Questions and Answers on Pharmaceutical Similarity Studies of Biosimilars

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I. Overview

Currently, several therapeutic biological products in my country have been applied for and approved as biosimilars.

Market approval, while contributing to the continued development of the industry, has also become a means to improve the accessibility of medicines for the Chinese people.

One of the important ways to have sex.

Currently, several guidelines have been issued regarding the research and evaluation of biosimilars, such as the "Guidelines for the Development and Evaluation of Biosimilars".

Technical Guidelines for the Research and Evaluation of Biosimilars (Trial) and the Evaluation of Biosimilar Similarity

Guidelines such as "Technical Guidelines for Extrapolation of Price and Indications" are provided because pharmaceutical research on biosimilars is relatively...

The situation is complex, and there are still common issues that need to be clarified during the application and review process for this type of product.

This document provides guidance and standards for pharmaceutical similarity studies of biosimilars, based on the current evaluation system.

Based on relevant guidelines, this document summarizes common issues and provides guidance for pharmaceutical research at different application stages.

The following suggestions are offered for reference.

This Q&A applies to products declared as Class 3.3 therapeutic biological products. With the advancement of science and technology...

With the development of technology and the accumulation of regulatory knowledge and experience, the technical requirements for pharmaceutical research of related products will not be...

Continuously improve and update.

II. Common Problems and Technical Requirements

(a) Research and development and production

1. What are the requirements for manufacturing process and scale when applying for clinical trials for biosimilars?

Based on the principle that quality originates from design, a comprehensive and in-depth study of reference drug quality should be conducted.

Based on the analysis of the relationship between the key quality attributes of the candidate drug and the manufacturing process, biosimilars are developed.

The research and development and production of biosimilars. Among these, production processes and scale are crucial factors affecting the quality of biosimilars.

Key factors should be considered, and the raw materials and production process flow should be rationally determined based on the research conducted.

Process, key process parameters, intermediate control items and limits, etc.

It is recommended to apply for clinical trial approval using the anticipated commercialization process and scale.

Production of similarity study samples and samples intended for clinical trials. If the production plan cannot meet this target...

The requirement is that production must be carried out using processes and scales compatible with the anticipated commercial production to support...

Holding a clinical trial application for a candidate drug. This includes recommending the manufacturing process used for the clinical trial application sample.

The process flow and main raw materials used in production remain consistent with the expected commercial production, and the specific processes...

The process parameters can be further improved and adjusted; it is recommended to maintain pharmaceutical comparability between the candidate drugs before and after the change.

Otherwise, further non-clinical and/or clinical bridging studies may be necessary.

It is strongly recommended that the commercial manufacturing process and scale be determined before the start of pivotal clinical trials, and

Used for the production of samples for subsequent pharmaceutical similarity studies and clinical trials to support the development of drug candidates.

City application.

2. Must the dosage form, strength, and formulation of the candidate drug be consistent with the reference drug?

In principle, the dosage form and strength of the candidate drug should be consistent with the reference drug. It is recommended that the candidate drug's formulation...

The prescription (types and dosages of excipients) should be consistent with the reference drug. If there are any discrepancies, the reasons should be explained.

We will ensure the rationality of the formulation and conduct in-depth, standardized, and comprehensive research on formulation development.

(II) Selection of Reference Drugs

1. What are the requirements for the source of the reference drug?

The reference drugs used in each stage of pharmaceutical comparative studies should, as far as possible, be selected from within China.

For original drugs that have been approved for marketing, it is encouraged to start collecting reference drugs as early as possible according to the research and development plan.

When obtaining approval for a reference drug in China is genuinely difficult (e.g., insufficient supply, batch shortages),

When submitting a declaration (e.g., for those with fewer cases) or planning to submit a global declaration, the source of information from different countries (regions) can be confirmed by referring to relevant information.

Provided that the drugs are comparable, the combination of drugs can be used in countries (regions) that have already been approved for marketing overseas.

Pharmaceutical similarity studies were conducted on the reference drug that was sold.

For reference drugs that have been approved for marketing overseas but have only been approved for clinical trials in my country

Clinical trial applications for candidate drugs can utilize products already approved for marketing in countries (regions) outside of China.

Pharmaceutical similarity studies should be conducted on the reference drug that is currently sold. When submitting a marketing application for a candidate drug, this should be combined with...

Based on the source of the drug and the results of comparative studies, and in accordance with the relevant technical requirements for biosimilars, standardized prescriptions should be prepared.

To conduct comprehensive pharmaceutical similarity studies.

