境外已上市境内未上市化学药品

药学研究与评价技术要求（试行）

1. Background

The imitation or import of chemical drugs that have been marketed overseas is a solution to the problem faced by Chinese patients.

An important means of drug availability and accessibility in areas of clinical need. To speed up the border

The research and development and marketing process of generic drugs and original drugs that have been marketed abroad but not yet marketed domestically, and

Strengthen scientific supervision and improve the quality and efficiency of review and approval. According to the "Drug Registration Administration"

"Administrative Measures" (State Administration for Market Regulation Order No. 27) and its supporting documents,

Formulate technical requirements for chemical drug research and evaluation to provide industry and regulatory agencies with

Technical reference for R&D and review.

2. Scope of application

This technical requirement applies to chemical drugs that have been marketed overseas but not marketed domestically.

It mainly includes two types of situations: (1) Domestic applicants imitate overseas products but do not sell them domestically.

Drugs listed as original research drugs, i.e. chemical drugs in Category 3; (2) Drugs marketed overseas

The product applies to be marketed in the country, that is, chemical drugs of category 5 (not applicable to original research drugs that have been

Chemical drugs marketed in the country (Category 5.2).

Applicable to APIs related to preparations that have been marketed overseas and are not marketed domestically.

to this technical requirement.

3. Basic considerations in pharmaceutical research and evaluation

This technical requirement is the basic technical requirement for pharmaceutical research and evaluation. applicant

As the responsible person for product declaration, we are responsible for product R&D, production and quality control.

Safety, security and compliance should be comprehensively and accurately understood, and corresponding

research work. Applicants need to combine product characteristics and refer to this technical requirement and national

Carry out pharmaceutical research according to relevant internal and external technical guidelines, and follow the current version of "M4: Pharmaceuticals for Human Use"

Common Technical Document (CTD) for Material Registration Application" format number and item sequence

processing (for inapplicable items, please indicate not applicable), submit a comprehensive and complete

pharmaceutical research information.

For registration applications for chemical drugs Class 3 and Class 5.2, applicants should comprehensively

Understand the marketing background, safety and efficacy data, and post-marketing adverse reactions of the reference preparation.

The situation should be monitored and its clinical value evaluated and confirmed. According to "Chemical Generic Ginseng

Submit an application for reference preparation selection according to the "Procedure for Selection and Determination of Comparative Preparations", or follow the national

Select appropriate reference preparations from the "Catalogue of Reference Preparations for Chemical Generic Drugs" issued by the National Food and Drug Administration.

than preparations. The active ingredients, dosage forms, indications and routes of administration of generic drugs should be consistent with

Same as the reference preparation. The quality of the generic drug should be consistent with that of the reference product.

Applicants should first fully investigate the public information on reference preparations (such as foreign drugs

regulatory agency review documents, drug inserts and labels and/or literature)

Prescription analysis, clarify the product target quality profile, analyze and determine the key qualities of the product

Quantitative attributes. Fully evaluate raw materials and excipients through prescription process and quality research

and the potential impact of packaging system-related characteristics on dosage form performance and manufacturing processes.

Confirm key material attributes; research and evaluate process parameters to determine the impact on product quality

Key process steps and key process parameters to establish effective process control.

Applicants should conduct quality studies using multiple batches of reference preparations as controls to ensure self-made products.

The quality of the preparation is consistent with that of the reference preparation. For situations where the reference preparation is unavailable,

It is recommended that it be carried out in accordance with internationally accepted and current domestic relevant pharmaceutical research technical requirements.

Research. By strengthening the control and process of raw materials, excipients and packaging systems,

Process control and product quality control, etc., so that the designed and developed production process can be sustained

Stable production of products that meet expected quality requirements.

For marketing authorization applications for chemical drugs in Category 5, the applicant should submit a document that reflects

The current version of CTD pharmaceutical research data for products marketed in China is summarized in

The drug certificate (CPP) states that the drug occurred between the first listing in the country and the declaration of import.

Major pharmaceutical changes such as process improvement and quality improvement (including approval by the drug regulatory agency)

(accurate change content, etc.) historical brief introduction, and provide research on major pharmaceutical changes when necessary.

Information, pay attention to imported registration samples and key clinical batch samples supporting Chinese registration

quality comparison.

Drug production should comply with Good Manufacturing Practices (GMP), through

Continuously improve the pharmaceutical production quality management system and reduce risks affecting drug quality

factors to ensure that the entire process of drug production continues to meet drug quality requirements.

Applicants should strengthen the management of the drug life cycle. After the drug is developed and launched on the market,

It is necessary to continue to pay attention to factors such as material attributes, prescription processes, production equipment, and batch sizes.

potential impact on drug quality, and continuously improve the control and process of key attributes of materials.

process control and product quality control to promote the continuous improvement of drug quality.

The drafting of this technical requirement is based on current scientific knowledge, and as relevant regulations

With the continuous improvement of pharmaceutical research and the continuous progress of science and technology, this technology requires

Please continue to revise and improve it.

4. Technical requirements for research and evaluation of Class 3 chemicals

(1) Technical requirements for raw materials

1.Production process

The production of APIs should follow a production process that is stable and capable of sustainable commercial production.

and the principle of qualified product quality. Main aspects of research and evaluation of API production processes

The content includes starting material selection and quality control, production process development, process processing

Process control and process verification, etc. Applicants should have a clear understanding of the research purpose of each stage

A clear understanding of the production process and an overall understanding of the production process in order to carry out scientific and reasonable

Research and obtain APIs that meet drug quality requirements.

1.1 Starting material selection and quality control

Based on the consideration of controlling the quality of pharmaceutical products from the source, the starting materials

The selection should refer to ICH Q11 and relevant EU technical requirements. to fermentation or plant

Extraction-based semi-synthetic APIs generally need to be developed from microorganisms or plants.

Begin to describe the production process. The applicant should evaluate the rationality of the selection of starting materials.

Assessment and confirmation.

Starting materials should be stable and capable of meeting the needs of large-scale production of APIs.

