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Social Organization Standard

T/CNPPA XXXX—XXXX

Technical Guidelines for Eye Drop Packaging Systems

(Draft for solicit public opinion online)

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Foreword

This document is drafted in accordance with the provisions of GB/T 1.1—2020 “Guidelines for Standardization Work Part 1: Structure and Drafting Rules for Standardization Documents”.

Please note that certain contents of this document may involve patents. The issuing organization of this document does not bear the responsibility for identifying patents.

This document is under the jurisdiction of the China Pharmaceutical Packaging Association.

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Introduction

According to the "General Requirements for Pharmaceutical Packaging Materials" in the 2020 edition of the Chinese Pharmacopoeia and the "Announcement on Further Improving the Review and Approval and Supervision of Drug-Related Matters" by the National Medical Products Administration, eye drop packaging systems are considered high-risk pharmaceutical packaging materials and should undergo technical investigation.

This document is compiled based on the investigation content of the "Requirements for Registration Data of Pharmaceutical Packaging Materials (Trial)" and combines relevant regulations, standards, and guidelines from domestic and international organizations related to pharmaceutical packaging materials.

The purpose of this document is to guide pharmaceutical packaging material registrants and drug marketing authorization holders (drug formulation registration applicants) to reach a technical consensus on packaging systems suitable for eye drops.

Technical Guidelines for Eye Drop Packaging Systems

1 Scope

This document applies to eye drop packaging systems and specifies the technical requirements for these systems.

2 Normative References

The following documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition (including all amendments) applies.

"Technical Guidelines for Sealing Studies of Chemical Drug Injection Packaging Systems (Trial)" (Announcement No. 33 of 2020 by the Center for Drug Evaluation, National Medical Products Administration)

"Good Manufacturing Practice for Drugs (2010 Revision) Appendix for Sterile Drugs" (Ministry of Health Order No. 79)

T/CNPPA 3025-2023 "Guidelines for quality agreement management of pharmaceutical packaging materials"

T/CNPPA 3017-2021 "Guidelines for Intrinsic Stability Studies of Plastic and Rubber Pharmaceutical Packaging Materials"

3 Terms and Definitions

3.1 Multi-Dose Packaging System

A container sealing system used for containing multiple use dose and does not alter the quality attributes of the remaining preparation in using.

3.2 Container closure system to prevent microbial ingress

A container closure system that allows delivery while preventing microbial intrusion to maintain the sterility of the remaining contents.

3.3 Single-Dose Packaging System

A container sealing system used for single-use sterile preparations.

3.4 BFIS

One type of BFS. After the packaging container is blow molded and the drug is filled,

the packaging component is inserted before the container is sealed.

3.5 Constituent Material

The substance used to manufacture the packaging component.

3.6 Packaging Component

Any part of the packaging system.

3.7 Container

A packaging component that directly contacts and holds the preparation, such as a bottle (commonly known as the bottle body).

3.8 Applicability

The ability of the packaging system to be compatible with the preparation, ensuring the drug meets all necessary safety and quality standards, including protection, compatibility, safety, and functionality.

3.9 Protection

The ability of the packaging system to protect the preparation by preventing factors that cause quality degradation, ensuring the preparation's quality throughout its shelf life.

3.10 Compatibility

The ability of the packaging component and the preparation not to interact excessively, leading to unacceptable quality changes in the preparation or the packaging component.

3.11 Safety

Ensuring that the constituent materials do not leach harmful or excessive substances into the preparation, ensuring patient safety during treatment. This usually includes chemical safety and biological safety. Chemical safety involves studying extractables from the packaging component to determine the types of chemicals that may migrate into the preparation (if necessary, determining the concentration), and conducting toxicological evaluations to determine safe exposure levels for specific routes of administration. Biological safety involves conducting biological tests on the packaging component that are appropriate for the specific route of administration to provide evidence of the safety of the constituent materials.