According to the "Regulations of the National Medical Products Administration on the Import of Original Reference Drugs for Clinical Research of Biosimilars",

Announcement on Relevant Matters (No. 44 of 2019) regarding the applicant's proposed choice and approval in my country.

Original drugs from the same company that have different places of origin for import registration or clinical trials can be used as reference drugs.

Before clinical trials begin, evidence of comparability between original drugs from different countries of origin should be provided, or evidence should be provided according to...

According to the relevant technical guidelines of my country's drug regulatory authorities on the research and evaluation of biosimilars

This requires conducting comparative studies of original drugs from different countries of origin and proving their comparability, in order to supplement...

The application should be submitted to the Center for Drug Evaluation of the National Medical Products Administration (NMPA) through the supplementary application method. At this time, the comparability study needs to be completed.

Building upon pharmaceutical comparative studies, this further encompasses non-clinical and/or clinical research to demonstrate that...

Comparability of reference drugs from the same source in terms of pharmacokinetic (PK)/pharmacokinetic (PD) aspects.

2. In multi-specification formulations, can a representative specification of the reference drug be selected for pharmaceutical similarity studies?

Sex research?

When different specifications of reference drugs have the same protein concentration and formulation composition, but different fill volumes...

Meanwhile, multiple batches of a representative specification or a combination of multiple specifications of reference drugs can be used to conduct research.

Quality attribute similarity study. At this point, attention should be paid to the impact of packaging materials that directly contact the drug on the formulation.

Potential impact on quality; stability similarity studies can be conducted based on sufficient and reasonable evidence.

Simplify research protocols, such as using brackets as a reference to relevant ICH guidelines.

When there are differences in protein concentration and formulation composition among different specifications of reference drugs, it is necessary to...

Pharmaceutical similarity studies were conducted on formulations of the corresponding specifications.

(III) Pharmaceutical similarity studies

1. What aspects are included in pharmaceutical similarity studies?

Overall, pharmaceutical similarity studies between candidate drugs and reference drugs include studies on the similarity of quality attributes.

Similarity studies include research on protein structure and stability. Quality attribute similarity studies typically include studies on protein structure and stability.

Evidence includes physicochemical properties, purity and impurities, biological activity, and immunological properties. Stability phase.

Similarity studies typically include forced degradation comparison studies and accelerated stability comparison studies; combined with product

The current status of product stability studies and usage characteristics may require further long-term comparative stability studies.

A comparative study of stability under simulated usage conditions.

2. Considerations regarding sample storage conditions and duration in pharmaceutical similarity studies?

Candidate drugs and reference drugs should be transported, stored, and used under specified conditions. Consideration should be given to...

The potential impact of storage time suggests avoiding the use of near-expiry reference drugs and newly prepared drugs.

Select drugs and conduct pharmaceutical similarity studies.

If a long-term stability comparison study has been conducted between the candidate drug and the reference drug, it is recommended to adopt...

Comparative analysis and trend analysis were performed on data from similar timeframes.

In principle, it is not recommended to store at a temperature lower than the storage conditions given in the instruction manual.

If it is necessary to conduct quality attribute similarity studies on existing reference drugs, then...

Explain your reasoning and provide sufficient research data to demonstrate that the storage conditions and duration will not affect the participants.

This has an adverse effect on the quality of the medicine.

3. What are the requirements for the study batches of the candidate drug and the reference drug in pharmaceutical similarity studies?

The batch requirements for candidate drugs and reference drugs need to be considered in conjunction with the specific circumstances of the drug, the application stage, and the research and development process.

The variability of the research projects and analytical methods was comprehensively determined. This was done to fully understand the candidate drug and the reference drug.

The quality attribute range meets the requirements of statistical tools, avoiding bias caused by individual batches.

It is recommended to collect as many batches and over as long a time span as possible within a reasonable range.

For biosimilars of drugs for the treatment of rare diseases or other special cases, pharmaceutical similarity studies

The batch numbers of the reference drug and candidate drug used can be communicated with the review agency in advance.

3.1 Clinical Trial Application

Based on the current evaluation system, clinical trial applications should, in principle, use no fewer than three batches of data.

The next step is to conduct a quality attribute similarity study on the candidate drug based on the proposed application process and scale of production, such as...

When considering development batches, their representativeness can be used as a reference; the reference drug should not be less than [a certain number].

Of the 6 batches, some were structural confirmation studies, including: molecular weight (containing sugars and dehydrogenated molecules).

