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Study guideline of laminated film/bag for single-dose oral solution

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Content

Foreword

This Standard is drafted in accordance with the rules listed in GB/T 1.1-2020 Directives for Standardization - Part 1: Rules for The Structure and Drafting of Standardizing Documents.

Please be aware that some contents in this standard may be patentable. China National Pharmaceutical Packaging Association shall not be held responsible for identifying any or all such patent rights.

This Standard was proposed by and is under the jurisdiction of China National Pharmaceutical Packaging Association.

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Introduction

Oral liquid dose includes oral solution, oral suspension, oral emulsion, syrup, mixture, liquor etc. The common packaging format for oral liquid dose includes glass bottle, plastic bottle, laminated sheet and laminated film/bag.

Oral liquid dose packaging can be classified as multiple-dose packaging or single- dose packaging due to packaging formats. Laminated film/bag usually applies to single- dose packaging of oral liquid dose. Generally, the volume of single-dose packaging is no more than 30ml. Laminated film/bag with different structure/component or other packaging format is allowed according to the specification and requirements of oral liquid dose. This guideline suggests that the administration route of oral liquid dose has low risk, but the possibility of interacting between oral liquid dose and packaging is significant.

Single-dose laminated film/bag provides some benefits of accurate dosage, non-antibacterial agent added formula, lower contamination risks for oral liquid dose. It also contains some convenient performances such as storage, transportation, and easy open. Generally laminated film/bag packaging can do prior printing so as to reduce the migration risk in using adhesive sticker from external labels.

Laminated film/bag of single-dose oral liquid should be selected based on well scientific principle. Necessary research content, test method and quality acceptance criteria should be determined based on the laminated film/bag with different structures and compositions, and the content of to-be-packaged oral liquid dose. The stability and uniformity during different batches of laminated film/bag should be guaranteed.

Specific test method or quality acceptance criteria (except for the quoted methods in China Pharmacopeia) or testing list is not provided in this guideline. These details should be determined according to the specific pharmaceutic dose form and administration route of specific container/packaging system. Meanwhile, the quality acceptance criteria should be formulated according to the specific component of package and container packaging system.

This guideline may not cover all kinds of oral liquid dose, interested parties should conduct analysis as well as verification and research work in actual condition. This guideline is complied with existing regulations, standard system and current cognitive level. Relevant content will be adjusted appropriately while regulations and standards are improved continuously along with the development of science and technology. It is not including the administration matter of registration and approval, so it must not be

referred as a regulation and should be used on the premise of relevant regulations.

Study guideline of laminated film/bag for single-dose oral solution

1 Scope

This guideline provides the selection principle of laminated film/bag for single-dose oral liquid (hereinafter referred to as laminated film/bag), which also includes the research on conformity (compliance), applicability, compatibility, functionality, stability, quality standard and other influential factors.

This guideline applies to the package selection of laminated film/bag for single-dose oral liquid. And it also refers as a guidance for pharmaceutical license holders to conduct relevant validation and research work. Pharmaceutical license holders can refer to this guideline when they select multiple-dose laminated film/bag for oral liquid dose.

2 Normative References

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

GB 9685 National Food Safety Standard - Using Standard of Food Contact Materials and Articles Additives

GB/T 17313 General Specification of Bag Forming, Filling and Sealing Machine

GB 31604.1 National Food Safety Standard - General Rules for Migration Test of Food Contact Materials and Articles

T/CNPPA 3017 Guidelines for Self-stability of Plastic and Rubber Pharmaceutical Packaging

Good Manufacturing Practice (2010 Revision)

Chinese Pharmacopoeia (2020 Version) (Part four)

Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials (Trial)

3 Terminology

3.1 Multiple-dose packaging

Multiple-dose packaging applies to multiple-dose preparation. It is a closure system as a container which the preparation’s safety, dosage, quality or purity is not changed while the remain is taken out.

3.2 Single-dose packaging

Single-dose packaging applies to single-dose preparation for single patient. It is a closure system with an opening feature for only once dose taken.

3.3 Laminated film/bag

A closure system of bag in end format, one of the common packaging forms for single-dose oral liquid.

3.4 Risk source substance

This kind of substance in the guideline refers to small molecule monomer, additives, auxiliaries and unintentionally added substances (such as degradation product, reaction by-product and impurity) in laminated film/bag which may affect the drug effectivity, safety or quality stability that could cause patient's health.

4 Selection Element

4.1 Overview

Common raw materials of laminated film/bag are listed as following, includes polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), polyamide (PA), aluminum foil (Al), ink, adhesive etc. Material selection and structure design should be conducted according to actual requirements of application.

Laminated film/bag of oral liquid dose should be selected based on the principle of good risk management principle and compliant material and supplier. Following conformity (compliance) requirement and taking full consideration to the characteristics and requirements of oral liquid dose is needed. Laminated film/bag also should meet the requirement of applicability (including protection, safety, compatibility and functionality), function and stability of preparation. It also should clarify the requirements for stable production and quality acceptance criteria, as well as other requirements of influence factors.

4.2 Conformity (Compliance)

Laminated film/bag of single-dose oral liquid should be complied with laws and regulations, as well as the requirement of quality guarantee system and quality agreement.

4.3 Applicability

4.3.1 Overview

In this guideline, applicability study refers to a series of test and research for conformity index which are performed to prove the conformity of proposed laminated film/bag to

expected applications of oral liquid dose, including full protection, material safety, compatibility with preparation and normal function research.

