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# Guidance of Equivalence Assessment for Pharmaceutical Package

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# Guidance of Equivalence Assessment for Pharmaceutical Package

## 1. Scope of Application

Based on the concept of quality risk management, this guidance is provided for assessment of equivalence/substitutability (hereinafter referred to as equivalence) of pharmaceutical package (pharmaceutical packaging system and components). The guidance of equivalence assessment for pharmaceutical package is mainly used for assessment of changes in the packaging materials and containers for the marketed drugs or pharmaceuticals by the pharmaceutical approval/registration number holder (drug marketing authorization holder or drug manufacturer) [1] or technical changes in the manufacturing process by the pharmaceutical package manufacturer [2], and for verification and confirmation of quality equivalence of pharmaceutical package before and after change.

The guidance is expected to be used for technical assessment in relation to changes of pharmaceutical package. As a technical instrument, the guidance provides the principles of pairwise comparison and equivalence judgment, which may be used for reference of other pairwise comparison study in relation to pharmaceutical package, such as the study on the effect of pharmaceutical package on drug quality consistency among drug consistency evaluation.

## 2. Terminology

2.1 Equivalence of pharmaceutical package: It refers to the consistency of quality characteristics or risk acceptability of pharmaceutical package before and after change of packaging materials and containers of marketed drugs or technical change in the manufacturing process of pharmaceutical package. Quality characteristics of pharmaceutical package include safety, protection, function and compatibility, namely applicability of pharmaceutical package.

**Note 1: Equivalence does not necessarily mean identity. Equivalence comparison is generally within the preset range of comparison standard, namely equivalence is determined if the post-change characteristics meet the preset standard acceptance range.**

2.2 Technical change: Technical change of pharmaceutical package refers to the change that requires for study and verification for subsequent risk evaluation of effect on drugs. In this guidance, technical change of pharmaceutical package includes: change of manufacturing site of pharmaceutical package, change of raw materials and formulation of pharmaceutical package, change of manufacturing process and process control of pharmaceutical package, packaging change of pharmaceutical package, and other changes that may affect quality and expected applicability of pharmaceutical package.

2.3 High-risk pharmaceutical package: It generally includes the pharmaceutical packages for inhalation, injection and ophthalmic preparations new packing materials; new structures and new usages of packaging materials; and the pharmaceutical packages to be supervised as specially required by China Food and Drug Administration.

2.4 Chemical equivalence: It means that there is no change of extractable and leachable profiles, such as increase in numbers and concentrations of extractable chemicals, after

change of pharmaceutical package based on E&L study or in other pairwise comparison study.

2.5 Toxicological equivalence: It means that, based on extractable and leachable study or in other pairwise comparison study, proper toxicological evaluation shows acceptable toxicological risk in compounds of chemical non-equivalence extractables after change of pharmaceutical package.

2.6 Biological equivalence of pharmaceutical package: The assessment result of chemical equivalence or toxicological equivalence of pharmaceutical package is used for exemption of the required biological test.

2.7 Safety assessment of pharmaceutical package: It includes toxicological evaluation of packaging system extract/migration material and relevant matters, in vivo and in vitro biological assessment of material/components, safety assessment of oral solid and liquid preparations with proper additives allowed by food laws and regulations, as well as the evidence and conclusion of adverse effects of packaging components not clinically tracked down if there is clinical evidence.

**3. General**

Based on the concept of risk management, equivalence assessment of pharmaceutical package refers to the assessment of changes of packaging materials and containers of marketed drugs or technical changes of pharmaceutical package in order to reduce unnecessary tests. First, equivalence assessment of pharmaceutical package should be planned in consideration of relevant laws, regulation, technical guidelines/guiding principles, standards and other requirements. Second, internal change management documents of manufacturer formed by risk assessment with relevant risk management standards and instruments are also important reference for equivalence study according to the concept of risk management.

