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S o c i a l O r g a n i z a t i o n S t a n d a r d

Guidance of Equivalence/Replaceability Assessment and Compatibility Studies for Postapproval Changes to Pharmaceutical Packages

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Table of Contents

Introduction

Packaging materials and containers are parts of drug products. Changes in packaging materials and containers may affect the physical and chemical attributes, impurity profiles, content, and stability of the drug products. The risk depends on the route of administration of the drug product, the performance of the packaging materials and containers, and the interactions between packaging and the drug product. In general, changing the pharmaceutical packaging materials and containers should have a beneficial effect on and must not adversely affect the quality of the drug product.

The postapproval changes in pharmaceutical packaging materials or containers/packaging systems (hereinafter referred to as pharmaceutical packaging), as well as changes in the manufacture process from pharmaceutical packaging suppliers, are both important contents of quality risk management throughout the product life-cycle by pharmaceutical manufacturers and pharmaceutical packaging suppliers, which is clearly stipulated in the " Drug Administration Law of the People's Republic of China", " Provisions for Drug Registration ", and " Measures for the Administration of Post-marketing Changes of Drugs (Trial)".

The " Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)" issued by the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) requires that when moderate or major changes occur to pharmaceutical packaging of drug products, equivalence/replaceability assessments should be conducted on pharmaceutical packaging of pre- and postchange.

The " T/CNPPA 3009-2020 Technical Guidance of Change Study of Pharmaceutical Package" of the China National Pharmaceutical Packaging Association proposes that "Marketing Authorization Holder (MAH) and registrants of pharmaceutical packaging carry out the equivalence/replaceability assessment of changes in pharmaceutical packaging based on comprehensive evaluations and studies of changes in pharmaceutical packaging collaboratively". This guidance proposes a specific approach based on the guiding ideology of the above-mentioned documents. It should be noted that the methods given are not the exclusive approach.

The equivalence/repeatability assessment and compatibility studies of pharmaceutical packaging are assessment of the suitability (including protection, functionality, safety, and compatibility) and the acceptability of risk of changes on alternating the suitability of the pre-and postchange pharmaceutical packaging, by no means to determine if they are identical.

This guidance is applicable to the equivalence/replaceability assessment and compatibility studies of postapproval changes to pharmaceutical packaging and is used to verify and confirm the acceptability of risk on suitability of the pre- and postchange pharmaceutical packaging.

The principle of pairwise comparison and the principles of equivalence/replaceability assessment in this guidance can also provide reference for other pairwise comparison studies related to pharmaceutical packaging.

Guidance of Equivalence/Replaceability Assessment and Compatibility Studies for Postapproval Changes to Pharmaceutical Packages

1. Scope

The guidance provides relevant terms, basic principles, study contents, results, and applications of equivalence/replaceability assessment and extractables and leachables studies of pharmaceutical packages.

This guidance is applicable to studies of postapproval changes to packaging of chemical drug products and can be referred to when evaluating postapproval changes to packaging of other drug products (biologics, herbal medicines, etc.) or, when necessary, drug products in clinical trial studies. In addition, pharmaceutical packaging changes initiated by pharmaceutical packaging suppliers (technical changes such as formulas, raw material sources, processes, etc.) can also be evaluated with reference to this guide.

2. Normative reference document

The following documents are essential for the application of this standard. For reference documents with reference dates, only the version of the reference date applies to this standard. The latest version (including all amendments) of any reference document with no dates also applies to this standard.

Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)

ICH Q3D Guideline for elemental impurities

T/CNPPA 3009-2020 Technical Guidance of Change Study of Pharmaceutical Package

3. Terminology

The following terms are only used in this guidance.

3.1

Equivalence/replaceability for pharmaceutical packages

When a postapproval change occurs to the packaging materials and containers (packaging system) or a technical manufacture process change occurs from the pharmaceutical packaging suppliers, the suitability (protection, functionality, safety, and compatibility) of pharmaceutical packaging should be acceptable. If the materials and/or types of the materials of construction of pre- and postchange are the same or similar, it is an equivalence study; if they are different, it is a replaceability study.

3.2

Chemical equivalence

Chemical equivalence means that no increase in the type and amount of extractables/leachables are found in the extractables/leachables profiles of pharmaceutical packages.