The compatibility of container/encapsulation system and packaging process should correspond to the valid period of oral liquid dose.

4.3.2 Protection

Generally, protection includes below properties.

Sealing property to ensure the result (solvent loss and microbial pollution) could conform to the requirement of preparation.

Barrier property to prevent gas and light.

Satisfying storage and transport conditions under different humidity, temperature and air pressure, such as stack and drop requirement.

Sterilization resistance. When oral liquid dose with sterilized process, the laminated film/bag should have sterilization resistance.

4.3.3 Safety

4.3.3.1 Overview

Safety refers to the study to identify and control the risk source substance. Determining and evaluating the maximum residual amount and/or specific migration amount of the risk source substance should be conducted when necessary.

4.3.3.2 Laminated film/bag is a low-risk pharmaceutical packaging according to the administration route of preparation. Its safety can be evaluated refers to current food contact materials safety evaluation standard (GB9685-2016, GB4806.6, GB4806.7, etc.).

4.3.3.3 Additives used in laminated film/bag should meet medical requirements. It also can refer to GB9685-2016 and supplemented announcement for additive of food contact materials. If materials and additives are not included in relevant standards, they should be considered as new materials and safety evaluation should be conducted.

4.3.3.4 Safety evaluation includes risk source substances identification and authentication, confirming the usage and maximal residual amount, and determining if the maximal migration amount of the risk source substance exceeds the specific migration limit in the regulation.

4.3.3.5 Risk source substance can be identified according to the ingredient of additive in recipe by referring to GB9685-2016 and its supplemented announcement.

Determining the requirement of additive limit, as well as setting and implementing research program, test condition and test method as the test scheme. Evaluate the test result at the same time.

4.3.3.6 If the additive used in laminated film/bag is excluded in GB9685-2016 and its supplemented announcement, material safety evaluation should be conducted further.

4.3.3.7 Make sure to control the safety risk while selecting ink and adhesive. It's better to reduce the ink and adhesive usage when printing and lamination effect is achieved so as to guarantee the drug quality and safety.

4.3.4 Compatibility

Migration risk evaluation of laminated film/bag for oral liquid dose can refer to GB31604.1-2015 to select the migration test condition for study. Compatibility research should be conducted according to Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials (Trial) if it is not applicable.

4.3.5 Functionality

4.3.5.1 Overview

The end shape, size and internal or external materials may affect the packaging functions, such as opening, printability and pressure resistance.

4.3.5.2 Generally the shape of laminated film/bag is a stick pack or sachet. Tearing force should be considered if easy opening property needed. It should be free from wiredrawing or burr after tearing, and have no splash, dropping or leakage during this process. If needed, the tearing method should be friendly and safe to children and the aged.

4.3.5.3 Pressure resistance. The pressure resistance can be carried out by the drop resistance test. This test can refer to GB/T 17313-2009.

4.3.5.4 Evaluation on integrity and definition of printing surface. The manufacturer should consider the influence of printing process on the barrier property of rolls during online printing. Supplier and buyer should reach an agreement on the special process, such as, the influence on printing's legibility by sterilization process, integrity of label for the roll, integrality of the surface, evaluation item, method and requirement for integrity evaluation in normal process.

4.4 Stability

4.4.1 Stability of laminated film/bag

The research on stability of laminated film/bag should be conducted according to technical requirement, and the quality stability period should be determined based on the research result.

The research on stability of laminated film/bag should be performed according to T/CNPPA 3017-2021 Chinese Pharmacopoeia Edition 4, 9001 Guideline Principle for Stability Test of Bulk Drugs and Preparations or the technical guideline principle of stability research issued by CDE.

4.4.2 Drug stability

The research on drug stability should be performed according to Chinese Pharmacopoeia Edition 4, 9001 Guideline Principle for Stability Test of Bulk Drugs and Preparations. The commercial or similar product with complete packaging should be used as the sample for stability test.

4.5 Quality acceptance criteria of laminated film/bag

The quality standard of laminated film/bag should reflect the quality stability and consistency of product, including but not limited to material and structure of laminated film/bag, appearance, identification, transit dose of vapor, residual solution, microbial limit and soluble substance.

Dissolution test of laminated film/bag should match the specification of material, process and packaging specification. And it can refer to the packaging standard of multiple-dose oral liquid. Generally, the test item includes clarity, absorbance, pH change value, readily oxidizable substance, non-volatile matter, heavy metal, etc. The actual using condition should be simulated when printing has influence on the result.

4.6 Other influence factors

4.6.1 Overview

The laminated film/bag should be selected based on the oral liquid dose. The influence from different processes, equipment, storage and transport condition should be considered, as well as following influence factors.

4.6.2 Process and equipment

Selecting proper filling, disinfection or sterilization process (if appropriate), packaging process and equipment. Keeping bag sealing smooth and indentation or embossing is clear, and it is free from corrugation, burn or penetration. The production date, lot and mark system should be clear and firm. The printing (opening) position should be consistent. The seal strength, width and load deviation should conform to the requirement of process standard.

4.6.3 Influence of absorbed and residual substance

The absorbed and residual substance may affect the administration dosage or reduce the effective component. The absorbed substance is mainly caused by the material of inner layer of laminated film/bag, while the residual substance is related to packaging design of laminated film/bag.

4.6.4 Proper drying condition

The drying mode has direct influence on the residue of volatile substance in laminated film, and proper drying parameter, such as drying temperature, drying time and vacuum degree.