ICS 11.120
CCS C 04

CNPPA

Social Organization Standard

T/CNPPA 3009-2020

Technical Guidance for Research on Changes of Pharmaceutical Packaging

Issued on 2020-05-29 Effective on 2020-05-29

Issued by China National Pharmaceutical Packaging Association

Table of Contents

1 General Provisions

This guidance is mainly used to guide pharmaceutical packaging registrants to carry out corresponding research on changes of pharmaceutical packaging in the process of production, and to assess the research results for the reference of drug marketing authorization holders.

The research conducted by the pharmaceutical packaging registrant in accordance with this guidance cannot substitute for the research conducted by the drug marketing authorization holder to assess the impact of the changes of pharmaceutical packaging on the quality of drugs. Drug marketing authorization holders should conduct corresponding research in accordance with relevant technical guidelines to comprehensively assess and verify the impact of change items on the safety, effectiveness and quality controllability of the drug.

The pharmaceutical packaging products in this guidance refer to products with the same or similar production process and materials and the same or similar functions, including different models and specifications. According to different processing stages, they can be divided into packaging materials, packaging components, and packaging systems.

The changes of pharmaceutical packaging in this guidance refers to the changes of the APIs and excipients, production process, quality standards and other aspects of the marketed pharmaceutical packaging products in the process of production. Change research refers to the research and verification for the proposed changes.

Due to the universality and diversity of pharmaceutical packaging products, and the complexity of changes, this guidance may not be applicable to all pharmaceutical packaging products and changes. The pharmaceutical packaging registrant can refer to this guidance to study and assess the relevant changes of pharmaceutical packaging according to the principle of risk assessment.

The changes of pharmaceutical packaging and the research on changes should be based on the previous registration of pharmaceutical packaging and the research and data accumulation in the actual process of production. The registrant can also carry out change research on the basis of continuous in-depth understanding of the pharmaceutical packaging, their processes, and quality control, to continuously improve and innovate the marketed pharmaceutical packaging.

2 Change Items and Change Contents

Changes of pharmaceutical packaging are divided into non-technical changes and technical changes.

2.1 Non-technical Changes

The change items (1) to (4) are non-technical changes, mainly including the changes of registration information of pharmaceutical packaging. The common non-technical change items [1] are:

(1) Changes of name of pharmaceutical packaging enterprise, registered address and production address;

(2) Changes of enterprise' certification documents;

(3) Changes of address for storing research data;

(4) Changes of domestic agent of imported pharmaceutical packaging.

2.2 Technical Changes

The change items (5) to (10) are technical changes, mainly including the changes of production address, formula and process, quality standards, etc. The common technical change items are:

(5) Changes of production sites, including site changes caused by relocation/reconstruction and expansion, production process transfer/sub-contract production, enterprise merger and reorganization, etc.

(6) Changes of raw materials and formulas, including changes of major raw material manufacturers, changes of major raw material polymer grade; changes of major additive manufacturers; changes of dosage ratios, etc.

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

(8) Changes of quality standards, including changes of the scope of use/specifications of the product; changes of physical and chemical properties and their test methods; changes of biological properties and their test methods; changes of service life and its basis of determination; etc.

(9) Changes of product packaging, including changes of packaging materials and packaging types used to package pharmaceutical packaging products.

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

3 Research on Technical Changes

The pharmaceutical packaging registrant shall determine the research protocols and items and conducts research and verification according to the risk category (high-risk and non-high-risk) and change items of the product, and adjusts the research contents and protocols according to the research results if necessary. The pharmaceutical packaging registrant shall make records of changes and manage the documents to ensure that the data of the change research is complete, accurate, true and traceable.

3.1 Basis of Change Research

When determining the research contents and protocols, the following three factors shall be considered:

(1) Reasons and basis for the changes: you can refer to the retrieval and analysis of literature materials;

(2) Possible impact on the quality of pharmaceutical packaging products: including the selection basis of quality standards, inspection items, and comparative studies of relevant inspection data, etc.;

(3) Possible impact on the expected applicability of the packaging system (including components): applicability includes protectiveness, compatibility, safety, and functionality [2].

a Protectiveness refers to the protective performance of the packaging system for a specific drug to avoid the adverse effects of light, temperature, gas, etc. on the drug during the validity period. Pharmaceutical packaging enterprises need to focus on investigating the barrier performance of packaging materials/components and the sealing performance of packaging systems.

b Compatibility refers to the test process of whether the pharmaceutical packaging interacts with the drug, resulting in migration or adsorption, thus affecting the quality and safety of the drug. Compatibility research includes extractables research and leaching research. You can refer to relevant national technical guidelines for specific research methods and evaluation [3] [4] [5]. Extractable research is mainly conducted by pharmaceutical packaging enterprises.

c Safety refers to that the constituent materials of packaging components shall not produce substances harmful to drugs and patients or excessive substances. Pharmaceutical packaging enterprises can make preliminary judgments by the additive regulations and bioreactivity test data of packaging components/systems.

d Functionality refers to the ability of the packaging system to function according to the expected design, such as satisfying the medication needs of special groups (children, the elderly, the blind, etc.), improving the patient's medication compliance, and the performance of attached drug delivery device.