3.12 Functionality

The ability of the packaging system to perform its intended function as designed. This mainly considers the functionality of the packaging system and the drug delivery function. The functionality of the packaging system refers to features that enhance patient compliance, reduce waste, and facilitate use. The drug delivery function refers to the ability of the packaging system to dispense the drug in a specific quantity or at a specific rate.

4 Classification and Application of Eye Drop Packaging Systems

Classification elements of eye drop packaging systems, see A.1;Classification of conventional eye drop packaging systems, see A.2.

Application of various eye drop packaging systems are as follows:

—— Multi-Dose Eye Drop Packaging System: During use, the eye drop should have the ability to prevent contamination by harmful microorganisms.

—— Multi-Dose Eye Drop Packaging System to prevent microbial ingress: During use, the antimicrobial container closure system should have the ability to prevent microbial ingress or contamination of the eye drop by harmful microorganisms.

—— BFS Single-Dose Eye Drop Packaging System: By reducing the bottle volume and the filling volume of the eye drop, single-use is achieved; during use, the eye drop does not need to have the ability to prevent contamination by harmful microorganisms.

—— BFS Multi-Dose Eye Drop Packaging System: During use, use tools (such as a spike inside a cap) to form a drop hole, and the eye drop should have the ability to prevent contamination by harmful microorganisms.

—— BFIS Multi-Dose Eye Drop Packaging System: To better control the drop volume, a pre-sterilized dropper is inserted after blow molding and filling, and then sealed; When the inserted packaging component does not have the function to prevent microbial ingress, the eye drop should have the ability to prevent harmful microbial contamination during the service life; When the inserted packaging component has the function to prevent microbial ingress, the device to prevent microbial ingress shall have the ability to prevent harmful microorganisms from contaminating the eye drop during the service life.

5 Constituent Material Technical Requirements

5.1 Compliance with Expected Applicability Requirements

The formulation is the basis for the packaging component and packaging system to meet the expected applicability requirements. During the formulation investigation process, the

expected applicability requirements should be comprehensively considered.

Protection and Functionality Considerations: The protection and functionality of the packaging component are most related to the physical properties of the materials in the formulation. The type, grade, and matching functional masterbatch of the resin should be selected based on the expected protection and functionality requirements of the packaging component.

Compatibility and Safety Considerations: The compatibility and safety of the packaging component are directly related to the compatibility and safety of the materials in the formulation. As eye drops are high-risk preparations, the compatibility and safety requirements for the packaging component are high, which means the compatibility and safety requirements for the materials in the formulation are also high. During the formulation investigation process, existing regulations and standards can be referred to, and constituent material that meet the requirements should be selected.

5.2 Adaptation to Production Process

The formulation of the packaging component should be compatible with the expected manufacturing process. For example, plastic container manufacturing processes usually include injection blow molding, injection stretch blow molding, extrusion blow molding (including BFS process). These three processes have different physical property requirements for the constituent material. The appropriate constituent material should be selected based on the expected manufacturing process. Other packaging components, except for containers, are usually manufactured using injection molding processes. The appropriate resin and functional masterbatch should be selected based on the injection molding process.

The formulation of the packaging component should be compatible with the sterilization process. Except for containers manufactured using the BFS process, other packaging components need to achieve sterility through sterilization processes. Sterilization processes usually include radiation sterilization and chemical sterilization. Common radiation sterilization methods include gamma radiation sterilization and electron beam radiation sterilization. These methods can easily affect the molecular structure of polymer materials. The formulation's tolerance to the maximum radiation dose should be considered during application. Common chemical sterilization methods include ethylene oxide sterilization. This method can easily leave residues of ethylene oxide and other by-products (such as 2-chloroethanol) in the packaging component. Suitable analytical processes should be developed.

6 Technical Requirements for Production Environment and Process Control

6.1 Production Environment Requirements

Focus should be on the impact of the production environment on visible foreign matter and microbial load in packaging components and/or packaging systems.