Equivalence assessment herein is a technical instrument for change evaluation or experimental study of pharmaceutical package. However, for certain changes, some specific subjective assessment sourced from the agreement between supplier and customer may be an important process before equivalence assessment of pharmaceutical package. In case of change of appearance or shape and structure of some products, the equivalence assessment procedure can only be entered prior to technical assessment, namely after evaluation is performed and consensus is reached.

Moreover, for material related changes, compliance test or evaluation of materials, such as the evidence of materials or components to be changed conforming to pharmaceutical requirements, is also an important consideration for entry into the equivalence assessment procedure.

3.1 Basic principles of equivalence study of pharmaceutical package

The basic principles of equivalence study of pharmaceutical package include:

1) For any change of pharmaceutical package, the change related risks should be firstly identified, and the content of assessment to be carried out should be determined on the basis of risk identification.

2) As a supplemental and technical instrument for relevant laws, regulations, technical guidelines/guiding principles and standards, equivalence study of pharmaceutical package

describes the technical route expected to be used for evaluation of quality conformance related to applicability (safety, protection, functionality and compatibility) of pharmaceutical package, namely the acceptability meets the intended purpose.

3) Based on the concept of risk management, pairwise comparison of product applicability before and after change is performed on the premise of conformance to mandatory standard or registration standard. Generally, pairwise comparison requires for presetting of the acceptable standard and range in full consideration of the approved product quality standard, internal quality control standard of manufacturer and the assessment result conforming to clinical requirement for the packaged drug.

4) Domestic and foreign accepted modern experimental techniques and assessment concepts, including extractable and leachable study technology, toxicological risk evaluation concept, biological assessment concept under the risk management framework, are fully utilized to reduce the repeated and unnecessary tests on the basis of scientific assessment and risk management.

5) In drug quality risk management activities, other pharmaceutical package related drug quality equivalence assessment, as a technical instrument, is performed based on the above-mentioned principle of pairwise comparison.

3.2 Main content of equivalence assessment of pharmaceutical package

If applicable, main content of equivalence assessment of pharmaceutical package includes:

1) Equivalence assessment based on risk identification and/or key protective characteristics as confirmed in regulatory documents;

2) Equivalence assessment based on risk identification and/or key functional characteristics as confirmed in regulatory documents;

3) Other applicability assessment based on risk identification and/or regulatory documents, such as assessment of important characteristics of material;

4) Change-related biological assessment based on risk identification and/or regulatory documents, and biological equivalence assessment in case of consistent type of main material of the changed pharmaceutical package (such as plastic, rubber, glass and metal);

5) Change-related compatibility study of package and drug or extract study based on risk identification and/or regulatory documents, and equivalence assessment of extractable profile in case of consistent type of main material of the changed pharmaceutical package (such as plastic, rubber, glass and metal);

The reference flow process diagram of equivalence assessment of pharmaceutical package is provided in Appendix 2.

## 4. Equivalence Assessment of Pharmaceutical Package

As a technical instrument, equivalence assessment of pharmaceutical package is applied to study and verification based on risk identification and/or regulatory documents. If applicable, these studies and verification generally include the above-mentioned equivalence assessment of key protective characteristics, equivalence assessment of key functional characteristics, equivalence assessment of other applicable quality characteristics, biological equivalence assessment and compatibility related equivalence assessment.

4.1 Equivalence assessment and judgment principle for protective characteristics of

pharmaceutical package

Protective characteristics of pharmaceutical package generally refer to packaging system or packaging components used to ensure sufficient protection of quality of preparation prior to the date of expiration. The pharmaceutical package related factors that may lead to quality degradation of preparation within the shelf life generally include: light, solvent loss, contact with reactive gas (such as oxygen) and invasion of alien microbes etc.

In equivalence study of pharmaceutical package, the corresponding key protective characteristics include but not limited to: integrity of packaging system, barrier property of packaging system or components, and light resistance of light-resistant pharmaceutical package. The key characteristics should be identified and confirmed based on relevance of various changes.