Industrial sources. Starting material suppliers should have complete production and quality control management

management system. If the starting materials come from multiple suppliers, it is recommended that the applicant refer to the

Conduct research on the relevant requirements of "Technical Guiding Principles for Research on Changes in Marketed Chemical Drugs".

The applicant should establish reasonable internal control standards for starting materials.

The quality control requirements for the starting materials of products should generally be stricter. for use in synthesis

Protected amino acids as starting materials for peptide drugs, their quality standards should include chirality

Purity check items.

For starting materials with complex chemical structures and production processes, the applicant

Process impurities (including toxic impurities,

residual solvents and elemental impurities, etc.) for comprehensive analysis. Applicants should research in detail

Investigate whether the type and content of impurities will affect subsequent reactions and final product quality, including

Including the generation, transformation and removal of major impurities, effectively controlling the impurities of starting materials,

Develop reasonable control items, analytical methods and limits, and implement analytical methods

Legal verification.

1.2 Production process development

Through sufficient research on the literature, the applicant can understand the

Basic production process information and critical quality attributes. Combined with quality risk management and control

manufacturing strategy and choose a scientific and reasonable process route. Passed laboratory tests and pilot tests

Scale up and commercialize production, gradually deepen the understanding of the entire production process, and continuously

Optimize process routes, accumulate more process knowledge and production experience, design and develop

Develop commercial production that can continuously and stably produce products that meet expected quality requirements

Craftsmanship.

Critical quality attributes of drug substances typically include those that affect product identity, purity and

The property or characteristic of stability. Control strategies for critical quality attributes typically include:

(1) Set it into the API quality standards and pass the testing of the final API

and/or determined through upstream control; (2) Do not include it in the quality standards of raw materials.

accurate, but quality assurance can be provided through upstream controls. Upstream control can generally

This can be done by using online testing, or by monitoring process parameters and/or material properties of the production process.

Determination of properties to predict critical quality attributes of APIs. Impurities may affect the drug

It affects the safety of preparations and is a critical quality attribute of raw materials.

For polymorphic drugs, applicants should pass precise

Optimize and screen the manufacturing process to prepare advantageous stable crystal forms to ensure batch-to-batch crystallization of raw materials.

type consistency.

For drugs that may contain nitrosamine impurities, applicants should first select

A production process that can avoid the generation of nitrosamine impurities. If the production process cannot avoid

To avoid the formation of nitrosamine impurities, detailed process control strategies can be formulated to

Ensure that the quality control of nitrosamine impurities during the production process is effective and meets requirements

beg.

1.3 Process control

API process control includes key process steps and their key processes

Process parameter and intermediate control.

The endpoint judgment and control means of key process steps should be supported by data.

The critical process parameters are related to the critical quality attributes of the API. Generally, the applicant should

Evaluate drug substance manufacturing processes during their development phase, based on process durability

Research results or historical data to determine the requirements for repeatable production operations

range of change. If a synthetic reaction involving the introduction of a new chiral center is involved, the applicant should

Provide detailed analysis methods and control strategies for isomer impurities.

For separated intermediates, the applicant should develop testing items, analysis

quality standards for analytical methods and acceptable standards, and explain the basis for setting quality standards.

according to. The main quality control methods for critical intermediates (such as impurity control methods) should be carried out

Including methodological verification of specificity and sensitivity. Applicants should transfer based on impurities

Chemicalization and elimination study results are provided to provide impurity limit formulation for API process control.

Reasonable basis.

1.4 Process verification

Applicants should complete commercial scale production process validation before applying for marketing of APIs.

To obtain the certificate, submit the process verification plan, process verification report and production process information form.

The verification of the aseptic process of raw materials should refer to the published "Aseptic Process Simulation Test".

Inspection Guidelines (Sterile API) and other relevant guidelines shall be implemented.

The production batch of registered API should meet at least 1 batch of process verification or 1 batch of preparation.

Determine the preparation production requirements for commercial production batches and compare them with the actual production line production equipment.

Capacity matching.

2. Characterization

2.1 Structure confirmation

The structural confirmation analysis and testing methods of raw materials include UV-visible absorption spectroscopy,

Infrared absorption spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis, specific rotation,

X-ray single crystal diffraction and/or X-ray powder diffraction, differential scanning calorimetry,

Thermogravimetric analysis and circular dichroism spectroscopy, etc. Applicants can combine process routes and multiple points

Analytical testing methods are used to comprehensively analyze the chemical structure of raw materials. may contain

It is recommended to use bulk drugs, polymorphic forms, crystallization water and/or crystallization solvent, etc.

Structural confirmation using appropriate analytical testing methods.

The applicant can compare the structure confirmation sample with the reference substance included in the pharmacopoeia or the

Conduct comparative studies on marketed products to confirm the consistency of the chemical structure of raw materials. right

If reference substances recorded in the pharmacopoeia cannot be obtained or compared with already marketed products,

It is recommended to conduct systematic research and confirmation on the chemical structure of raw materials. Structure confirmation sample

Usually the purification conditions should be clearly stated and its purity should be stated. Critical quality for pharmaceutical preparations

For polymorphic drugs that affect the stability of the drug, studies are required to prove the consistency of the crystal form between batches and the consistency of the crystal form.

Type placement process stability. Eutectic drugs have special physical and chemical properties, definite

Components and stoichiometric ratios can be determined by X-ray single crystal diffraction, X-ray powder

Diffraction, solid-phase nuclear magnetic resonance spectroscopy, infrared absorption spectroscopy, differential scanning calorimetry

and/or crystal morphology and other analytical methods for structural confirmation.

2.2 Impurity spectrum analysis

Impurity spectrum analysis of raw materials includes process impurities and degradation impurities. applicant

It can combine the production process, reaction mechanism, structural characteristics and degradation of raw materials.

Comprehensive analysis of potential impurities and impurities such as routes, compendial standards and/or other literature

source.