For packaging components produced using sterilization processes, the production environment should be compatible with the production environment of the packaged drugs. The production environment of packaging components should effectively reduce the risk of introducing visible foreign matter and ensure that the microbial load of the packaging components meets the expected microbial limit requirements. The level of clean area should refer to “Appendix of Sterile Drugs in the Drug Manufacturing Quality Management Practice” (Revised in 2010).

For packaging systems produced using the BFS process, the production environment should comply with the requirements of “Good Manufacturing Practice for Drugs (2010 Revision) Appendix for Sterile Drugs”.

6.2 Production Process Control Requirements

Quality attributes related to the suitability of packaging components and packaging systems should be considered as critical quality attributes. Process parameters identified based on critical quality attributes should be considered as critical process parameters and should be controlled. Equipment identified based on critical quality attributes should be considered as critical equipment and should be controlled.

The production process should be fully validated, or sufficient information should be provided to prove that the production process can stably produce packaging components and/or packaging systems that meet quality requirements. The effectiveness of the radiation sterilization process can refer to ISO 11137; the effectiveness of the ethylene oxide sterilization process can refer to ISO 11135. This process may leave residues of ethylene oxide (EO) and 2-chloroethanol (ECH) in the packaging components, and the residual amounts of EO and ECH should be controlled within a reasonable range to ensure safety.

Packaging materials should meet the requirements of the sterilization process. When using radiation sterilization, the packaging materials should still meet the packaging requirements of the packaging components within the service life after being irradiated with the maximum dose. When using gas sterilization, the packaging materials should be breathable to ensure the final sterilization effect.

7 Quality Investigation

7.1 Quality Investigation of constituent material

The specific investigation content of constituent material should be developed in accordance with the expected applicability requirements, as well as relevant domestic and

international regulations and standards (see B.1).

7.2 Quality Investigation of packaging component and packaging system

Specific investigation content for packaging components and packaging systems is developed based on expected applicability requirements (see B.2) and combined with applicable domestic and international references (see B.3).

7.3 Evaluation on Seal Integrity

The seal integrity evaluation of the packaging system, which can be carried out after association with the preparation, should refer to “Technical Guidelines for Sealing Studies of Chemical Drug Injection Packaging Systems (Trial)”.

7.4 Quality Standard

Based on the constituent material, the quality investigation results of packaging components and packaging systems, and in combination with the production process, risk assessment should be conducted. Inspection items with higher risks should be included in the quality standards to form the registration standards for packaging components and packaging systems.

When packaging components and/or packaging systems are associated with specific formulations, the additional requirements of the formulation and its marketing authorization holder (or drug formulation registration applicant) should also be fully considered. If necessary, protocol standards and/or associated standards should be formulated.

The above content can be referred to T/CNPPA 3025-2023 “Guidelines for quality agreement management of pharmaceutical packaging materials”.

8 Self-Stability investigation

Material-related self-stability investigation should be conducted according to the T/CNPPA 3017-2021 “Guidelines for Intrinsic Stability Studies of Plastic and Rubber Pharmaceutical Packaging Materials” to formulate corresponding investigation content and determine the service life based on the investigation results; Function-related self-stability investigation should assess the function-related risks in the whole life cycle of the packaging system, and formulate corresponding investigation contents according to the evaluation results.

Appendix A

(Normative)

Classification of Eye Drop Packaging Systems

A.1 Classification elements of eye drop packaging systems

Aseptic implementation	Number of use	Special function
Sterilization BFS BFIS+ Sterilization	Multiple Single-use	Prevent microbial ingress

A.2 Classification of conventional eye drop packaging systems

Classification	Aseptic implementation	Number of use	Special function
Multi-Dose Eye Drop Packaging System	Sterilization	Multiple	No
Multi-Dose Eye Drop Packaging System to prevent microbial ingress	Sterilization	Multiple	To prevent microbial ingress
BFS Single-Dose Eye Drop Packaging System	BFS	Single-use	No
BFS Multi-Dose Eye Drop Packaging System	BFS	Multiple	No
BFIS Multi-Dose Eye Drop Packaging System	BFIS+ Sterilization	Multiple	No