3.2 Contents of Change Research

Change research usually uses comparative analysis method, including (but not limited to) the following:

(1) Literature search and analysis of reasons for changes;

(2) Comparative analysis of product quality standards, inspection items and inspection data;

(3) Research and comparative analysis of production process and process control, including sterilization (if applicable);

(4) Regulatory compliance of APIs and excipients and additives, such as related additive contents in U.S. CFR21 [6], EP Appendix 3.1 of European Pharmacopoeia [7], etc.;

(5) The impact research and comparative analysis of the stability of packaging materials are generally applicable to polymer materials such as plastics and rubber, which can be carried out according to relevant technical guidelines;

(6) Research and comparative analysis of extractables of packaging materials/components;

(7) Research and comparative analysis of barrier performance of packaging components/systems;

(8) Research and comparative analysis of the integrity of the packaging system;

(9) Research and comparative analysis of functionality of packaging systems;

(10) Other research items that have special requirements or are deemed necessary by regulatory authorities or pharmaceutical enterprises.

4 Comprehensive Assessment

According to the comparative analysis before and after the changes, the pharmaceutical packaging registrant shall conduct a comprehensive assessment of the changes of the pharmaceutical packaging in combination with the drugs that may be packaged. The assessment includes the impact of the changes of pharmaceutical packaging on the quality of the pharmaceutical packaging products and the expected applicability (including protectiveness, compatibility, safety, and functionality) of the packaging system (including components).

The drug marketing authorization holder and pharmaceutical packaging registrant shall, based on the results of research on changes of pharmaceutical packaging and comprehensive assessment, jointly carry out the equivalence evaluation on the changes of pharmaceutical packaging.

In the process of quality activities such as change management of pharmaceutical packaging, the equivalence evaluation of pharmaceutical packaging usually refers to the evaluation process of the consistency of quality attributes before and after the changes of the safety, protectiveness, functionality and compatibility (if applicable) of pharmaceutical packaging products based on the principle of paired comparison through appropriate technical means.

5 Application of Change Research

For the same pharmaceutical packaging, different change items have different impacts on the quality of drugs, and the same change items may not have the same impact on the quality of different drugs.

Drug marketing authorization holder and pharmaceutical packaging registrant should maintain close cooperation, reach an agreement on the classification, change items and research, change procedures and other contents of the changes of pharmaceutical packaging through quality agreement and other ways on the basis of meeting the requirements of laws and regulations, and communicate with each other in a timely manner.

On the basis of the change items, change research and comprehensive assessment provided by the pharmaceutical packaging registrant, the drug marketing authorization holder can study and assess the risks and the extent of impact of the changes of pharmaceutical packaging on the safety, effectiveness and quality controllability of drugs according to the characteristics and requirements of the drugs to be packaged, and classify and declare the changes according to the relevant regulatory documents.

If the AEP and AEP supplier of the marketed pharmaceutical preparations are changed, the research shall be conducted in accordance with the *Technical Guidelines for Research on Changes of Marketed Pharmaceuticals (I)*, *Technical Guidelines for Research on Changes of Production Process of Marketed Pharmaceuticals, Technical Guidelines for Research on Changes of Traditional Chinese Medicine (I)* and the relevant guidelines for research on changes of marketed biological products, and it shall be implemented in accordance with the relevant provisions of the current drug registration regulation.

6 Interpretations of Terms

Pharmaceutical packaging products: refer to products with the same or similar production process and materials and the same or similar functions, including different models and specifications. According to different processing stages, they can be divided into packaging materials, packaging components, and packaging systems.

Changes of pharmaceutical packaging: refer to the changes of the APIs and excipients, production technology, quality standards and other aspects of the marketed pharmaceutical packaging products in the process of production. Change research refers to the research and verification for the proposed changes.

Pharmaceutical packaging registrant: refers to the pharmaceutical packaging supplier who has registered the products held on the designated registration platform and obtained the registration number according to the technical requirements of the registration materials. The pharmaceutical packaging registrant is responsible for maintaining the registration information on the registration platform and is responsible for the authenticity and integrity of the registration materials.