Process impurities refer to impurities introduced during the production process, including starting materials and

The impurities, intermediates, reaction by-products, residual reagents/solvents/catalysts introduced by it

Chemical agents and elemental impurities, etc.

Degradation impurities refer to the degradation reactions of drugs through hydrolysis, oxidation, ring opening, polymerization, etc.

Impurities should be produced. Degradation impurities are closely related to the structural characteristics of raw materials.

The applicant can refer to the structural characteristics of the raw material drug, pharmacopoeia standards or impurities recorded in the literature.

Analyze possible degradation impurities in terms of structure, forced degradation test and stability investigation.

quality and degradation pathways, through process control and the use of appropriate packaging and storage strips.

parts to reduce the generation of degradation impurities.

3. Quality control of raw materials

3.1 Quality standards

Quality standards include testing items, analytical methods and acceptance standards. conform to

Standard refers to testing according to the proposed analytical method, and the results meet the acceptable standards.

The setting of API quality standard testing items must be both universal and

Targeted and able to reflect changes in product quality. Quality standard testing items

Generally includes but is not limited to characteristics, identification, inspection and content (potency) determination.

Inspection items should usually take into account the safety, effectiveness and purity/potency of the API.

Including pH value/acidity, solution clarity and color, general impurities (chlorination

substances, sulfates, ignition residues, etc.), related substances, isomers, mutagenic complexes

Impurities (including nitrosamine impurities), residual solvents, elemental impurities, loss on drying/

Moisture, bacterial endotoxins and/or microbial limits, etc. With the production process of API

stability, through the accumulation of product quality testing data and product quality awareness

By gradually improving, the quality control of raw materials can be continuously adjusted and improved.

Applicants should refer to guidelines such as ICH Q2 and Q6A, based on

To meet the requirements of consistent preparation quality, rationally formulate API quality standard testing items and

Acceptance standards and provide sufficient supporting test data and literature.

For APIs that have been included in pharmacopoeia standards, applicants should first consider selecting

Use pharmacopoeia standard test items and analytical methods. Analytical Methodology Key Confirmation Pharmacopoeia

Whether the standard testing methods and conditions are applicable. If the research results show that the method is suitable,

Applicants can continue to use pharmacopoeia standard analysis methods; if they need to establish new analysis methods,

Corresponding methodological verification should be carried out and it should be proved that the new method is not inferior to the pharmacopoeial method.

For APIs that have been included in the Chinese Pharmacopoeia, the quality indicators are generally not lower than those in China Pharmacopoeia requirements.

3.2 Quality research

Applicants may refer to the ICH guidelines (Q2, Q3A, Q3C, Q3D, Q6A and M7, etc.), "Technical Guiding Principles for Research on Impurities in Chemical Drugs", "Chemistry Technical Guiding Principles for Research on Drug Residual Solvents", "Chemical Drug Quality Control Analysis Technical Guidelines for Method Validation", "Standardization of the Establishment of Quality Standards for Chemical Drugs" "Process Technology Guiding Principles" and other general chapters of the Chinese Pharmacopoeia for the evaluation of raw materials. Quality research, providing quality research data on raw materials, including typical samples of representative samples Map. Analytical methods should be standardized in accordance with Chinese Pharmacopoeia and ICH guidelines Methodological validation.

(1) Related substances

Applicants should conduct a comprehensive impurity spectrum analysis and combine it with relevant literature. Scientifically select relevant substance analysis methods and conduct standardized methodological verification and/or validation. recognize.

For those that have already been included in pharmacopoeia standards, the applicant should combine the raw material drug process The applicability of the pharmacopoeia standard analytical method for line analysis, and the proposed analytical method for related substances The separation and detection capabilities and impurity control requirements of the method should not be lower than the pharmacopoeial standards. applicant Impurity reference substances with limited concentrations can be added to the raw materials to prove that the proposed Related substance analysis methods can separate the target impurities individually and/or separate the impurities from the main components. effective separation; for those that have not been included in pharmacopoeia standards, high impurity-rich Samples (such as crude product or crude stock solution, appropriate degradation samples, end-of-stability samples

etc.), conduct comparative and optimal research on chromatographic conditions, based on the detection ability of impurities

Strive to select appropriate chromatographic conditions, establish analysis methods for relevant substances, and use complex

Quality control standards were used for methodological verification.

When measuring the impurity content, the applicant can choose the external standard method, internal standard method, or addition method.

The principal component self-contrast method with correction factors and the principal component self-contrast method without correction factors

Comparison method. For the principal component self-pair with and without correction factors

By law, applicants should conduct research on correction factors.

Enantiomers need to be studied using chiral chromatographic analysis methods.

(2) Mutagenic impurities

Based on the production process and degradation pathways of the starting materials and APIs, the applicant

Potential mutagenic impurities of raw materials should be analyzed and studied, refer to ICH

M7 Develop reasonable control strategies. For advanced cancer drug use, target-based

Applicants may refer to ICH M7 and S9 for the indications and medication groups.

Strategies for the control of mutagenic impurities. Nitrosamine impurities refer to the "Chemical Drugs" published

"Technical Guiding Principles for Research on Nitrosamine Impurities (Trial)" is implemented.

(3) Elemental impurities

Through scientific and risk-based assessments, refer to the ICH Q3D guidelines,

Applicants can assess whether there are elemental impurities derived from the drug substance, including

Catalysts and inorganic reagents and production equipment added during the raw materials and API processes

Elemental impurities introduced by equipment and packaging systems, etc. Applicants should evaluate these sources

The impact of elemental impurities on preparations and formulating reasonable control strategies.

3.3 Establishment of quality standard limits

Applicants should conduct comparative studies on pharmacopoeia methods to determine reasonable analytical methods.

method, refer to the ICH guidelines to formulate reasonable acceptance limits for API quality standards.

Every time.

For those that have not been included in pharmacopoeia standards, they should be combined with self-prepared raw materials.

Comparative study results on the quality of prepared preparations and reference preparations, and develop reasonable quality standards

Acceptable limits.

