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Social Organization Standard

T/CNPPA XXXX—XXXX

Technical Requirements for Container closure systems to prevent microbial ingress for Eye Drops

(Draft for solicit public opinion online)

Issued on Effective on

Issued by China National Pharmaceutical Packaging Association

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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.

Drafting units of this document:

The main drafter of this document is:

Technical Requirements for Container closure systems to prevent microbial ingress for Eye Drops

1 Scope

This document specifies the technical requirements for microbial ingress preventing container closure systems for eye drops.

2 Normative References

The following documents are essential 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 Evaluation of Chemical Drug Injection Packaging Systems (Trial)” (Announcement No. 33 of 2020 by the Center for Drug Evaluation, National Medical Products Administration)

3 Terms and Definitions

3.1 Container closure system to prevent microbial ingress

A container closure system that can prevent microbial invasion while allowing delivery, thereby protecting the remaining contents and maintaining sterility.

3.2 Liquid channel

The channel, which let the remaining contents go through from inside of container to outside of the packaging system.

3.3 Ventilation channel

The channel, which let air go through from outside of the packaging system to inside of container.

3.4 Physical Fit Seal

A seal achieved through the tight fit of surfaces of two different components.

4 Design Requirements for Container closure systems to prevent microbial ingress

4.1 General Design Requirements

Container closure systems to prevent microbial ingress for eye drops should be able to prevent microbial invasion while allowing delivery, to protect the remaining liquid and maintain sterility.

To achieve the delivery function, the container closure system to prevent microbial ingress should have a liquid channel that can prevent microbial invasion of the remaining liquid. The delivery process will cause a negative pressure in the packaging system due to the reduction in liquid volume, affecting subsequent delivery processes; therefore, the packaging system should have a design to balance the negative pressure, which should also prevent microbial invasion of the remaining liquid. Additionally, eye drops using container closure systems to prevent microbial ingress usually do not contain preservatives, and there is a risk of microbial proliferation in the residual liquid outside the dropper after delivery, which should be considered in the design. The above design requirements have been applied in container closure systems to prevent microbial ingress for eye drops (such as OSD, Novelia, etc.), but the specific designs of different antibacterial devices are not the same, and even involve design patents.

4.2 Design Requirements for Liquid Channels

Based on the different sealing designs of liquid channels, they can be divided into dropper seal design and liquid channel seal design.

Dropper Seal Design Requirements: The dropper should have a movable seal that can seal the dropper in a non-delivery state; during delivery, the seal can move under external force to open the dropper, allowing the liquid to drip out; after delivery, the seal can return to seal the dropper, preventing microbial invasion of the remaining liquid through the liquid channel.

Liquid Channel Seal Design Requirements: The dropper is in a non-sealed state, and the liquid channel should have a movable seal that can seal the liquid channel in a non-delivery state; during delivery, the seal can move under external force to open the liquid channel, allowing the liquid to drip out through the liquid channel and dropper; after delivery, the seal can return to seal the liquid channel, preventing microbial invasion of the remaining liquid through the liquid channel. Since the dropper is always in a non-sealed state, the liquid channel between the dropper and the seal is in a non-sealed state; after delivery, this part of the liquid channel will be filled with liquid, posing a risk of microbial proliferation; therefore, a component to prevent microbial ingress should be designed below the dropper to address this risk.

4.3 Design Requirements for Balancing Negative Pressure

Based on the different principles of balancing pressure differences, they can be divided

into designs without ventilation and designs with ventilation.

Design Requirements without Ventilation: To balance the negative pressure generated in the packaging system during delivery, the container closure system to prevent microbial ingress should match a self-collapsing container, which balances the negative pressure in the packaging system through the deformation of the self-collapsing container.

Design Requirements with Ventilation: To balance the negative pressure generated in the packaging system during delivery, a ventilation channel should be designed, and a component to prevent microbial ingress should be designed in the ventilation channel. When negative pressure is generated in the packaging system, air can enter the packaging system through the ventilation channel to balance the negative pressure; the air passes through the component to prevent microbial ingress, to prevent microbial invasion of the remaining eye drops in the packaging system.

