have also increased confusion and differences in the preparation of clinical trial drugs.

wrong risk.

should be based on the above particularities, as well as the characteristics and clinical

According to the requirements of trial design, etc., the drugs for clinical trials shall be controlled accordingly.

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 drugs for clinical trials can be adjusted according to the research and development rules. For the research and development of drugs urgently needed for the prevention and control of public health emergencies, the preparation of drugs for clinical trials shall be carried out according to the emergency needs and in accordance with the principles of safety, reliability and scientific feasibility.

Chapter 3 Quality Management

Article 5 The preparation unit of the drug for clinical trial shall establish a quality management system based on risks, which shall cover the necessary factors affecting the quality of the drug for clinical trial, and establish a document system to ensure the effective operation of the quality management system.

Article 6 The applicant shall be responsible for the quality of the drug for clinical trial. If the clinical trial drug is commissioned to prepare, the applicant should audit and confirm the quality management system of the entrusted unit, and sign a commission agreement and a quality agreement to clearly define the responsibilities of all parties to ensure that the clinical trial drug meets the intended use and quality requirements.

Article 7 In the event of changes in the preparation site, prescription process, batch size, quality standards, key raw and auxiliary materials, and packaging materials of clinical trial drugs, as well as technology transfer, changes that may affect the safety of clinical trial drugs shall be evaluated. Changes and assessments should be documented to ensure that the relevant activities can be traced back. Deviations from the preparation process, quality standards, and other deviations that may affect the quality of drugs for clinical trials should be investigated and evaluated, and corresponding records should be kept.

Chapter IV Personnel

Article 8 The personnel involved in the preparation of drugs for clinical trials shall have appropriate qualifications and be trained, and have the ability to perform corresponding duties. Personnel in charge of preparation and quality management shall not serve concurrently. Article 9 The applicant shall have a person responsible for release to be responsible for the release of clinical trial drugs. (1) Qualification:

The person responsible for release shall have at least a bachelor's degree in pharmacy or related majors (or intermediate professional technical title or 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 the necessary professional theoretical knowledge and have undergone training related to release. (2) Main responsibilities:

The person responsible for release shall undertake the responsibilities for the release of clinical trial drugs, ensure that the preparation of each batch of clinical trial drugs released conforms to relevant regulations and quality standards, and issue release audit records.

Chapter V Plant, Facilities and Equipment

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

assessment. Article 11 The drugs for clinical trials and other clinical trials shall be conducted according to the characteristics of the drugs for clinical trials, such as toxicity, pharmacological activity and potential sensitization, and in combination with the applicable population of the species, the route of administration, the risks of the subjects and other factors. Drug or marketed

Feasibility assessment for collinear production of pharmaceutical products. When collinear production, 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 stage of clinical trials, such as the recognition of the toxicity and pharmacological activity of the experimental drugs, etc.

Insufficient knowledge, the preparation of test drugs should use dedicated or independent facilities and equipment.

Chapter VI Material Management

Article 12 The quality standards for raw and auxiliary materials and packaging materials shall be established, the details of which shall be adapted to the stage of drug research and development, and shall be re-evaluated and updated in due course. The preparation unit shall conduct corresponding inspections and inspections on the raw and auxiliary materials and packaging materials used in the preparation of clinical trial drugs, and release them for use only after they pass the test. The excipients and packaging materials used in the early clinical trial drugs can be released according to the inspection report of the supplier, but at least they should be identified or checked to ensure that they are correct. If the drug for clinical trial is a sterile drug, the excipients used in its preparation and the packaging materials that are in direct contact with the drug shall also undergo safety inspections such as microorganisms and bacterial endotoxins. Article 13 Operating procedures shall be established to manage the retained samples of materials. Each batch of raw and auxiliary materials and packaging materials in direct contact with the drug used for the preparation of the drug for clinical trial should be kept samples. The number of retained samples should at least meet the needs of identification. The sample retention time should not be shorter than the sample retention time of the corresponding clinical trial drug (except raw and auxiliary materials with poor stability). For packaging materials (such as infusion bottles) that are in direct contact with drugs, if samples of the finished product have been reserved, it is not necessary to reserve samples separately.