3.3

Toxicological risk assessment

Toxicological risk assessment, in this guidance, is a human health risk assessment of extractables/leachables from pharmaceutical packaging. Literatures or toxicology databases can be used to evaluate the acceptable daily exposure of a compound and the relevant toxicity endpoint of concern under a certain exposure and risk level (for example, for carcinogenic substances, an excess risk of 10^{-5} or 10^{-6} is commonly used).

3.4

Safety assessment of pharmaceutical packages

Safety assessment can be an in vivo/in vitro biological reactivity test of materials/components or a toxicological risk assessment of extractables/leachables from a compatibility study of a drug and its packaging system.

3.5

Prior knowledge

The prior knowledge in this guidance refers to information and data about drugs and pharmaceutical packaging materials collected by packaging material/component suppliers and pharmaceutical drug product manufacturers. Prior knowledge may include but not limited to: component formulations (such as material compositions, additives, process aids, catalysts, antioxidants, and pigments, etc.), material/component compliance information (such as compliance with pharmacopoeias or relevant standards), bioreactivity tests, transmissible spongiform encephalopathy/bovine spongiform encephalopathy (TSE/BSE) statement, special concern substance statement, chemical compatibility, historical extractables study and safety evaluation report, processes of component manufacturing or pretreatment (such as sterilization, cleaning, siliconization, surface treatment), records of materials/components used in drug products (such as the drug product characteristics of formulation and process approved, clinical information), drug formulation, and process characteristics, etc.

4. Basic principles for equivalence/replaceability assessment and compatibility studies of pharmaceutical packages

The basic principles of equivalence/replaceability assessment and compatibility studies of pharmaceutical packaging may include:

4.1. The risk-based principle

For any changes to pharmaceutical packaging, identify possible risk initiated by the changes based on the characteristics of drug products, packaging materials, and the possibility of interactions between drug products and packaging, and the corresponding assessment required can be confirmed.

4.2. The principle of pairwise comparison

Under the prerequisite of following regulatory or registration standards, the suitability assessment can be conducted by comparing pharmaceutical packaging before and after changes in pairs. Pairwise comparison requires to setup a pre-established acceptable criteria and range, which should take into full considerations the quality standards approved for the pharmaceutical packaging, any risk in quality, key manufacturing process parameters, insurances of the safety of drug products, and needs in clinical usage, etc.

4.3. The principle of cost-effective

Redundant and unnecessary experiments should be avoided based on scientific evaluations and risk management by making full use of prior knowledge, adopting consensus modern experimental techniques and assessment concepts, for instance extractables/leachables studies and toxicological risk assessment concept, and biological safety evaluation under the risk management framework, etc.

4.4. The principle of suitability

The equivalence/replaceability assessment and compatibility studies focus on the evaluations of suitability (protection, functionality, safety, and compatibility) of pharmaceutical packaging.

5. Contents of equivalence/replaceability assessment and compatibility study of pharmaceutical packages

5.1. Equivalence/ replaceability assessment

An equivalence/replaceability assessment commonly consists of the collecting of prior knowledge and risk assessment, the protection and functionality studies of pharmaceutical packaging, the chemical equivalence research, and the safety assessment, etc.

According to the "Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)" by CDE, there are two types of equivalence/replaceability assessments:

1) If the materials and/or types of the pre- and postchange pharmaceutical packaging materials are the same or similar, the study can be called an equivalence assessment, in which the results of the chemical equivalence study can be used for further safety assessment.

2) If the materials and/or types of the pre- and postchange pharmaceutical packaging materials are different, it is a replaceability assessment, in which it is usually necessary to carry out a comprehensive safety assessment per relevant standards and guidelines.

In an equivalence/replaceability assessment of a pharmaceutical packaging, one should take full advantages of risk management tools and appropriate risk assessment methods to carry out relevant studies.

5.1.1. Prior knowledge collecting and risk assessment

Prior knowledge can be collected for risk identification, risk analysis, and risk characterization. When applying a prior knowledge, a comprehensive assessment should consider the nature of the change, the clinical use of the drug, and the characteristics of the drug and the pharmaceutical packaging. After fully evaluating the prior knowledge collected, if one can conclude that the risks related to protection, functionality, safety, and compatibility pre- and postchange of the pharmaceutical packaging are acceptable, the equivalence/replaceability assessment and compatibility studies are completed.

If there are still risks based on the assessment of prior knowledge of pre- and postchange pharmaceutical packaging, further equivalence/replaceability assessments and compatibility studies should proceed.