(Molecular weight of sugar), amino acid sequence and coverage (secondary mass spectrometry), glycosylation modification sites, poly(hydroxyl group of sugars), amino acid sequence and coverage (secondary mass spectrometry), poly(hydroxyl group of sugars ...

Collective identification, circular dichroism spectroscopy, thermal stability analysis, infrared spectroscopy (if applicable), fluorescence spectroscopy

(If applicable) at least three batches of the reference drug are required in comparative studies. For products such as peptides,

Fourier transform infrared spectroscopy, Raman spectroscopy, nuclear magnetic resonance spectroscopy, and crystal X-ray spectroscopy can be used.

The correctness of its structure was further confirmed by methods such as diffraction, analytical ultracentrifugation, or field-flow separation.

For impurity studies, it is recommended to use advanced, sensitive, and robust detection methods on no fewer than three batches.

The candidate drug and three batches of reference drug were compared for impurity profiles according to the proposed manufacturing process and scale.

For comparative studies, if more batches of data are available, they should be analyzed together, and at least 1...

Batch samples were subjected to necessary impurity enrichment and identification studies, such as various isomers or drug candidates.

New impurities appearing in the solution, etc.

Stability similarity studies recommend using no fewer than three batches, according to the proposed application process and specifications.

Accelerated stability studies were conducted on the candidate drug produced in the model compared with three batches of the reference drug, employing numerous methods.

Forced degradation comparison studies were conducted on one batch of samples from each group. For samples with complex drug delivery processes or those that may...

For formulations requiring multiple administration, at least one batch of samples must be used to simulate usage conditions.

Stability comparison study under [various conditions].

3.2 Listing Approval Application

Based on the current evaluation system, when applying for market access authorization, the purity, isomers, and glycosyl groups should be considered.

Quality attributes that are highly susceptible to fluctuations due to process variations, such as chemical modifications, and the number of batches of candidate drugs and reference drugs.

The quantity must meet statistical requirements; in principle, it is recommended to use no fewer than 6 representative batches of candidate drugs.

A quality attribute similarity study was conducted with 10 batches of reference drugs. Regarding the reduction mentioned in Section 3.1...

For structural confirmation studies that do not require batch testing, it is recommended to use at least three batches of samples for comparative analysis.

For research.

Batch requirements for samples in impurity studies and stability similarity studies, and clinical trial applications

The results are basically the same, but forced degradation comparison studies require the use of no fewer than three batches of samples for each study.

The candidate drugs used in the study must be samples produced using the proposed commercialization process and at scale.

4. What are the key considerations in pharmaceutical similarity studies?

4.1 Study on the similarity of quality attributes

When reference drugs from different sources are used in a study on the similarity of quality attributes, it is recommended that the analysis...

The actual test results and statistical ranges of reference drugs from different sources are grouped and listed. In each...

Provided that the reference drugs from different sources are comparable, the test results of the reference drugs from different sources can be compared.

The results were combined into a single dataset for statistical analysis. Simultaneously, the reference drug batches used in clinical trials were also analyzed.

Studies on the similarity of quality attributes should be included concurrently. When the sample batches for the study on the similarity of quality attributes are complete...

When the required quantity is met, it is recommended to refer to the "Biosimilar Drug Similarity Evaluation and Indication Extrapolation Techniques".

The "Guiding Principles" establish corresponding similarity acceptance criteria based on the risk level of the reference drug's quality attributes.

Subject to standards. In principle, when using equivalence verification or the quality range method for verification, the standard bias is...

The coefficient before difference should generally be ÿ3.0, for biological activities directly related to the product's mechanism of action.

Sexual testing requires further tightening of this coefficient; if other special circumstances still exist, it can be discussed in advance with the review committee.

The evaluation agency will be contacted. The actual test results of the candidate drug should fall within the range established using statistical tools.

Within the similarity criteria.

To fully analyze the potential differences between the candidate drug and the reference drug and assess their impact, when

When the test results of the selected drug exceed the range of the test results of the reference drug, supporting analytical data is required.

To demonstrate that the differences will not adversely affect the clinical safety and efficacy of the candidate drug.

When multiple key quality attributes related to the product's mechanism of action (such as translation) are present in the candidate drug,

The modification properties, affinity activity, and cell biological activity of this drug differ significantly from the reference drug, requiring caution.

The feasibility of developing a biosimilar should be considered. Furthermore, the completeness of the research project needs to be addressed.

For testing, it is recommended to cover items closely related to product safety and efficacy, such as insoluble particles.

Level, etc.