Acceptance standards for quality control testing items related to safety should be safe

Supported by clinical trial data or literature, meeting the preparation production process and key quality requirements

Property requirements.

Relevant substance testing items should generally include known specific impurities, unknown individual impurities

Impurities and total impurities. Acceptance limits for relevant substances should generally be in accordance with ICH

Q3A and/or EU Antibiotic Guidelines and other requirements, applicants need to provide them when necessary

Safety test data to demonstrate the safety of impurities.

4. Stability

Stability studies of APIs include influencing factor tests, accelerated tests and long-term

If necessary, an intermediate condition test should be carried out.

Applicants can refer to ICH Q1A, Q1B and "Chemical Drugs (API

and Preparations) Stability Research Technical Guidelines" to conduct stability studies.

When submitting an application for API registration, the applicant should generally provide 3 batches of samples 6

Stability study data of accelerated test and long-term test of not less than 6 months

(Including typical diagrams). Accelerated testing and long-term testing should be in compliance with GMP conditions

The test samples should be registered batches that can represent commercial production scale.

Stability testing protocols and stability commitments should generally be submitted.

For liquid APIs, applicants should conduct packaging material compatibility studies.

(2) Preparation technical requirements

1. Prescription process

Applicants should fully understand the reference preparation and combine it with the reference preparation.

Clinical application, pharmacokinetics and other characteristics, based on safety and effectiveness evaluation

Determine product development goals and base on target product quality profile and related research

As a result, the critical quality attributes of the developed product are identified. Developed through prescription processes

and production process verification to clarify APIs, excipients, packaging systems and production processes

Factors that play an important role in product quality, establish corresponding material control,

Process control and other control strategies. Through prescription process research, design and development

A commercial production process that can sustainably and stably produce products that meet expected quality requirements.

For product batches that have been studied in clinical trials, applicants need to provide key

Batch prescription and process information such as clinical trial batches and human bioequivalence test batches.

In principle, the formulation process of the product to be marketed should be the same as that of batches that have been confirmed to be clinically equivalent.

Prescription process remains consistent.

1.1 Prescription

(1) API

Applicants should conduct research on the physical and chemical properties and biological characteristics of raw materials.

Research, based on the principle of risk assessment, fully evaluate the impact of the relevant characteristics of raw materials on the formulation

potential impact on energy and production processes, and identify key material attributes. Pharmacology of raw materials

Chemical properties and biological characteristics mainly include but are not limited to solubility, particle size distribution,

Crystal form, moisture, stability and permeability, etc.

(2) Excipients

Applicants should evaluate the relevant characteristics of excipients based on their role in the preparation.

Potential impact on formulation performance and production process, specify the type and amount of excipients

Select basis.

Usually, the type of reference preparation should be selected based on the formulation composition of the reference preparation.

Consistent excipients, you can also choose appropriate excipients according to the research situation but need to provide

Sufficient basis. The dosage or concentration of excipients usually needs to comply with FDA IID limit requirements.

Or provide sufficient basis (for example, it has been approved overseas for this route of administration and systemic exposure).

exposure levels of other formulated products). Special attention should be paid to excipients used in pediatric formulations

Type and dosage are reasonable.

(3) Prescription design

Applicants should conduct in-depth research on the public information of the reference preparation and analyze it through the prescription.

etc. to determine the product target quality profile. If the formulation composition of the reference preparation is available,

The prescription composition and its source can be provided as a basis for product prescription design. Apply

People can refer to ICH Q8 to develop the formulation process of pharmaceutical products and fully evaluate the raw materials and auxiliary materials.

Investigate and determine the potential impact of material-related characteristics on critical quality attributes of pharmaceutical products.

Determine the formulation factors that play a key role in the performance and quality of pharmaceutical products.

It is recommended that applicants consider the proposed production process to

Impact on product performance and quality. If the product involves special design, the applicant should provide

Provide design basis and supporting research data. Applicants need to clarify that the product originates from the formulary

The evolution of the formulation from initial planning to final commercial production.

Please refer to the relevant requirements of ICH Q8 for overdosing.

1.2 Process research

Applicants should consider the dosage form characteristics of the product to be developed and the formulation of the preparation.

Characteristics and existing knowledge to select processes. Refer to ICH Q8 to carry out product engineering

Art development. If necessary, the temporary storage conditions and temporary storage period of intermediate products should be coordinated.

step inspection.

For the research and selection of sterilization/sterile processes, please refer to "Sterilization of Chemical Injections"

and Guiding Principles for Aseptic Process Research and Verification (Trial). Injections should also refer to

"Technical Guidelines for Research on Sealing of Chemical Injection Packaging Systems (Trial)",

"Research Technology on System Compatibility of Plastic Components Used in the Production of Chemical Injections"

Technical Guide (Trial)" etc.

1.3 Process control

Preparation product production process control needs to be based on in-depth process research

On top of that. Applicants should base their application on existing production experience, knowledge and relevant research

The research results confirm the key process steps, key process parameters and their acceptable range,

And establish control standards for key intermediate products. List all critical process steps and

Process parameter control range, providing research data to support the determination of key process steps

Rationality and rationality of process parameter control range.

1.4 Process verification

Before applying for marketing authorization of pharmaceutical products, the applicant should usually complete the commercial scale

Production process verification, submit process verification plan, process verification report and production process

Art information sheet.

During the process validation phase, it is recommended to increase sampling frequency and quantity to support production

Product quality meets requirements.

Sterile preparations should be subject to sterilization/aseptic process testing in accordance with relevant guidelines.

Certification, provide verification plan and verification report. Sterilization/aseptic process validation should support the proposed

Customized commercial production and mass production of products meet the requirements.

1.5 Production batch size

The sample batch of registration batch of generic drugs shall refer to the "Registration batch of chemical generic drugs" published.

"General Requirements for Production Scale (Trial)" is implemented. Human bioequivalence test

The production scale of validation or critical clinical batch samples should be within the proposed commercial production

Produced on production lines and production equipment, the prescription, process, and production equipment should in principle be in accordance with the supplier's

Industrial production remains consistent.