5.1.2. Protection and functionality studies of pharmaceutical packaging

Generally, the protection and functionality of a pharmaceutical packaging have been included in its specification or the quality agreements. A protection and functionality study of a pharmaceutical packaging after the change should consider the quality standards or quality agreements, as well as specification and manufacture process.

5.1.3. Chemical equivalence study

When the materials and/or types of the pre- and postchange pharmaceutical packaging are the same or similar, one should conduct a chemical equivalence study; whereas when the materials are different, no chemical equivalence study is required.

When the component formula information is insufficient but needed by the risk assessment, the formula can be confirmed through experiments.

The principles for determining a chemical equivalent status are as follows:

Under the same experimental conditions (extraction and/or simulated extraction), chemical equivalence can be confirmed by comparisons of extractables profiles of the pre- and postchange pharmaceutical packaging.

(1) For organic extractables, there should be no extra peak or peak of increasing area with an amount greater than or equals to the analytical evaluation threshold (AET) in the extractable profiles after the change.

Note: The scenario where a slight increase in the peak area of a compound can also be regarded as a chemical equivalent status through appropriate assessment. For example, it is generally accepted to assess through evaluating the uncertainty of the semi-quantitative analytical method used as well as the slight increase in the peak area of the compound.

(2) For inorganic elemental impurites, there should be no new element or no significant increase in the level of element migrated per "ICH Q3D Guideline for elemental impurities" and other related documents.

Except for glass and metal materials without organic coatings, generally chemical equivalence requires that (1) and (2) are met at the same time.

5.1.4. Safety assessment

No further safety assessment is required for a pharmaceutical packaging on occasion of a chemically equivalent status and an acceptable in vitro cytotoxicity test result (except for inorganic materials such as

glass). Otherwise, a safety assessment should be carried out.

Note: Under normal circumstances, glass (such as soda-lime and borosilicate glass), metals and alloys that do not contain lead, nickel, chromium, and zirconium, etc., and ceramic packaging do not require biological reactivity test, and therefore no need for an in vitro cytotoxicity test.

A safety assessment consists of two parts: in vivo and in vitro biological evaluation of materials/components and toxicological risk assessment of extractables/leachables from the compatibility study.

(1) When the materials and/or types of the pre- and postchange pharmaceutical packaging are the same or similar, if the extractables profile cannot be concluded as chemical equivalent, a qualitative and quantitative analysis of the extractables of the extra peak or peak of increased area with an amount greater than or equals to the AET should be conducted following by a toxicological risk assessment to evaluate its suitability.

Note: When a toxicological risk assessment of a chemical non-equivalent pharmaceutical packaging shows local biological reactivity such as irritation effect, it is suggested to assess the necessity to conduct irritation assays per relevant standards or guidelines with considerations of the clinical exposure situation (for ophthalmic, ointment drug with contact to compromised skin or mucous membranes, etc.), or to derive the acceptable limit for irritation through a toxicological risk assessment. Otherwise, the required irritation tests should be carried out.

The result of the toxicological risk assessment is used to determine whether the safety of the packaging is acceptable.

(2) When the material and/or type of packaging materials and containers are altered, in vivo and in vitro biological evaluation and compatibility study of the pharmaceutical packaging after change should be carried out per relevant standards and guidelines.

5.2. Compatibility study

Compatibility studies can use extractables and/or leachables studies and adsorption studies to prove that there is no severe interaction between the packaging system and the drug during the production, storage, and administration of the drug that leads to changes in the effectiveness and stability of the drug, or any safety risk.

The prior knowledge collecting and risk assessment are also applicable to compatibility studies.

5.2.1. The material and/or type of the pre- and postchange pharmaceutical packaging are the same or similar

The chemical equivalence study under the same experimental conditions and safety assessment can be regarded as part of the compatibility study, on top of which it is evaluated whether further compatibility study is needed to assess the acceptability of the risk from compatibility of the drug and the pharmaceutical packaging.