Generally, most protective characteristics are already covered by the quality standard for pharmaceutical package and are tested in case of change of pharmaceutical package. Standard conformance is the basic principle for equivalence judgment of protective characteristics. Nevertheless, in change study, identification of key protective characteristics, application of the principle of pairwise comparison on the basis of standard conformance and comparison of verification results may help further understanding difference or variation trend of the key characteristics before and after change. Secondly, if applicable, the demonstrated and evaluated internal quality control standard of manufacturer as required for clinical application of the packaged drug is also one of the judgment criteria of equivalence.

4.2 Equivalence assessment and judgment principle for functional characteristics of pharmaceutical package

Functional characteristics of pharmaceutical package generally refer to the ability to function as designed, including drug delivery and use that are assessed as per the intended purpose. Besides, functional characteristics of pharmaceutical package include some special designs for specific intended purpose, such as multi-chamber bag, functional adsorption package, child-resistant package and auto-disable package for prevention of repeated use.

In equivalence study of pharmaceutical package, the corresponding key functional characteristics may include: dosing accuracy related characteristics, penetration resistance and sealing performance in the use process. For the specially designed pharmaceutical package, it is required to consider the key characteristics required for the design expectation, such as dry joint related characteristics of multi-chamber bag. As described above, the characteristics are generally covered by the quality standard for pharmaceutical package and are tested in case of change of pharmaceutical package. The key characteristics should be identified and confirmed based on relevance of various changes.

Standard conformance is the basic principle for equivalence judgment of functional characteristics. Nevertheless, in change study, identification of the key characteristics and comparison of verification results on the basis of standard conformance may help further understanding difference or variation trend of the key characteristics before and after change. Meanwhile, if applicable, the demonstrated and evaluated internal quality control standard of manufacturer as required for clinical application of the packaged drug is also

one of the judgment criteria of equivalence.

4.3 Equivalence assessment and judgment principle for other applicable quality characteristics of pharmaceutical package

For packaging components of some materials, change may trigger assessment closely related to material characteristics or process, such as water resistance assessment of glass package, corrosion resistance assessment of metal package and fastness assessment of coating.

Standard conformance is the basic principle for equivalence judgment of these quality characteristics. If not covered by product quality standard, the quality characteristics should be conforming to the demonstrated acceptance standard. On the basis of conformance to the aforesaid standard, pairwise comparison of the verification results may help further understanding difference or variation trend of the key characteristics before and after change. If applicable, the demonstrated and evaluated internal quality control standard of manufacturer as required for clinical application of the packaged drug is also one of the judgment criteria of equivalence.

4.4 Safety-related equivalence assessment and judgment principle for pharmaceutical package

When safety-related assessment of pharmaceutical package is triggered by a change, content of the required assessment generally includes: in vivo and in vitro biological assessment of material/component, toxicological evaluation of packaging system extractable and leachable material and relevant matters.

For safety-related equivalence assessment of pharmaceutical package, it is suggested to collect technical information in relation to a change, biological assessment and compatibility study, and collect and evaluate historical research data prior to experimental study. If evaluation and demonstration show that new test is not required, the equivalence study and assessment report may be formed, and the change be accepted.

**Note 2: For most of non-high-risk pharmaceutical packages, the compatibility/biological assessment related equivalence study may not be required if the drug formulation does not have special characteristics (such as acid-base properties and lipid solubility) relative to the package used.**

4.4.1 Biological equivalence assessment method and judgment principle for pharmaceutical package

Biological assessment is an important part of safety assessment of pharmaceutical package. Certain changes of pharmaceutical package may relate to biological assessment or test. It should be noted that, in practice of biological assessment, biological equivalence assessment is one of the important applied techniques aimed to reduce animal test.

The reference standards for biological assessment or test of pharmaceutical package include: USP <87> Biological Reactivity Tests, In Vitro, USP <88> Biological Reactivity Tests, In Vivo, ISO 10993 (GB 16886) standards for biological evaluation of medical devices, and relevant general rules/guidance principles in Chinese Pharmacopoeia 2020.