If there is sub-batch production during the commercial production of pharmaceutical products, the applicant should research

Study and formulate quality control requirements for sub-batch, and demonstrate sub-batch distribution during process development and verification.

the necessity and the rationality of the sub-batch control strategy; in proving the various aspects of the production process

On the basis of uniform quality among sub-batches, multiple sub-batches can be combined into one batch;

Clarify the correspondence between sub-batch composition and finished product batches, and carry out sub-batch storage if necessary

Time bound research.

2. Quality control of original and auxiliary packages

2.1 API

If the applicant uses purchased raw materials for preparation production, it must be combined with the raw materials

The process route provided by the manufacturer fully researches and evaluates the quality of the API.

Evaluate and formulate internal control standards for raw materials to achieve consistent quality between homemade preparations and reference preparations

purpose. For example, the crystal form and/or particle size distribution of the raw material may affect the quality of the preparation.

response, it should be included in the internal control standards for raw materials and exclusive testing items should be formulated for control.

system. The particle size distribution of raw materials should be based on human bioequivalence test batches and critical clinical trials.

Actual Measurement of Particle Size Distribution of APIs Used in Bed Batch and Process Validation Batch Samples

Data serve as the basis for setting limits.

Applicants should conduct a comprehensive review of API suppliers and API quality.

planning and evaluation, and ensure the stability of the supply chain in subsequent commercial production. like

If a change occurs, the applicant must conduct research and application in accordance with relevant technical guidelines.

2.2 Excipients

The excipients used should meet the requirements of the dosage form of the preparation product. Applicants should clearly

Monitor the key quality attributes of excipients and formulate reasonable internal control standards. remove

Except for special circumstances, excipients should comply with the requirements of the Chinese Pharmacopoeia, or USP, EP, JP

Wait for the request. For special excipients, applicants need to pay attention to the impact of differences between batches of excipients on drugs.

The impact on quality and establishing reasonable internal control standards based on risks. of animal origin

Excipients should have a TSE/BSE risk statement.

2.3 Packaging materials and containers in direct contact with pharmaceuticals

Packaging materials and containers that come into direct contact with drugs should comply with the requirements issued by the State Food and Drug Administration.

Cloth pharmaceutical packaging material standards, or USP, EP, JP and other requirements.

Applicants should base their decision on the packaging system of the reference preparation and the characteristics of the product to be developed.

characteristics and clinical use, choose a packaging system that can ensure drug quality,

Used to support the consistent quality of homemade preparations and reference preparations.

Based on the route of administration and risk assessment of the formulated product, the applicant should follow the relevant

Technical guidelines or specifications for compatibility of selected packaging materials and containers

Sexual and functional research and evaluation; based on accelerated test and long-term test study results

Determine the rationality of packaging materials and containers used to ensure drug quality and

Same as the reference preparation.

3. Quality control of preparations

3.1 Quality standards

It is recommended that applicants scientifically

Formulate quality standards for pharmaceutical products and provide the basis for formulating quality standards for pharmaceutical products

experimental data and literature. The target quality profile of a product is to determine the formulation

The basis for the key quality attribute. The critical quality attributes of the drug product should generally include, but are not limited to

Regarding properties, identification, related substances (including isomer impurities), mutagenic impurities,

Elemental impurities, microbiological limits, sterility and content determination, etc.

Applicants should refer to guidelines such as ICH Q2 and Q6A, based on

requirements for consistent quality of preparations, and reasonable setting of preparation quality standard testing items and

Accept the standards and provide sufficient supporting test data and literature.

For preparations that have been included in pharmacopoeia standards, applicants may first consider selecting

Use pharmacopoeia standard test items and analytical methods. Analytical methodology should focus on confirming drugs

Whether the standard testing methods and conditions are suitable. If the research results show that the method is suitable,

Applicants can continue to use pharmacopoeia standard analysis methods; if they need to establish new detection methods,

Corresponding methodological verification should be carried out and it should be proved that the new method is not inferior to the pharmacopoeial method.

For preparations that have been included in the Chinese Pharmacopoeia, the quality index should generally not be lower than that of the Chinese Pharmacopoeia.

Pharmacopoeia requirements.

3.2 Quality research

Applicants may refer to the ICH guidelines (Q2, Q3B, Q3C, Q3D,

Q6A and M7, etc.), "Technical Guiding Principles for Research on Impurities in Chemical Drugs", "Chemistry

Technical Guidelines for Validation of Analytical Methods for Drug Quality Control", "Chemical Drug Quality

"Technical Guiding Principles for the Standardization Process of Standard Establishment", etc., as well as the fourth part of the Chinese Pharmacopoeia

General principles conduct quality research on preparation products and provide preparation quality research data, including

Typical spectrum of a representative sample. Analytical methods should be in accordance with Chinese Pharmacopoeia and ICH guidelines

Guidelines for standardized methodological verification.

(1) Related substances

Research on related substances in preparations should focus on degradation products. Degradation products

Substances include degradation products of APIs, reactions between APIs and excipients and/or inner packaging materials

product. Process impurities of APIs generally do not need to be monitored in the preparation, but they need to be

Pay attention to whether process impurities interfere with the detection of degradation products. Applicants should be in full

Based on comprehensive analysis of impurity spectra and combined with relevant literature, scientifically select relevant substances

Analytical methods, subject to standardized methodological verification and/or validation.

For those that have already been included in pharmacopoeia standards, the applicant should analyze the pharmacopoeia standards analysis

The applicability of the method, and the preparation of analytical methods for separation and detection of relevant substances in pharmaceutical products

Capacity and impurity control requirements should be no less than pharmacopoeial standards. Applicants can prepare

Impurity reference substance with a limit concentration is added to prove the proposed analysis method of related substances.

The method can separate target impurities individually and/or effectively separate their main components; for pharmaceuticals

If the classical standards have not been included, samples rich in impurities (such as appropriately degraded samples) can be used.

products, end-stage stability samples, etc.), conduct comparative and optimal research on chromatographic conditions,

Select appropriate chromatographic conditions based on the ability to detect impurities and establish relevant substances

Analytical methods, and use impurity reference standards for methodological verification.