Chapter VII Document Management

Article 14 The prescription technology and operation for the preparation of clinical trial drugs shall be formulated

procedures, as well as documents such as quality standards and inspection procedures for raw and auxiliary materials, packaging materials, intermediate products and finished products used. The content of the document should reflect the acquired product knowledge as comprehensively as possible, at least covering the key quality attributes and key process parameters of the known or potential clinical trial drug at the current development stage.

Documents such as formulation technology, quality standards, and operating procedures should be evaluated at different stages of drug development, and updated if necessary. The updated document should comprehensively take into account the latest data obtained, applicable technical requirements and regulatory requirements, and should be able to trace the revision history of the document. Article 15 During the preparation of clinical trial drugs, if the prescription process is adjusted or changed, the different prescription processes shall be uniquely identified and numbered, which 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 preservation of drug codes in the packaging of drugs for clinical trials.

Where blinded trials are involved, procedures and documents for emergency unblinding should also be formulated. Article 17 The applicant shall establish a drug file for clinical trial, and continuously update it with the progress of drug research and development to ensure traceability.

(1) The file shall at least include the following contents: 1. An overview of the research situation of the drug for clinical trial, including chemical structure, physicochemical properties, biological properties, pharmacological and toxicological properties, proposed clinical indications and characteristics of the drug population, etc.; 2. Original Manufacturer information of excipients and packaging materials in direct contact with drugs; 3. Quality standards and analytical methods of raw and excipients, packaging materials in direct contact with drugs, intermediate products, bulk liquids, semi-finished products and finished products; 4. Prescription process; 5. Intermediate Control Method;

6. Previous finished product

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

agreement with 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 reference drugs (if applicable); 13. If

the drugs used in clinical trials are traditional Chinese medicine preparations, the

base of the medicinal materials used, the medicinal parts, the place of origin, and

the harvesting period must also be included. The processing method of the decoction pieces, the quality standards of the medicinal materials and the decoction pieces, etc.; 14. If the drug for clinical trial is a biological product, it shall include

Information on bacterial (viral) species and cell lines/strains. (2) The

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

for clinical trial is operated with different preparation steps in different sites, the applicant shall collect and save the above-mentioned relevant documents or their certified copies of all sites in the archives. Article 18 The archives of drugs for clinical trials shall be kept for at least 2 years after the drugs are withdrawn from the market. If the drug is not

approved for marketing, it should be kept until 2 years after the termination of clinical trials or the termination of registration application.

Chapter 8 Preparation Management

Section 1 Preparation

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

Article 20 During process development, key quality attributes should be gradually identified, key process parameters should be determined, and appropriate intermediate controls should be performed on the preparation process. With the in-depth understanding of quality attributes and the accumulation of preparation process data, the process specification is formulated, and the process parameters and control scope are clarified.

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

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

For process validation in the confirmatory clinical trial stage, its scope and extent should be determined based on risk assessment. If the drug for clinical trial is a sterile drug, the verification of the sterilization process or sterile production process shall comply with the current relevant technical requirements to ensure that its sterility assurance level meets the requirements; if the drug for clinical trial is a biological product, it shall also ensure that the virus, 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 shall be able to ensure the uniform quality of the same batch of products. After the formulation process is determined, the consistency of the batch-to-batch quality of the drug for clinical trial should be ensured.

Article 23 When a drug for clinical trial is prepared in different sites, it should be When conducting a comparative study of drug quality between different sites.

Section 2 Control Drugs

Article 24 When using a listed drug for a controlled trial, the quality of the control drug shall be ensured. In a blinded trial, the control drug needs to be changed in packaging and labeling.

When performing operations such as labeling, it should be fully evaluated and there should be data (such as stability, dissolution, etc.) to prove that the operations performed did not have a significant impact on the quality of the original product.

Article 25 When the reference drug is repackaged with different packaging materials due to the needs of the blind test, the use period of the reference drug after repacking should not exceed the validity period of the original product.

In the blinded trial, when the duration of use of the test drug and the reference drug is inconsistent, the validity period The labeling should be based on the most recent expiry date.

Article 26 When a placebo is used to conduct a controlled trial, the prescription process of the placebo shall be determined, so as to avoid the appearance and character of the placebo causing unblinding. The materials used in the preparation of placebos should meet the corresponding quality requirements. Quality standards for placebo should be established, and only those who pass the test can be released for clinical trials. The storage conditions and shelf life of placebo should be determined based on stability studies.