For high-risk pharmaceutical package of polymer material, proper endpoints of biological assessment should generally be considered based on clinical contact property of the packaged drug. Meanwhile, proper extraction and leaching solvent and parameters should be selected for biological assessment or test of the packaging material or components

according to formulation and process characteristics of the packaged drug.

For change assessment of pharmaceutical package, biological equivalence assessment procedures of pharmaceutical package include:

1) The method of extractable and leachable comparison of pharmaceutical packaging material or components is used for assessment of chemical equivalence before and after change on the basis of relevant information collected.

2) In vitro cytotoxicity test is performed and exemption of the required biological test is considered on the basis of chemical equivalence.

3) Qualitative and quantitative analysis of non-equivalent extractable is performed for the extractable profile where chemical equivalence is not determined.

4) If possible, relevant toxicological risk evaluation is performed according to clinical use characteristics of the drug to be packaged for judgment of toxicological equivalence.

For certain changes, such as technical change by pharmaceutical package manufacturer, as most high-risk pharmaceutical packages are actually used for drugs with different formulation characteristics and diversity of clinical application of drugs may hinder toxicological risk evaluation of extractable based on clinical use characteristics of specific drug, especially the dosage characteristic, the worst-case assumption of non-chemically equivalent extractable, such as the assumption that all compounds extracted under the demonstration conditions are released into human body within 24h, is adopted for toxicological equivalence assessment. Otherwise, the assessment may be performed by the drug manufacturer according to clinical contact characteristics of the packaged drug.

As an optional instrument of biological risk assessment for reducing unnecessary animal test, biological equivalence assessment is generally used for evaluation of high-risk pharmaceutical packages.

**Note 3: For glass, even of high-risk variety, biological test or assessment is generally not used for safety evaluation. For metal materials, special attention should be paid to the selected and verified metal material designation and its corrosion resistance during processing and expected use. For new materials, process and coating products with safety application history of exposure route of the same or higher risk, biological assessment may be performed in reference to the above procedure if required.**

The judgment principles of chemical equivalence and toxicological equivalence are detailed in “Appendix 1 Judgment Principles of Chemical Equivalence and Toxicological Equivalence”.

4.4.2 Equivalence assessment and judgment principle for compatibility study of pharmaceutical package and drugs

The reference guidelines for compatibility study of pharmaceutical package and drugs include: the “technical guidance for compatibility study of chemical injection and plastic packaging materials”, the “technical guidance for compatibility study of chemical injection and glass packaging materials” and the “technical guidance for compatibility study of chemical drugs and Elastomeric Seals” issued by NMPA, USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and USP <1664> Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems. In the above guidelines, compatibility study of pharmaceutical package includes extractable study and leachable study, meanwhile, the extractable and leachable study

results require for the corresponding toxicological risk assessment for compatibility related safety assessment.

Some changes of pharmaceutical package may trigger risk re-evaluation of compatibility study, especially re-evaluation of extractable profile. Equivalence assessment procedures of drug compatibility study include:

1) For high-risk pharmaceutical package, proper extraction solvent and parameters are generally selected based on prescription and process characteristics of the drug to be packaged if possible for pairwise comparison of extractable spectrum of pharmaceutical packaging material or component and for assessment of chemical equivalence before and after change.

2) On the premise of chemical equivalence, in vitro cytotoxicity test is performed, and exemption of the required toxicological risk evaluation of extractable is considered.

3) During equivalence study of extractable profile by the drug manufacturer, equivalence study of the simulated extractable profile is performed and chemical equivalence before and after change is evaluated if possible.

4) Where chemical equivalence of extractable profile/simulated extractable profile is not determined, qualitative and quantitative analysis of non-equivalent extractable is performed.

5) If possible, relevant toxicological risk evaluation is performed based on clinical use characteristics of the drug to be packaged for judgment of toxicological equivalence.