4.2 Stability Similarity Study

Forced degradation and accelerated stability comparison studies are used to analyze the quality changes of candidate drugs and reference drugs.

An effective research method for studying trends in drug development requires research projects to be based on the proposed shelf-life standards of candidate drugs.

It also adds sensitive indicators that affect product safety and effectiveness, such as special post-translation modifications.

Decoration, etc., to comprehensively reflect changes in the key quality attributes of candidate drugs and reference drugs. Mandatory reduction

The study suggests including multiple sensitive conditions such as high temperature, light, and vibration.

In principle, in forced degradation and accelerated stability comparison studies between candidate drugs and reference drugs,

The sensitive conditions and degradation pathways exhibited by quality attributes closely related to product safety and efficacy

There should be no significant difference in diameter or degradation rate.

5. What are the key considerations in impurity research?

5.1 Product-related impurities

For all types of biosimilars, it is necessary to conduct impurity profile comparison studies between the candidate drug and the reference drug.

The study analyzes and evaluates the types and amounts of impurities and their impact on product safety (including immunogenicity).

Potential impact on effectiveness. In principle, for impurities that may affect the above aspects, their effectiveness should be considered in the candidate...

The content of the selected drug should not be higher than that of the reference drug. Meanwhile, due to the raw materials and production processes used in production...

Due to differences in factors such as these, candidate drugs may contain impurities that are not present in the reference drug, or in varying amounts.

The level of impurities is slightly higher than that of the reference drug. In this case, the cause should be thoroughly analyzed, taking into account both non-clinical and...

/or evaluate based on clinical research data, and optimize as necessary to ensure product safety.

(Including immunogenicity) and efficacy have no adverse effects.

For biosimilars with large molecular weights and complex structures and post-translational modifications, it is necessary to...

Based on different mass properties, charge isomers, molecular size variants, and hydrophobic isomers are classified.

The different components obtained were separated and identified. Further enrichment was performed if necessary, and the composition was further refined.

Its composition and biological activity will be studied to fully assess its potential impact on product safety and efficacy.

It has an impact.

For peptide biosimilars such as liraglutide and teriparatide, when the candidate drug contains

New impurities not present in the reference drug, and whose content exceeds 0.10%, should be identified through enrichment or other methods.

Qualitative and/or quantitative research methods are used.

5.2 Process-related impurities

Because there may be differences in the host expression system and manufacturing process between candidate drugs and reference drugs.

The requirements differ and need to be considered in conjunction with the control limits and human exposure data for similar products in the current edition of the Chinese Pharmacopoeia.

A safety assessment should be conducted considering factors such as quantity and safety thresholds to reasonably formulate impurity standards.

limit.

(iv) Other

1. What are the key considerations in the quality control of candidate drugs?

The quality standards for candidate drugs must be based on the results of quality studies and a deep understanding of the manufacturing process and product.

The quality is a factor, and the quality range of key clinical trial batches and representative batches should also be considered.

The stability study results are reasonably formulated. It is recommended to use advanced, sensitive, and robust analytical methods.

Conduct quality control and provide standardized and complete methodological research data when applying for clinical trials.

In principle, the quality standards for the proposed candidate drug substance and formulation must ensure their quality control capabilities.

It is not inferior to the reference drug.

2. When a candidate drug undergoes significant changes in its manufacturing process after approval for market launch, a comparability study should be conducted.

What are the requirements for a similarity study?

When a candidate drug undergoes significant changes in its manufacturing process after being approved for marketing, the relevant regulations should be followed.

Technical Guidelines for Pharmaceutical Change Research of Pharmaceutical Products (Trial Implementation), ICH Q5E and other guidelines

Conduct risk assessments and comparability studies. This is based on a thorough understanding of the relationship between production processes and product quality.

Based on this, if the assessment concludes that the changes may have a potential impact on the quality of the candidate drug, then it is necessary to...

A similarity study was conducted with a reference drug, and the test results were compared with those of the reference drug obtained in previous studies.

Comparative analysis was conducted to provide supporting data.

3. What considerations are there regarding the functional additives included in the product?

For functional excipients, it is necessary to conduct necessary quality, stability and...

Functional studies, establishing comprehensive incoming inspection quality standards, and evaluating their performance in candidate drugs and reference drugs.

Comparative studies should be conducted on the functional activities of the drugs. For example, attention should be paid to the post-translational modification of water in hyaluronidase.

The effect of concentration on its biological activity requires isophase analysis using multiple batches of samples to investigate the effect of concentration on protamine sulfate.

Point research, etc.