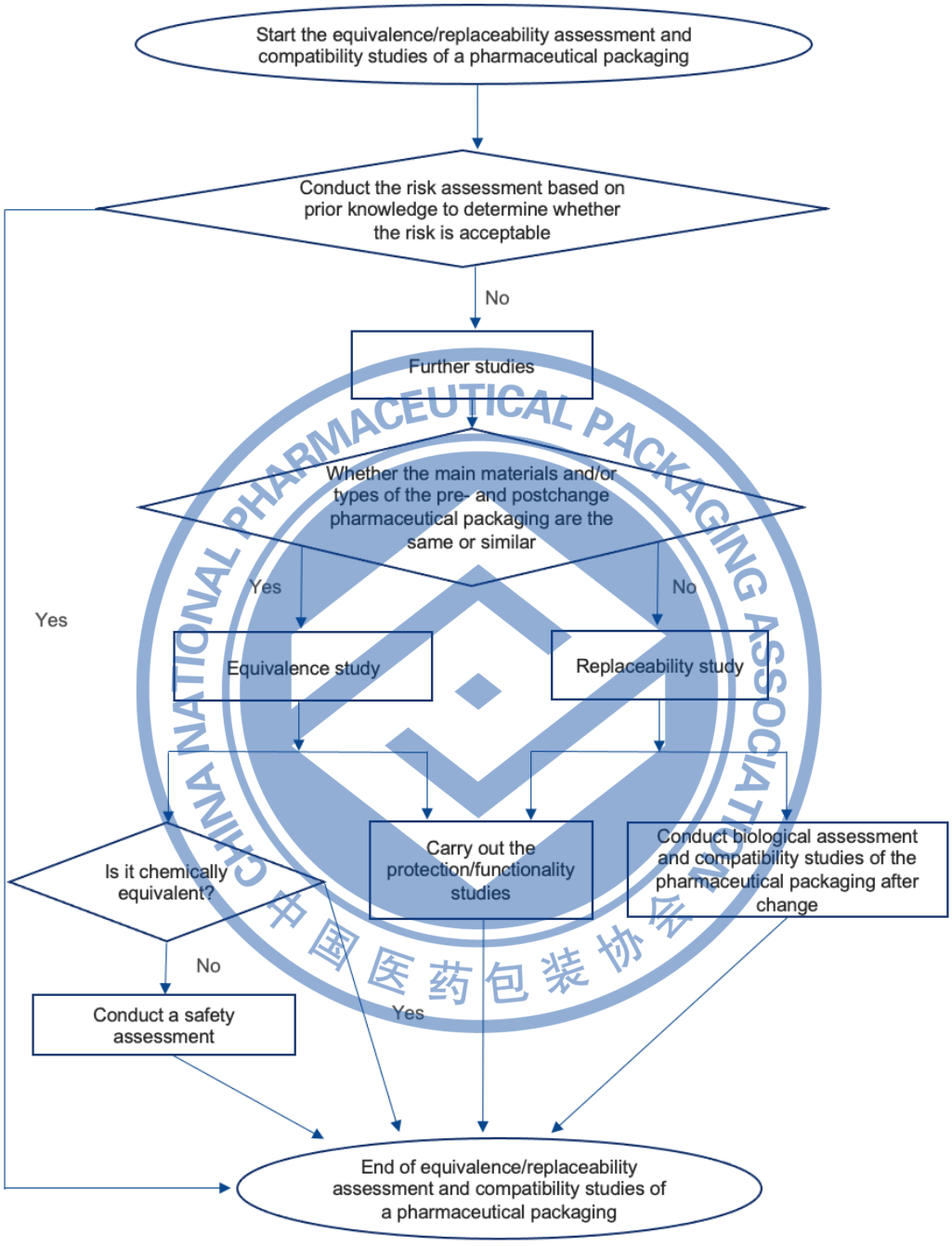
5.2.2. The material and/or type of pharmaceutical packaging are changed

A comprehensive compatibility study should be carried out per relevant guidelines to determine the acceptability of the risk from compatibility after the change.

6. Results and applications of equivalence/replaceability assessment and compatibility studies of pharmaceutical packages

The equivalence/replaceability assessment and compatibility studies of pharmaceutical packages are important studies when the pharmaceutical packaging materials and containers are changed post approval. For different types of changes to the pharmaceutical packaging, the studies and assessment required can be different. The Marketing Authorization Holder (MAH) /pharmaceutical manufacturer should carry out studies on the change of pharmaceutical packaging in accordance with the relevant guidance such as “Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)”, for instances, compatibility studies, packaging process verification, quality comparison studies, stability comparison studies, etc., to comprehensively evaluate whether it is acceptable for the postapproval changes of the packaging materials and containers.

Appendix 1 Flow Diagram of Equivalence/Replicability Assessment and Compatibility Studies of Pharmaceutical Packages



Appendix 2 Common Changes of Pharmaceutical Packages

(Informational appendix)

1. (I) Minor Changes

(1) Changing the packaged content of a drug substance or a drug product in a single-dose container, e.g., number of grams per pouch, number of capsules per sheet, number of injection vials per box, etc.