Similarly, under certain conditions, such as technical change by pharmaceutical package manufacturer, toxicological risk evaluation of extractable is performed as most high-risk pharmaceutical packages are actually used for drugs with different formulation characteristics and diversity of clinical application of drugs may hinder toxicological risk evaluation of extractable based on clinical use characteristics of specific drug, especially the dosage characteristic. If required, the worst-case assumption of non-chemically equivalent extractables, such as the assumption that all compounds extracted under the demonstration conditions are released into human body within 24h, is adopted for toxicological equivalence assessment. Otherwise, the assessment may be performed by the drug manufacturer according to clinical contact characteristics of the packaged drug.

6) For drug manufacturer, if toxicological equivalence is not determined based on the above extractable study result, further leachable and its toxicological evaluation may be performed to judge whether the risk of actual leachable of the packaged drug is acceptable.

The judgment principles of chemical equivalence and toxicological equivalence are detailed in “Appendix 1 Judgment Principles of Chemical Equivalence and Toxicological Equivalence”.

4.5 Post-change standard conformance test of pharmaceutical package

After the above applicable equivalence study and other required change study, standard conformance test of the pharmaceutical package to be changed is performed according to the approved standard. Under the circumstance that a change may simultaneously related to change of quality standard for pharmaceutical package, the quality standard to be adopted for the proposed change should be demonstrated and verified.

## 5. Result and Application of Equivalence Assessment of Pharmaceutical Package

Equivalence assessment of pharmaceutical package is an important part of the change assessment performed in case of change of packaging material and container or technical change by pharmaceutical package manufacturer in the manufacturing process. The equivalence assessment described herein may not cover all content of assessment as required for certain change of pharmaceutical package; therefore, the assessment/study result formed hereunder should be used together with other study results for determining whether to accept a proposed change of pharmaceutical package in full consideration of risk management requirements and clinical expectations.

In practice, other verification items required by relevant technical laws and regulations and/or confirmed by risk identification, and if applicable, the required process verification result and stability verification result of the packaged drug should be used for completing the final change assessment and drawing the conclusion whether the assessment is accepted.

## Appendix 1 Judgment Principles of Chemical Equivalence and Toxicological Equivalence

1. General Judgment Principles of Chemical Equivalence

The samples subject to change or pairwise comparison are to be taken under the demonstrated condition, and difference in the extractable profile is compared for peaks higher than the analytical evaluation threshold (AET); there should be no redundant peak in the extractable profile of post-change samples or peak of rising area [note 2].

**Note 4: Chemical equivalence may be determined despite of slight increase of compound peak area as properly justified. If the method of semi-quantitative analysis is used for statistical evaluation of variation, the demonstration should be based on the degree of slight increase of compound peak area.**

2. General Judgment Principles of Toxicological Equivalence

2.1 In the above-mentioned principle, a pharmaceutical package with chemical equivalence as confirmed by assessment will be simultaneously deemed as having toxicological equivalence.

2.2 For a pharmaceutical package without chemical equivalence as conformed by assessment in the above principle, the identified non-chemically equivalent extractable/leachable will be subject to toxicological risk evaluation according to relevant guidance or standard, and the package will be deemed as having toxicological equivalence if such toxicological risk is acceptable [note 3].

**Note 5: In case of chemical inequivalence, toxicological evaluation may discover local biological reaction of the compound, such as irritative reaction, which is to be surveyed according to relevant standard or guidance and clinical contact nature of pharmaceutical package (such as ophthalmic preparation, damaged skin and ointment preparation for mucosa application), or the acceptable limit of irritation should be derived by toxicological risk evaluation; otherwise, the required irritation test should be carried out.**

As a feasible technical instrument, chemical equivalence and toxicological equivalence assessment can be used for prediction of safety related risks in the early stage of change assessment, besides for exempting unnecessary animal test and reducing the workload of qualitative and quantitative analysis of compatibility study and re-assessment and toxicological evaluation.

Study and judgment of chemical equivalence and toxicological equivalence should be performed by the experienced chemist and toxicologist.