Drug marketing authorization holder: refers to an enterprise or drug research and development institution that has obtained the drug registration certificate. The drug marketing

authorization holder is liable for non-clinical research, clinical trials, production and operation, post-market research, monitoring, reporting and handling of adverse drug reaction according to the law.

Packaging component: refers to any component in the container sealing system. Packaging components are divided into packaging components that directly contact drugs and secondary packaging components. Secondary packaging components refer to the packaging components that are not in direct contact with drugs.

Packaging system: refers to the sum of all packaging components that contain and protect drugs. The packaging system includes packaging components that directly contact the drugs and secondary packaging components. Secondary packaging components have the function of providing additional protection for the drugs.

High-risk pharmaceutical packaging [9]: includes pharmaceutical packaging for inhalation preparations, injections, and ophthalmic preparations; pharmaceutical packaging for new materials, structures and uses; pharmaceutical packaging specially supervised by the China Food and Drug Administration according to the monitoring data.

Stability of packaging materials: is to investigate the regularity of changes with time of packaging materials and containers in direct contact with drugs under the specified temperature and humidity environment, usually including influence factor research, accelerated tests and long-term tests. The research on the stability of pharmaceutical packaging is generally carried out by pharmaceutical packaging manufacturers to confirm the quality stability period of their products under the specified storage conditions. It is an important consideration for pharmaceutical manufacturers to select pharmaceutical packaging for applicability evaluation, and it provides references for pharmaceutical manufacturers to store, transport and use pharmaceutical packaging under specified conditions.

Integrity of packaging system: refers to the ability of the container sealing system to prevent leakage. It means that the packaging system can prevent product loss, prevent the entry of microorganisms, and restrict the entry of gases or other substances, so as to ensure that the products meet all necessary safety and quality standards.

References

1. *Technical Guidelines for Research on Changes of Marketed Pharmaceuticals (I)*, issued on January 2008

2. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics — Chemistry, Manufacturing and Controls Documentation, May 1999

3. *Technical Guidelines for Research on Compatibility of Pharmaceutical Injections and Pharmaceutical Glass Packaging Containers (Trial)*, issued on July 28, 2015

4. *Technical Guidelines for Research on Compatibility of Pharmaceutical Injections and Plastic Packaging Materials (Trial)*, issued on September 07, 2012

5. *Technical Guidelines for Research on Compatibility of Pharmaceuticals and Elastomer Seals (Trial)*, issued on April 26, 2018

6. CFR 21- Code of Federal Regulations

7. Appendix 3.1 "Materials for Packaging Containers", *European Pharmacopoeia*

8. "Assessment of Extractables in Pharmaceutical Packaging/Delivery System" <1663>, *United States Pharmacopoeia*

9. *Announcement of China Food and Drug Administration on Matters Concerning the Associated Review and Approval of Pharmaceutical Packaging, Pharmaceutical Excipients and Drugs (No. 134, 2016)*, issued on August 10, 2016

10. *Announcement of National Medical Products Administration on Issues Concerning the Further Improvement of Drug-related Associated Review & Approval and Supervision (No. 56, 2019)*, issued on July 16, 2019

11. *Provisions for Drug Registration* (Decree No. 27 of State Administration for Market Regulation), issued on March 30, 2020

12. *Provisions for the Supervision and Administration of Drug Production* (Decree No. 28 of State Administration for Market Regulation), issued on March 30, 2020

Table 1

Example Table of Technical Change Items and Change Research Contents of High-risk Pharmaceutical Packaging

Change Items \ Change Research Contents		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
		Literature search and analysis of reasons for changes	Comparative analysis of product quality standards, inspection items and inspection data	Research and comparative analysis of production process and process control	Regulatory compliance of APIs and excipients and additives	Research and comparative analysis of the impact of stability of packaging materials	Research and comparative analysis of extractables of packaging materials/components	Research and comparative analysis of barrier performance of packaging components/systems	Research and comparative analysis of integrity of packaging system	Research and comparative analysis of functionality of packaging systems	Other special or necessary research items
Changes of production sites (5)	Relocation/ reconstruction and expansion	±	+	+	-	-	+	-	-	-	+
	Production process transfer/sub-contract production	±	+	+	-	-	-	-	-	-	+
	Merger and reorganization of enterprises	±	+	-	-	-	-	-	-	-	+
Changes of raw materials and formulas (6)	Changes of major raw material manufacturers	±	+	-	-	+	+	+	-	-	+
	Changes of major raw material polymer grades	±	+	-	+	+	+	+	-	-	+
	Changes of major additive suppliers	±	+	-	-	-	+	-	-	-	+
	Changes of dosage ratios	±	+	+	±	±	+	+	-	-	+
Changes of production process and process control (7)	Changes of production flow (e.g. injection/extrusion)	±	+	+	-	+	+	+	+	+	+
	Changes of key processing steps	±	+	+	-	+	+	+	+	+	+
	Changes of sterilization process	±	+	+	-	+	+	+	+	+	+
	Changes of main production equipment	±	+	+	-	-	-	-	-	-	+