Excipients, solvents and/or complex matrices may have an impact on impurity detection

For analysis methods, applicants should research and determine a reasonable method for excipient solvent peak deduction.

Impurity content determination using principal components with and without correction factors

Self-control method, correction factors should be studied.

Enantiomers need to be studied using chiral chromatographic analysis methods.

(2) Mutagenic impurities

Through understanding the reference preparation and relevant literature, according to the production process of the preparation,

process and degradation pathways, and analyze and study potential mutagenic impurities in preparations.

Refer to ICH M7 to develop a reasonable control strategy. For advanced tumor drugs, it is necessary to

Based on the indications and medication population, mutagenic impurities are formulated with reference to ICH M7 and S9

control strategy. Nitrosamine impurities refer to the published "Nitrosamines in Chemical Drugs"

Implementation of Technical Guidelines for Research on Similar Impurities (Trial).

(3) Elemental impurities

Use scientific and risk-based assessments to determine

Control strategies for elemental impurities in customized dosage forms, including APIs, excipients, and packaging systems

Elemental impurities that may be introduced by systems, production equipment, etc. Peritoneal dialysis solution, parenteral camp

If nutritional injections or reference preparations have been labeled with aluminum content, generic drugs should be

Aluminum element inspection items are formulated in the quality standards.

(4) Dissolution

Applicants can develop and establish a dissolution method based on the dissolution characteristics of the reference formulation.

Such as using pharmacopoeia standards, FDA dissolution database or Japanese IF files and other publicly available

The dissolution method has been published, and the applicant is recommended to conduct method applicability studies;

If a published dissolution method is not used, the corresponding basis must be provided; if there is a lack of

Refer to the dissolution method, it is recommended that the applicant based on the drug pH-solubility curve,

For information such as sink conditions, refer to relevant dissolution technical guidelines and combine them with the preparation.

Product characterization and development of dissolution methods. The research process needs to pay attention to the test of method discrimination

Check.

3.3 Quality Comparative Study

A comprehensive quality comparison of homemade preparations with reference preparations (including impurity profiles

Compare), the quality of the two should be consistent. In principle, multiple batches of samples should be provided for the reference preparation.

product inspection data, and fully examine the key quality attributes closely related to the preparation products.

sex.

In principle, the types of impurities in homemade preparations should not exceed those in reference preparations.

The amount should not exceed the impurity limits of the reference product. If homemade preparations appear to exceed identification

For new impurities that have limits or defined limits, the applicant should analyze the causes of their occurrence and take

Corresponding measures should be taken to reduce impurity content, and safety test data should be provided for discussion if necessary.

Confirm the safety of impurities.

Develop homemade preparations and reference preparations with reference to relevant technical guidelines.

Comparative study of dissolution profiles. When comparing dissolution curves, the reference preparation should provide more

Batch sample data should also examine the intra-batch and inter-batch uniformity of the dissolution behavior of the reference preparation.

The similarity judgment of dissolution curves should comply with the "Dissolution Test of Common Oral Solid Preparations"

Technical Guiding Principles", "Measurement and Comparison Guidelines for Dissolution Curves of Common Oral Solid Preparations

Guiding Principles and other relevant requirements.

3.4 Establishment of quality standard limits

Applicants should fully grasp the key quality attributes of pharmaceutical products,

Combined with the quality research results and stability inspection results of multiple batches of samples, a scientific

Scientific, reasonable and controllable quality standards. The determination of quality standard limits should be based on

Considerations for drug safety, effectiveness and quality consistency with reference preparations, including

Systematic errors in analytical methods.

Determination of limits for testing items such as related substances, mutagenic impurities and elemental impurities

It is necessary to combine the test results or literature basis, and consider the route of administration, dosage and

Clinical usage, etc. Impurity limits are generally determined by comparison with a reference product

Spend. If it has been included in pharmacopoeia standards and other public information, pharmacopoeia methods should be compared.

Conduct more research to determine a reasonable analytical method, and the limit setting should not be higher than the pharmacopoeia standard.

limit. Acceptance limits for relevant substances should generally be in accordance with ICH Q3B and/or European

Alliance Antibiotic Guidelines and other requirements, applicants must provide safety tests when necessary

Data to demonstrate the safety of impurities.

On the basis of the dissolution curve study, according to the dissolution characteristics of the reference preparation,

Dissolution results of clinical trial batches and/or samples used in human bioequivalence studies,

Establish reasonable dissolution standards.

4. Stability

Preparation stability research includes influencing factor testing, accelerated testing and long-term testing

If necessary, intermediate conditions should be tested and inspected.

Applicants can refer to ICH Q1A, Q1B and "Chemical Drugs (API

and Preparations) Stability Research Technical Guidelines" to conduct stability studies.

When submitting a preparation registration application, the applicant should generally provide 3 batches of 6 samples

Stability research data under monthly accelerated testing and long-term testing conditions of not less than 6 months

Materials (including typical diagrams). Accelerated testing and long-term testing should be carried out in compliance with GMP regulations

Conducted under certain conditions, the test samples should be registered batches that can represent commercial production scale.

times, it is recommended to use no less than 2 batches of raw materials to produce different batches of preparations.

Determine storage conditions based on stability study results and reference preparation information, generic drugs

The stability should be no less than that of the reference preparation.

Stability testing protocols and stability commitments should generally be submitted.

According to the characteristics of the preparation product, examine the suitability of the packaging system for storage and transportation

sex.

5. Technical requirements for research and evaluation of five categories of chemicals

Category 5 chemical drugs are drugs that have been marketed overseas, including Category 5.1 and Category 5.2.

Applicants should refer to the requirements of internationally accepted and current relevant domestic technical guidelines when developing the application.

carry out research, among which chemicals in category 5.2 need to be selected and confirmed with appropriate reference preparations.