## Appendix 2 Flow Process Diagram of Equivalence Assessment of Pharmaceutical Package

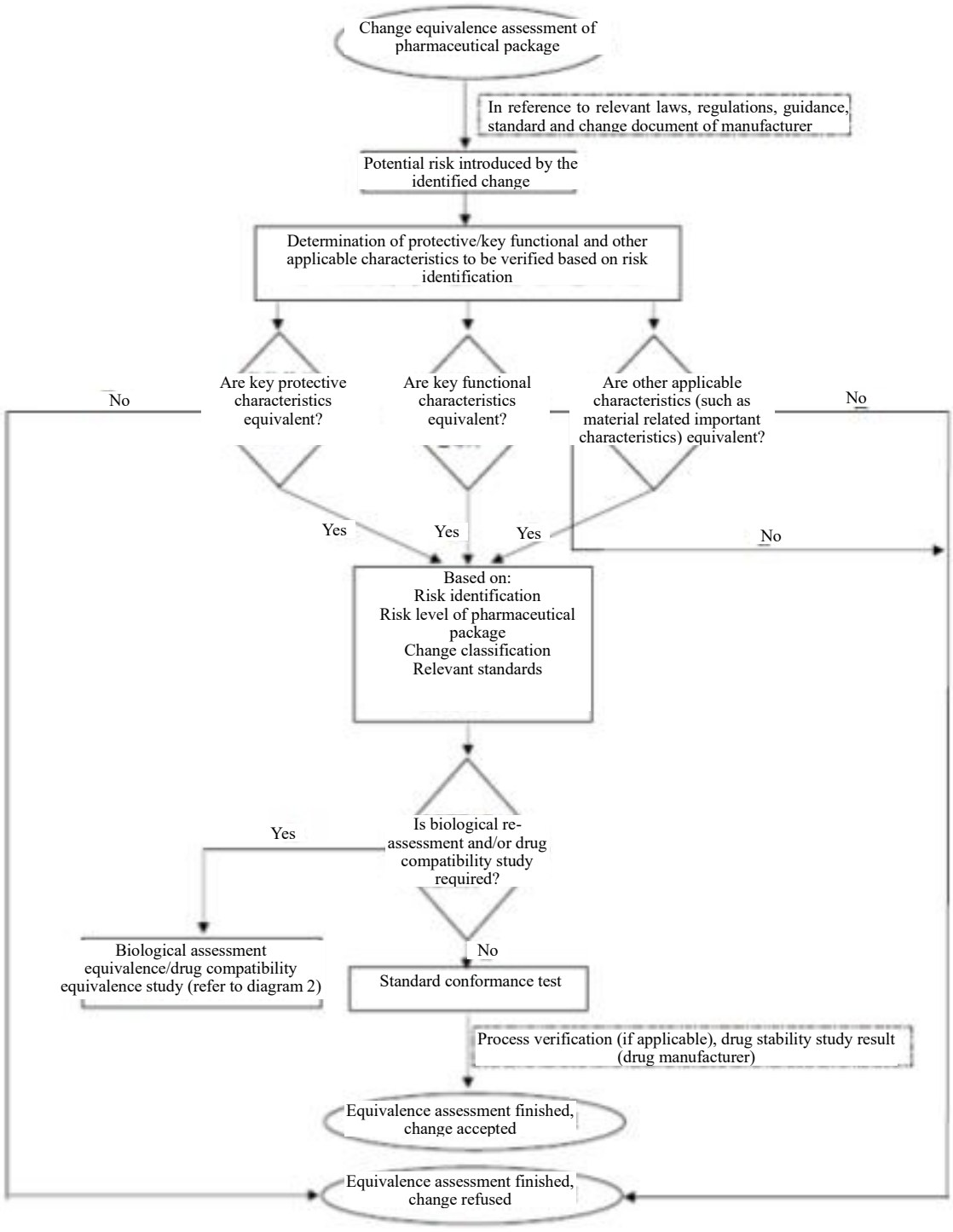


**Diagram 1 Flow process of equivalence assessment of pharmaceutical package**

1. In most cases, the extraction parameters for biological assessment and drug compatibility study may be shared or stricter parameters be used.
2. In vitro cytotoxicity test and local irritative reaction evaluation are generally required.