Appendix B

(Informative)

Reference regulations, standards and guidelines for quality Investigation

B.1 Regulations and Standards for Resin Quality Investigation

No.	Standard	Example
1	EU	<3.1.4>, <3.1.5>, <3.1.6> and applicable sections
2	USA	21CFR PART 177 applicable sections, USP<661.1>, <87> and applicable sections
3	ICH	ICH Q3D

B.2 Applicability Investigation Projects for Packaging Components and Systems

No.	Applicability Category	Example
1	Protection	Seal integrity, water vapor transmission rate, gas (e.g., oxygen) transmission rate, light transmission rate, etc.
2	Compatibility	Additives, extractable elements, etc.
3	Safety	Chemical safety of extractables, biological safety, etc.
4	Functionality	Drop volume, tamper evidence, application force, function to prevent microbial ingress, residual contents monitoring etc.

B.3 Quality Investigation for Packaging Components and Systems

No.	Standard	Example
1	China	National standards for pharmaceutical packaging materials, "Technical Guidelines for Sealing Studies of Chemical Drug Injection Packaging Systems (Trial)" and related guidelines
2	EU	EP<3.2.2> and related guidelines
3	USA	USP<661.2>, <87>, <1663>, <1207> and applicable sections
4	ICH	ICH Q3D, ICH M7

References

[1] National Medical Products Administration “Announcement on Further Improving the Review and Approval and Supervision of Drug-Related Matters” by the National Medical Products Administration, Attachment 2 “Requirements for Registration Data of Pharmaceutical Packaging Materials (Trial)” (Announcement No. 56 of 2019)

[2] “Chinese pharmacopeia” (2020 Edition) <0105> eye-drops preparations

[3] ICH. Q3D（R2）：Guidelines for elemental impurities

[4] ICH. M7（R2）Appendix：Application of ICH M7 principles to the calculation of acceptable intakes of compounds

[5] National Medical Products Administration “Chinese pharmacopeia” (2025 Revision) <5302> General rules for plastic bottles and components for eye drops (Draft for solicit public opinion)

[6] National Medical Products Administration “Good Manufacturing Practice for Pharmaceutical Packaging Materials (Draft for solicit public opinion) (2024)

[7] National Medical Products Administration center for drug evaluation “Technical guidelines for pharmaceutical research of chemical generic solution eye drops” (Announcement No. 8 of 2023)

[8] USP<87>Biological Reactivity Tests, In Vitro

[9] USP<659>Packaging and Storage Requirents.

[10] USP <661.1> Plastic Materials of Construction

[11] USP <661.2>Plastic Packaging Systems for Pharmaceutical Use

[12] USP<1207> Package Integrity Evaluation-sterile Products.

[13] USP <1663>Associated with Pharmaceutical Packaging/Delivery Systems

[14]FDA. Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing, and Controls Documentation （May 1999）.

[15]FDA. Guidance for Industry:Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry

[16]21 Cfr§ 177 Indirect Food Additives:Polymers

[17]21 Cfr§ 211.132 Tamper-evident Packaging Requirements for Over-the-counter (OTC) Human Drug Products.

[18] EP<3.1.4> Polyethylene without Additives for Containers for Parenteral Preparations and for Ophthalmic Preparations

[19] EP<3.1.5> Polyethylene with Additives for Containers for Parenteral Preparations and for Ophthalmic Preparations

[20] EP<3.1.6> Polypropylene for Containers and Closures for Parenteral Preparations and Ophthalmic Preparations

[21] EP<3.2.2> Plastic Containers and Closures for Pharmaceutical Use

[22] EU. Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use- Annex 1. Manufacture of Sterile Medicinal Products

[23] ISO 11135：Sterilization of Health-care Products– Ethylene Oxide

[24] ISO 11137：Sterilization of Health-care Products – Radiation

[25] ISO 14644：Cleanrooms and Associated Controlled Environments