On this basis, you should also refer to the “Research and Evaluation Technology for Category 3 Chemical Drugs” in this technical requirement.

Carry out pharmaceutical research with relevant content related to "Technical Requirements". During the stage of applying for marketing authorization, apply for

People should follow "M4: Common Technical Document (CTD) for human drug registration application"

Organize and submit application materials with format number and project sequence, including information that can reflect the application process

Current version of CTD pharmaceutical research data on products marketed in China, summarizing CPP certificates

The book records the process improvements and quality that occurred between the country’s first listing and the declaration for import.

Major pharmaceutical changes such as volume improvement (including changes approved by the drug regulatory agency, etc.)

Historical introduction, providing research information on major changes in pharmacy when necessary. provide representation

Batch analytical data for batch samples, including critical clinical trial batches (such as overseas III

Phase 1 clinical trial batch, domestic clinical trial batch), import inspection batch, process verification

List summary information of batch samples, indicating drugs imported into China and drugs marketed overseas

The products have similarities and differences in terms of production lines, raw and auxiliary packages, prescription processes and quality control.

6. References

1. ICH Steering Committee. Harmonised Tripartite Guideline Q1A: Stability Testing of New Drug Substances and Products. 2003

2. ICH Steering Committee. Harmonised Tripartite Guideline Q1B: Stability Testing: Photostability Testing of New Drug Substances And Products. 1996

3.ICH Steering Committee. Harmonised Tripartite Guideline Q2: Validation of Analytical Products: Text and Methodology 1996

4.ICH Steering Committee, Harmonised Tripartite Guideline Q3A: Impurities in New Drug Substances, 2006

5.ICH Steering Committee, Harmonised Tripartite Guideline Q3B: Impurities in New Drug Products, 2006

6.ICH Steering Committee, Harmonised Tripartite Guideline Q3C: Impurities: Guideline for Residual Solvents,

2016

7.ICH Steering Committee. Harmonised Tripartite Guideline Q3D: Guideline for Elemental Impurities. 2014

8.ICH Steering Committee. Harmonised Tripartite Guideline Q6A: Specifications: Test Procedures and Acceptance Criteria for new Drug Substances and New Drug Products: Chemical Substances. 1999

9.ICH Steering Committee, Harmonised Tripartite Guideline Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, 2000

10. ICH Steering Committee, Harmonised Tripartite Guideline Q8: Pharmaceutical Development. August, 2009

11. ICH Steering Committee, Harmonised Tripartite Guideline Q11: Development Manufacture of Drug Substances ÿChemical Entities and Biotechnological/Biological Entitiesÿ, 2012

12. ICH Steering Committee. Harmonised Tripartite Guideline M7: Assessment and Control of DNA Reactive ÿMutagenicÿ Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. 2017

13. ICH Steering Committee. Harmonised Tripartite Guideline M9: Biopharmaceutics Classification System-based

Biowaivers. 2019

14. State Food and Drug Administration. "State Food and Drug Administration's Notice on the Release of Chemical Drugs"
Notice on Product Registration Classification and Application Document Requirements (No. 44, 2020)

15. Center for Drug Evaluation of the State Drug Administration. "About the Release < Chemistry
Technical Requirements for Quality and Efficacy Consistency Evaluation of Generic Drug Injections>etc. 3
Notice of Documents" (No. 2, 2020)

16. Drug Evaluation Center of the State Drug Administration. "Chemical Drug Injection
Guiding Principles for Research and Verification of Agent Sterilization and Aseptic Processes (Trial)" (2020 No.
No. 53)

17. Drug Evaluation Center of the State Drug Administration. "Chemical Drug Injection
Technical Guidelines for System Compatibility Study of Plastic Components Used in Agent Production (Trial)ÿ
(No. 33 of 2020)

18. Drug Evaluation Center of the State Drug Administration. Chemical Drug Injections
Technical Guidelines for Sealing Properties of Packaging Systems (Trial)" (No. 33, 2020)

19. Drug Evaluation Center of the State Food and Drug Administration. "For Children"
Guiding Principles for the Pharmaceutical Development of Drugs (Chemical Drugs) (Trial)" (No. 67, 2020
Number)

20. Drug Evaluation Center of the State Drug Administration. "Chemical Drugs Central Asia"
Technical Guiding Principles for Research on Nitamine Impurities (Trial)" (No. 1, 2020)

21. State Food and Drug Administration. "State Food and Drug Administration's Notice on Further Improving
Announcement on Matters Related to Drug-Related Review, Approval and Supervision Work" (2019 No.
No. 56)

22. State Food and Drug Administration. "Selection and Application of Reference Preparations for Chemical Generic Drugs"
Determination of Procedures" (No. 25, 2019)

23. State Food and Drug Administration. "About the release of sterilizing filtration technology and application
Notice on the Guidelines for Use and Three Other Guidelines" (2018 No. 85)

24. State Food and Drug Administration. "State Food and Drug Administration's Regulation on Regulation
Notice on Application Document Requirements for Long-term Stability Study of Integrated Chemical Generic Drugs" (2018
Year No. 82)

25. State Food and Drug Administration. "Chemicals and Elastomers
Technical Guiding Principles for Seal Compatibility Research (Trial)" (No. 14, 2018)

26. Center for Drug Evaluation of the State Drug Administration. "Notes on Chemical Generic Drugs"
General Requirements for Registration and Batch Production Scale (Trial)" (2018.6)

27. State Food and Drug Administration. "State Administration of Food and Drug Administration's Notice on the Release of Chemical Drugs"
Notice on Requirements for Classified Application Materials for New Product Registration (Trial Implementation)" (2016 No. 80
Number)

28. State Food and Drug Administration. "Human Bioequivalence Test"
Guiding Principles on Exemptions (No. 87 of 2016)

29. State Food and Drug Administration. "Mechanical Testing of Drug Dissolution Apparatus"
Guiding Principles for Certification (No. 78, 2016)

30. State Food and Drug Administration. "Common Oral Solid Preparations Dissolved
Guiding Principles for Curve Determination and Comparison (No. 61, 2016)