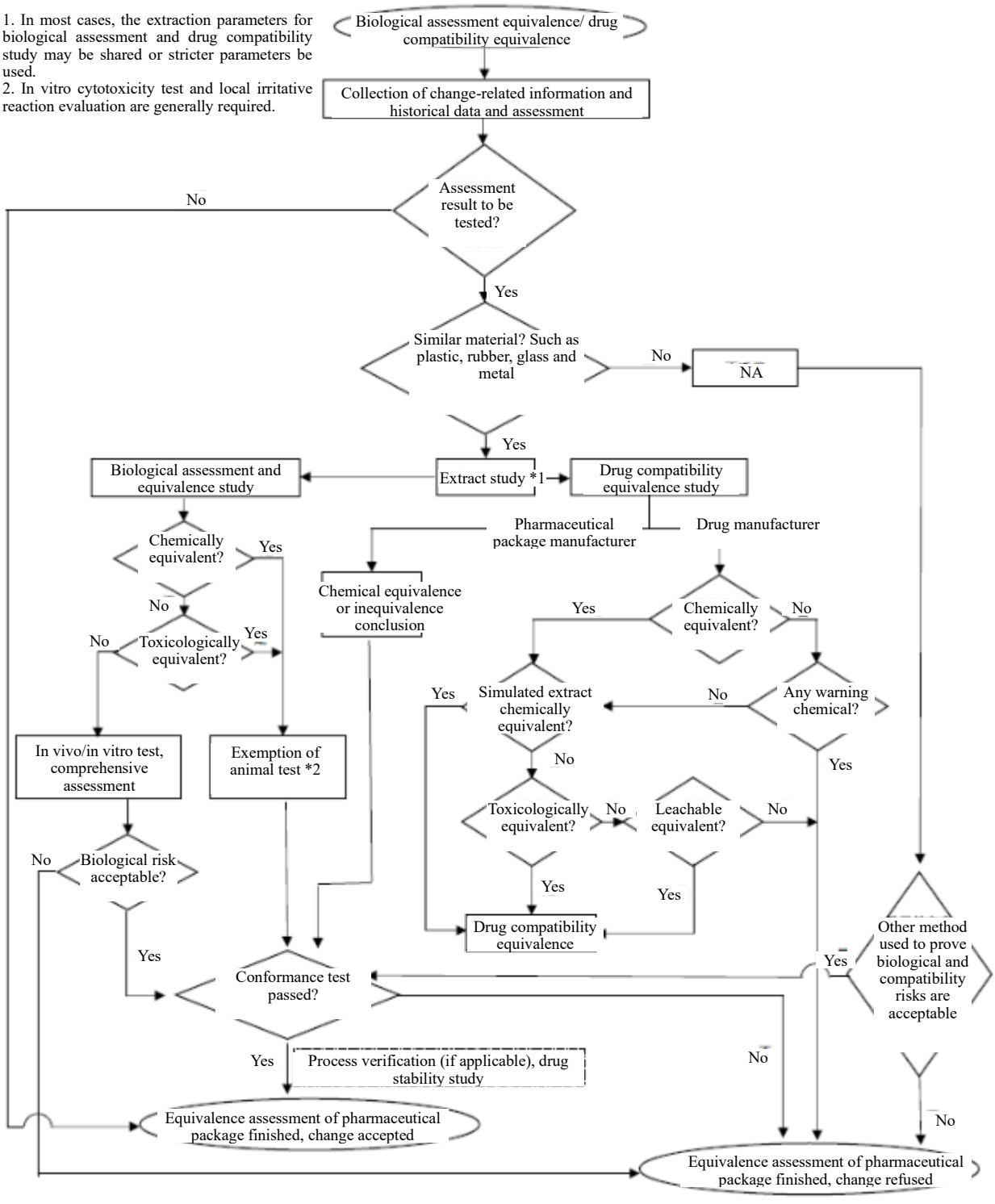


**Diagram 2 Flow Process of Biological Assessment Equivalence/Drug Compatibility Equivalence Study**

**References**

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