Section 3 Packaging and Labeling

Article 27 Drugs for clinical trials are usually provided to subjects in clinical trials in the form of individual packages. The sample size for the design of the clinical trial protocol and the quantity of clinical trial drugs required for quality inspection, sample retention and change research should be fully considered, 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 each stage of operation, a material balance calculation should be performed and deviations from the material balance should be accounted for or investigated.

Article 28 In order to ensure the accuracy of packaging and labeling of drugs for clinical trials, operating procedures should be established, and measures to prevent mislabeling should be specified, such as balancing the number of labels, clearing the site, and conducting intermediate control inspections by trained personnel. Wait. Where blinded trials are involved, effective measures shall also be taken to prevent the trial drug and the reference drug (including

Placebo) with labelling errors. For operations that need to remove the original product labels and packaging, corresponding measures should be taken to prevent contamination, cross-contamination, confusion and errors between the test drug and the reference drug (including placebo).

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

Article 30 The test drug and the reference drug are usually not allowed to be packaged in the same packaging line at the same time. For clinical trials that need to be packaged simultaneously 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 trials should be clear and legible, usually including

Include the following: (1)

The name of the applicant for the clinical trial, the drug used in the clinical trial, etc.; (2) The batch

number and/or serial number identifying the product and the

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

(3) Clinical trial number or other unique code corresponding to the clinical trial; (4) The words "only for clinical

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

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

(6) Specifications and instructions for use (may be accompanied by instructions for use or other provided to the subjects The written description of the applicant, the content should meet 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 labeling to avoid misuse. Article 32

Both the inner and outer packaging shall contain all the label contents in Article 31 of this appendix. If the size of the inner package 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 shall be marked. Article 33 If the validity period needs to be changed, the drug for clinical trial shall be affixed with an additional label, and the additional label shall be marked with the new validity period and at the same time cover the original validity period. The original batch number or drug code must not be overwritten when affixing additional labels. After the applicant's evaluation, the additional label operation of changing the validity period can be carried out in the institution conducting the clinical trial. The operation of affixing additional labels shall be carried out in accordance with the operating procedures approved by the applicant, the operators shall be trained and approved, and the operation site shall be reviewed and confirmed by personnel.

Attachment of additional labels should be properly documented and traceable in clinical trial related documents or batch records. The applicant shall conduct a quality review of the clinical trial drugs operated with additional labels.

Article 34 According to the blinding requirements of the clinical trial protocol, the similarity in appearance and other characteristics of the drug packaging for clinical trials shall be checked and recorded to ensure the effectiveness of the blinding.

Chapter 9 Quality Control

Article 35 Quality control activities shall be organized and implemented in accordance with quality standards and relevant operating procedures. Each batch of clinical trial drugs must be inspected to confirm compliance with quality standards. An investigation and evaluation should be carried out on the inspection results exceeding the standard.

Article 36 Samples of each batch of clinical trial drugs shall be kept:

(1) The reserved sample should include the test drug and placebo, and the packaging of the reserved sample should be

When the packaging form is the same as that of the clinical trial drug, the number of retained samples should generally be at least enough 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 is retained.

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

(3) If the package of the drug for clinical trial is changed, the package shall be the same as the package before and after the change. Samples shall be reserved separately for each form, and at least one finished product with the smallest package shall be reserved for each form of packaging.

(4) The reserved samples shall include the blinded clinical trial drugs, and at least one complete package of the trial drugs and reference drugs (including placebo) shall be kept for checking the information of the products when necessary.

(5) The sample retention period of the drug for clinical trial shall be subject to 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 drug for clinical trial two years. Article 37 A stability study plan shall be formulated, and the sample packaging for stability study shall be consistent with the packaging form of the drug for clinical trial. For clinical trial drugs whose packaging materials are changed, the stability of the samples after the packaging changes should be investigated.