	Changes of main inspection equipment	±	+	-	-	-	-	-	-	-	+
	Changes of materials like starting materials, additives and cleaning agents in direct contact with the product used in the production process	±	+	+	-	-	-	-	-	-	+
	Changes of online automatic detection methods and frequencies	±	+	-	-	-	-	-	-	-	+
	Changes of semi-finished product quality control	±	+	-	-	-	-	-	-	-	+
Changes of quality standards (8)	Changes of scope of use/specifications & sizes of the product	±	+	-	-	-	-	-	±	±	+
	Changes of physical and chemical properties and their test methods	±	+	-	-	±	±	±	-	-	+
	Changes of biological properties and their test methods	±	+	±	-	-	-	-	-	-	+
	Changes of service life and its basis of determination	±	+	-	-	±	-	-	-	-	+
Changes of product packaging (9)	Changes of packaging materials and packaging forms	±	+	±	-	+	+	-	+	+	+
Other technical changes that may		±	+	±	±	±	±	±	±	±	+

affect the quality of pharmaceutical packaging and their expected applicability (10)										

Note: 1. "+" represents the need for research, if not applicable, the reasons shall be given; "-" represents the exemption from research; "±" represents whether to do research according to the specific circumstances.

2. The research to be carried out in the above table is the basic research items. Due to the different contents of the changes and the application of the preparation as well as the preliminary research results, additional item research may be required and then re-assessment.
3. * Changes of product specifications refers to changes of specifications (sizes) with the same materials and same process conditions. If the process is different (such as the amount of film coating), the research shall be carried out with reference to the changes of technological process.

Table 2

Example Table of Technical Change Items and Change Research Contents of Non-high-risk Pharmaceutical Packaging

Change Items \ Change Research Contents		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
		Literature search and analysis of reasons for changes	Comparative analysis of product quality standards, inspection items and inspection data	Research and comparative analysis of production process and process control	Regulatory compliance of APIs and excipients and additives	Research and comparative analysis of the impact of stability of packaging materials	Research and comparative analysis of extractables of packaging materials/components	Research and comparative analysis of barrier performance of packaging components/systems	Research and comparative analysis of integrity of packaging system	Research and comparative analysis of functionality of packaging systems	Other special or necessary research items
Changes of production sites (5)	Relocation/reconstruction and expansion	±	+	+	-	-	-	-	-	-	+
	Production process transfer/sub-contract production	±	+	+	-	-	-	-	-	-	+
	Merger and reorganization of enterprises	±	+	-	-	-	-	-	-	-	+
Changes of raw materials and formulas (6)	Changes of major raw material manufacturers	±	+	-	-	±	-	-	-	-	+
	Changes of major raw material polymer grades	±	+	-	+	+	-	+	-	-	+
	Changes of major additive suppliers	±	+	-	-	-	-	-	-	-	+
	Changes of dosage ratios	±	+	-	+	+	-	+	-	-	+
	Changes of production flow (e.g. injection/extrusion)	±	+	+	-	-	-	+	±	±	+
	Changes of key processing steps	±	+	+	-	-	-	±	±	±	+
	Changes of main	±	+	+	-	-	-	-	-	-	+

	production equipment										
	Changes of online automatic detection methods and frequencies	±	+	±	-	-	-	-	-	-	+
Changes of quality standards (8)	Changes of scope of use/specifications*sizes of the product	±	+	-	-	-	-	-	±	±	+
	Changes of physical and chemical properties and their test methods	±	+	-	-	-	-	-	-	-	+
	Changes of biological properties and their test methods	±	+	-	-	-	-	-	-	-	+
	Changes of service life and its basis of determination	±	+	-	-	+	-	-	-	-	+
Changes of product packaging (9)	Changes of packaging materials and packaging forms	±	+	-	-	-	-	-	-	+	+
Other technical changes that may affect the quality of pharmaceutical packaging and their expected applicability (10)		±	+	±	±	±	±	±	±	±	+

Note: 1. "+" represents the need for research, "-" represents the exemption from research; "±" represents whether to do research according to the specific circumstances.

2. The research to be carried out in the above table is the basic research items. Due to the different contents of the changes and characteristics of drugs to be packaged as well as the preliminary research results, more research may be needed.

3. * Changes of product specifications refers to changes of specifications (sizes) with the same materials and same process conditions. If the process is different (such as the amount of film coating), the research shall be carried out with reference to the "Changes of technological process".