4.4 Design Considerations for Reducing the Risk of Microbial Proliferation in Residual Liquid

The risk of microbial proliferation mainly depends on the volume of residual liquid outside the dropper and the speed of microbial proliferation; therefore, the following aspects can be considered:

—— Optimize the design of the dropper to reduce the volume of residual liquid outside the dropper.

—— Use a liquid absorption component to transfer the residual liquid, reducing the volume of residual liquid outside the dropper.

—— Use a component to prevent microbial ingress to contact the residual liquid outside the dropper to inhibit microbial proliferation.

The above design considerations can be used alone or in combination; additionally, if necessary, users should be advised on the correct handling methods for the residual liquid outside the dropper.

5 Evaluation on Function to prevent microbial ingress

5.1 Evaluation on Function to prevent microbial ingress of Liquid Channels

Fill a certain amount of content into the packaging system, immerse only the dosing orifice of the dropper in the bacterial solution, and simulate the delivery process, finally conducting a sterility test on the remaining content. The following Evaluation points can be considered:

—— Microbial Requirements: Preferably select small, mobile microorganisms.

—— Culture Medium Requirements: The culture medium used in the bacterial solution

should promote the growth of the selected microorganisms; when the content is a culture medium, it should promote the growth of the selected microorganisms.

—— Microbial Concentration Requirements: The appropriate predetermined level should be met throughout the test (usually the minimum concentration used is 105 CFU/mL).

—— Content Filling Volume: After completing the entire simulated delivery process, there should be enough remaining content in the packaging system to meet the requirements of the sterility test.

—— Number of Simulated Delivery Processes: The appropriate predetermined level should be met.

—— Temperature During the Test: The temperature should be sufficient to support the proliferation and growth of microorganisms.

—— Culture Temperature and Time: The selected stability should be able to maintain the proliferation and growth of microorganisms, and the selected time should ensure that the number of microorganisms meets the requirements of the sterility test.

5.2 Evaluation on Function to prevent microbial ingress of Ventilation

Fill a certain amount of culture medium into the packaging system, expose to an aerosol of bacteria or bacterial spores and simulate the delivery process, finally conducting a sterility test on the remaining content. The following Evaluation points can be considered:

—— Microbial Requirements: Preferably select small microorganisms.

—— Culture Medium Requirements: Should promote the growth of the selected microorganisms.

—— Microbial Concentration Requirements: The appropriate predetermined level should be met throughout the test (should exceed the microbial conditions of the expected use environment).

—— Content Filling Volume: After completing the entire simulated delivery process, there should be enough remaining content in the packaging system to meet the requirements of the sterility test.

—— Number of Simulated Delivery Processes: The appropriate predetermined level should be met.

—— Temperature During the Test: The temperature should be sufficient to support the proliferation and growth of microorganisms.

—— Culture Temperature and Time: The selected stability should be able to maintain the proliferation and growth of microorganisms, and the selected time should ensure that the number of microorganisms meets the requirements of the sterility test.

Alternatively, provide other Evaluation data to prove the function to prevent microbial ingress of the ventilation channel.

6 Evaluation on Seal Integrity

The container closure system is composed of a plurality of components preventing microbial ingress through physical combination and sealing and form with the container through physical combination and sealing a container closure system, which cannot reach the maximum theoretical possible leakage limit value of the test principle; According to the <Technical Guidelines for Sealing Evaluation of Chemical Injection Packaging Systems (Trial)>, at least two methods (one of which recommends microbial challenge method) should be used for closure integrity evaluation, and the sensitivity of the two methods should be compared and studied.

When conducting closure integrity studies, special attention needs to be paid to the suitability of the packaging system and the selected method; If necessary, the experimental conditions can be adjusted reasonably.

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” <0105> eye-drops preparations

[3] “Chinese pharmacopeia” <9624> Guidelines for quality control of plastic packaging systems and components for pharmaceutical packaging

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

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

[6] USP<1207> Package integrity evaluation-sterile products.

[7] USP<1207.2> Package integrity leak test technologies.