(2) Changing the materials of construction and/or types of packaging materials and containers for drug substances and nonsterile solid drug products not specified in the moderate change and major changes in this guideline. The post-change packaging materials and containers have been used in marketed drugs with the same route of administration and have the same or better applicability.

(3) Changing suppliers, sizes and/or shapes of packaging materials and containers not specified in the moderate change and major changes in this guideline.

2. (II) Moderate Changes

(1) Changing the packaged content of a drug product in a multi-dose container, e.g., number of tablets per bottle, number of grams per vial, number of milliliters per vial, etc.

(2) Changing materials of construction and/or types of packaging materials and containers for liquid/semi-solid drug products (except inhaled preparations, injections, ophthalmic preparations, etc.), sterile and/or liquid drug substances, e.g., changing from polypropylene bottles for oral liquid preparations to polyester bottles for oral liquid preparations.

(3) Changing materials of construction and/or types of packaging materials and containers for nonsterile solid drug products in the following circumstances, e.g., changes among blisters, bottles and pouches; a change from double aluminum blisters to aluminum-plastic blisters, etc.

(4) Changing suppliers, sizes and/or shapes of packaging materials and containers for injections.

3. (III) Major Changes

(1) Changing materials of construction and/or types of packaging materials and containers for inhaled preparations, injections, ophthalmic preparations, etc., e.g., changing from three-layer coextrusion infusion bags to five-layer coextrusion infusion bags, from polypropylene infusion bottles to upright polypropylene infusion bags, from soda lime glass infusion bottles to five-layer co-extrusion infusion bags.

(2) Changing the supplier, size and/or shape of a metered-dose inhaler.

(3) Deleting the secondary package that provides additional drug production (e.g., high-barrier outer bag).

(4) Changing to new-purpose packaging materials and containers of novel materials of construction, novel structures, and increased risks.

(5) Changing packaging materials and containers included into registration management, where the postchange packaging materials and containers have not been registered or the registration status is I.

4. Technical changes in the manufacture process of pharmaceutical packaging

(1) Change of manufacture site. Including site changes due to relocation/reconstruction and expansion, manufacture technology transfer/contracted manufacturing, enterprise mergers and reorganizations, etc.

(2) Changes in raw materials and formulations. Including changes in major raw material manufacturers; changes in brands of main raw polymer; changes in major additive manufacturers; changes in dosage ratios, etc.

(3) Changes in production technology and process control. Including process changes (such as injection molding/extrusion); process changes in key processing steps; changes in sterilization process; changes in main production equipment; changes in main inspection equipment; starting materials, additives used in the production process that are in direct contact with the product, Changes in materials such as cleaning agents; changes in online automatic detection methods and frequencies; changes in quality control of semi-finished products, etc.

(4) Changes in quality standards. Including changes in the scope of use, specifications, and dimensions of the product; changes in physical and chemical properties and their test methods; changes

in biological properties and their test methods; changes in the period of use and the basis for determination, etc.

(5) Product packaging changes. Including changes in packaging materials and packaging styles used for packaging pharmaceutical packages.

(6) Other technical changes that may affect the quality of pharmaceutical packaging and their expected applicability.

Note: The above-mentioned common changes are quoted from the " Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)" and "T/CNPPA 3009-2020 Technical Guidelines for the Study of Changes in Pharmaceutical Packaging Materials"

References

[1] CDE, Technical Guiding Principle for Pharmaceutical Change Study of Marketed Drugs (exposure draft)

[2] T/CNPPA 3009-2020 Technical Guidance of Change Study of Pharmaceutical Package

[3] Guidance for Industry Changes to an Approved NDA or ANDA, FDA, 2004

[4] Biological evaluation of medical devices —Part 18: Chemical characterization of medical device materials within a risk management process

[5] Technical Guidance of Compatibility Study of Parenteral Chemical Drug Products and Plastic Packaging Materials

[6] Technical Guidance of Compatibility Study of Parenteral Chemical Drug Products and Pharmaceutical Glass Packaging

[7] Technical Guidance for Compatibility Study of Chemical Drugs and Elastomeric Seals

[8] USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

[9] USP <1664> Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems

[10] ISO 10993.1-2018 Biological evaluation of medical devices —Part 1: Evaluation and testing within a risk management process

[11] ICH Q3D Guideline for elemental impurities