31. State Food and Drug Administration. "Taking Pharmacokinetic Parameters as the Endpoint
"Technical Guiding Principles for Human Bioequivalence Research on Generic Chemical Drugs"

(No. 61 of 2016)

32. State Food and Drug Administration. "Chemical Drug Injections and Drugs
Technical Guidelines for Compatibility Research on Glass Packaging Containers (Trial)" (2015
No. 40)

33. State Food and Drug Administration. "Common Oral Solid Preparations Dissolved
"Technical Guiding Principles for Outbound Testing" (No. 3, 2015)

34. State Food and Drug Administration. "Chemical Drugs (APIs and
Preparations) Stability Research Technical Guidelines (No. 3, 2015)

35. State Food and Drug Administration. "Chemical Drug Injections and Plastic
Technical Guiding Principles for Compatibility Research on Packaging Materials (Trial)" (State Food and Drug Administration Note
(2012) No. 267)

36. State Food and Drug Administration. "About strengthening pharmaceutical glass packaging
Notice on the Supervision and Administration of Injectable Drugs (Food and Drug Administration Note [2012] No. 132)

37. State Food and Drug Administration. "Basic Technology of Chemical Injections"
Technical Requirements (Trial)" (State Food and Drug Administration Note [2008] No. 7)

38. State Food and Drug Administration. "Preparation and Preparation of Chemical Drug Raw Materials"
Technical Guiding Principles for Structure Confirmation Research (State Food and Drug Administration Note [2005] No. 106)

39. State Food and Drug Administration. "Chemical Drug Preparation Research Technology
Guiding Principles" (State Food and Drug Administration Note [2005] No. 106)

40. State Food and Drug Administration. "Establishment of Quality Standards for Chemical Drugs"
Technical Guiding Principles for the Standardization Process" (State Food and Drug Administration Note [2005] No. 106)

41. State Food and Drug Administration. "Analysis of Quality Control of Chemical Drugs"

42. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. GuidancesÿDrugsÿÿ Generics: https://www.fda.gov/Drugs/Guidance Compliance Regulatory Information/Guidances/ucm064995. htm

43. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Generic Drug Development: https://www.fda.gov/Drugs/Development Approval Process/How Drugs are Developed and Approved/Approval Applications/Abbreviated New Drug Application ANDA Generics/ucm142112. htm

44. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs. September 2020

45. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Transdermal and Topical Delivery System–Product Development and Quality Consideration. November 2019

46. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Identification of Manufacturing Establishments in Applications

Submitted to CBER and CDER Questions and Answers. October 2019

47. Food and Drug Administration, Center for Drug Evaluation and Research ÿ CDER ÿ . Using the Inactive Ingredient Database Guidance for Industry. July 2019

48. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Quality Attribute Considerations for Chewable Tablets. August 2018

49. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Metered Dose Inhaler ÿMDIÿand Dry Powder Inhaler ÿDPIÿ Products-Quality Considerations. April 2018

50. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Regulatory Classification of Pharmaceutical Co-crystals. February 2018

51. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ, Office of Generic Drugs. Filing Review of Abbreviated New Drug Applications, MAPP 5200.14. September 2017

52. Food and Drug Administration, Center for Drug

Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards. December, 2016

53. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits. August 2016

54. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ, Office of Pharmaceutical Quality. Manual of Policies and Procedures ÿMAPPÿ, Policy and Procedures, 5015.10, Chemistry Review of Question-Based Review ÿQbRÿ Submissions. December 2014

55. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers. May 2014

56. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDAs: Impurities in Drug Products. October 2010

57. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Drug Substance Chemistry, Manufacturing and Controls

Information. August 2010

58. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDAs: Impurities in Drug Substances. July 2009

59. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Orally Disintergrating Tablets. December 2008

60. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism. July 2007

61. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Changes to an Approved NDA or ANDA. April 2004

62. Food and Drug Administration, Center for Drug Evaluation and Research ÿCDERÿ. Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documention. July 2002

63. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Sterilisation of the Medicinal Products, Active Substance, Excipient and Primary Container. March 2019

64. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Impurities-Calculation of Thresholds for Impurities.December2018

65. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Dissolution Specification for Generic Oral Immediate Release Products. August 2017

66. European Medicines Agency, Committee for Medicinal Products for Human Use ÿ CHMP ÿ . Pharmaceutical Development of Medicines for Use in the Older Population. August 2017

67. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Process Validation for Finished Products– Information and Data to Be Provided in Regulatory Submissions. December 2016

68. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Reflection Paper on Chemical Structure and Properties Criteria to Be Considered for the Evaluation of New Active Substance ÿNASÿ Status of Chemical Substances. December 2015

69. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Reflection Paper on the Use of Cocrystals of Active Substances in Medicinal Products. May

2015

70. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Quality of Oral Modified Release Products. March 2014

71. European Medicines Agency, Committee for Medicinal Products for Human Use ÿ CHMP ÿ . Pharmaceutical Development of Medicines for Paediatric Use. August 2013

72. European Medicines Agency, Committee for Medicinal Products for Human Use ÿCHMPÿ. Settings Specifications for Related Impurities in Antibiotics. July 2012

73. European Medicines Agency, Committee for Medicinal Products for Human Use ÿ CHMP ÿ EMA/CHMP/QWP/799402/2011: Reflection Paper on the Pharmaceutical Development of Intravenous Medicinal Products Containing Active Substances Solubilised in Micellar Systems. March 2012

74. European Medicines Agency, Committee for Medicinal Products for Human Use ÿ CHMP ÿ . Guideline on the Investigation of Bioequivalence. January 2010

75. European Medicines Agency, Committee for Medicinal Products for Human Use ÿ CHMP ÿ . Guideline on the Investigation of Bioequivalence. January 2010

76. American Society for Testing and Materials ÿASTMÿ E2709, Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure [S]. 2011

77. American Society for Testing and Materials ÿASTMÿ E2810, Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units [S]. 2011