Chapter 10 Release

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

(1) Before approving the release, the person responsible for release shall evaluate the quality of 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, and subsequent investigations and evaluations have been completed; 3. The packaging of drugs for clinical trials meets the requirements, and the labels are correct; 4. .The production conditions meet the requirements; 5. The confirmation status of the facilities and equipment, the verification status of the preparation process and the inspection method; 6. The release of the raw and auxiliary materials and the inspection results of the intermediate products and finished products; (if applicable); 8. Stability study data and trends (if applicable); 9. Storage conditions; 10. Qualification certificate for reference/standard product (if applicable); 12. Proof of legal origin of the reference drug (if applicable); 13. Other requirements related to the quality of the batch of clinical trial drugs.

(2) There should be clear conclusions in the quality evaluation of drugs for clinical trials, such as approval of Approved release, non-release or other decisions, and signed by the person responsible for release. (3) The release review record of the drug for clinical trial shall be issued.

Chapter 11 Shipping

Article 39 Before the clinical trial drug is shipped to the clinical trial institution, the applicant shall at least confirm the following contents and keep relevant records:

(1) The drug for clinical trial has been approved for release; (2) The relevant requirements necessary for the initiation of clinical trial have been met, such as ethics committee (3) Inspection and confirmation of transportation conditions.

Article 40 The delivery of clinical trial drugs shall be carried out according to the applicant's delivery instructions and specific requirements. Article 41 The applicant shall select an appropriate transportation method according to the packaging, quality attributes and storage requirements of the clinical trial drug, take corresponding measures to prevent deterioration, damage, pollution, temperature control failure, etc., and confirm the clinical trial drug Drugs are sent to designated clinical trial institutions. Article 42 The clinical trial drugs delivered to the clinical trial institutions shall at least be accompanied by a certificate of conformity, a delivery list and a receipt confirmation form for the personnel of the research institution.

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

Article 43 Drugs for clinical trial shall generally not be directly transferred 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 the transfer of clinical trial drugs, which can only be implemented after full assessment and approval by the applicant.

Chapter 12 Complaints and Recalls

Article 44 For complaints arising from quality problems of drugs used in clinical trials, the applicant shall investigate together with the preparation unit and the clinical trial institution to assess the potential impact on the safety of subjects, clinical trials and drug research and development. Person in charge of release and clinical trial

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

Article 45 When it is necessary to recall a drug for clinical trial, the applicant shall organize the recall in a timely manner according to the operating procedures. Clinical investigators and supervisors shall perform corresponding responsibilities during the recall of clinical trial drugs.

Article 46 When a supplier of a reference drug or other therapeutic drugs specified in the clinical trial protocol initiates a drug recall, if the product quality and safety issues are involved, the applicant shall recall all the issued drugs immediately after being informed of the recall information.

Chapter 13 Recall and Destruction Article

47 The applicant shall establish corresponding operating procedures to clarify the procedures and requirements for the recovery of clinical trial drugs. The recovery should be recorded. The withdrawn clinical trial drugs should be clearly marked and stored in a controlled and dedicated area.

Article 48 The withdrawn clinical trial drugs shall not be used for clinical trials again. If necessary, the applicant should fully evaluate the quality of the withdrawn clinical trial drug, and there is evidence to prove that the quality of the withdrawn clinical trial drug is not affected, and can be reused after disposing of it in accordance with the corresponding operating procedures. Article 49 The applicant is responsible for the destruction of unused and withdrawn clinical trial drugs. If a clinical trial institution or a third party is authorized to destroy it, it shall authorize in writing, and the applicant shall conduct inspection if necessary to prevent the clinical trial drug from being used for other purposes. The unused and withdrawn clinical trial drugs can be destroyed only after the balance between the issued, used and recovered quantities of the clinical trial drugs has been confirmed.

Destruction should have complete records, including at least the reason for destruction, the time of destruction, the batch number and/or drug code involved in the destruction, the actual number of destruction, the destroyer, the supervisor and other information. Destruction

The records should be kept by the applicant.

Chapter 14 Supplementary Provisions

Article 50 The meanings of the following terms in this appendix are: (1) Person in charge of release refers to a person who has certain professional qualifications and experience in drug research and development and production quality management, and assumes the responsibility for the release of each batch of clinical trial drugs. (2) The archives of the drug for clinical trial include the research and development, preparation, packaging, quality inspection, release and

A set of documents and records for related activities such as shipping.

(3) Drug codes are assigned to the codes of each individual package by random grouping.

(4) Early clinical trials

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 APIs used in clinical trial drugs shall be implemented with reference to this appendix.