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Application Guide for Moist Heat Sterilization Bag for Pharmaceutical Packaging Materials

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Content

Preface

This document was drafted according to the rules of GB/T 1.1-2020 <Guidelines for Standardization Work Part 1: Structure and Drafting Rules of Standardization Documents>.

Please note that some of the contents of this document may be associated with patents. The issuing agency of this document is not responsible for identifying those patents.

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

Drafting unit of this document:

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Introduction

Moist heat sterilization bag for pharmaceutical packaging materials is suitable for packaging, in-process transferring, transportation, and articles awaiting moist heat sterilization. Moist heat sterilization bag is a functional packaging material used in the production process for ready-to-use rubber stoppers, aluminum caps and other products.

With the increasing requirements for drug quality, the state began to classify and control pharmaceutical packaging materials since 2000 [1]. As a new format of pharmaceutical packaging, ready-to-use pharmaceutical packaging materials have emerged and are growing rapidly as they are convenient to use with simplified operations and waste reduction; they also provide flexibility for multi-variety and small-batch of special drugs. As the current packaging standards for pharmaceutical packaging materials are struggling to meet the higher requirements of ready-to-use pharmaceutical packaging materials, this document has been developed to ensure that terminal-sterilized pharmaceutical closures used in pharmaceutical packaging operations are packaged in suitable bags and can be sterilized by moist heat sterilization.

This document is used to guide manufacturers of ready-to-use pharmaceutical closures to select suitable packaging bags, which is conducive to the consistency of control standards between manufacturers and end-users, ensuring the quality of packaged products to meet the requirements of use.

This document may not cover all types of moist heat sterilization bags and relevant parties shall analyze the actual situation and carry out relevant verification tests. This document has been developed under the current system of regulations and standards with current level of knowledge, and may be appropriately adjusted as regulations & standards continue to evolve as science & technology continue to develop. It does not include administrative matters involved in registration approval and is not enforceable as a regulation.

Application Guide for Moist Heat Sterilization Bag for Pharmaceutical Packaging Materials

1 Scope

This document provides guidance on technical requirements, test methods, inspection rules, identification, packaging for transportation and storage, etc. for moist heat sterilizable bag for pharmaceutical closures.

This standard applies to packaging bags for pharmaceutical closures (such as rubber stoppers, aluminum caps and their assembly) that can be sterilized by moist heat.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

GB/T 451.2-2002 Paper and board—Determination of grammage

GB/T 454-2020 Paper--Determination of bursting strength

GB/T 455-2002 Paper and board determination of tearing resistance

GB/T 458-2008 Paper and board--Determination of air permeance

GB/T 2410-2008 Determination of the luminous transmittance and haze of transparent plastics

GB/T 4744-2013 Textiles-Testing and evaluation for water resistance--Hydrostatic pressure method

GB/T 6672-2001 Plastics film and sheeting-- Determination of thickness by mechanical scanning

GB/T 12914-2018 Paper and board-Determination of tensile properties-Constant rate of elongation method (20mm/min)

GB 18278.1-2015 Sterilization of health care products--Moist heat-Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices

GB/T 19633.1-2015 Packaging for terminally sterilized medical devices- Part 1: Requirements for materials, sterile barrier systems and packaging systems

GB/T 19973.1-2015 Sterilization of medical devices--Microbiological methods-Part 1: Determination of a population of microorganisms on products

GB/T 42061-2022 Medical devices --Quality management systems-Requirements for regulatory purposes

YBB 00082003-2015 Test for Gas Transmission

YBB 00092003-2015 Test for Water Transmission

YBB 00102005-2015 3-layer Co-extrusion Films and Bags Used for Infusion

YBB 00132002-2015 General Requirement for laminated Films and Pouches for Pharmaceutical Packaging

YY/T 0313-2014 Medical polymer products-Requirement for package and information supplied by manufacturer

YY/T 0681.4-2021 Test methods for sterile medical device package-Part 4: Detecting seal leaks in porous packages by dye penetration

YY/T 0681.10-2011 Test methods for sterile medical device package-Part 10: Test for microbial barrier ranking of porous package material

YY/T 0698.9-2009 Packaging materials for terminally sterilized medical devices-Part 10: Adhesive coated nonwoven materials of polyolefins for use in the manufacture of sealable pouches, reels and lids-Requirements and test methods

T/CNPPA 3017-2021 Guideline for Self-Stability Study on Plastic and Rubber Pharmaceutical Packaging Materials

China Pharmacopoeia (2020) (Part 4)

ASTM D 2724-2019 Standard Test Methods for Bonded, Fused, and Laminated Apparel Fabrics

3 Terms and definitions

The following terms and definitions apply to this document.

3.1 Welded seal

The welded seal is formed as a result by the heat-sealing process between the porous material and the impermeable material.

3.2 Batch

Batch means a specific quantity of products which are produced by the same production process, with the same dimensions, same printing, same packaging and same raw materials during the same cycle of manufacture.

4 Technical requirements and test methods

4.1 General requirements for materials

The moist heat sterilization bag for pharmaceutical closures (hereinafter referred to as the bag) is made of a layer of porous (packaging) material and a layer of impermeable material melting sealed, the material used shall meet the requirements of GB/T 19633.1-5.1.7 and 5.1.9 in GB/T 19633.1-2015.

4.2 Porous material

4.2.1Porous material shall be high-density polyethylene flash-spun non-woven fabric with following technical specifications listed in Table 1 and microbial barrier requirements.

Table 1 Porous material properties, specifications, and testing methods

Property	**Technical specification**	**Test method**
Basis weight	shall be within ± 7 % of the nominal value stated by the manufacturer	GB/T 451.2-2002
Air permeance	not less than 1 μm/Pa · s at an air pressure of 1.47 kPa	GB/T 458-2008
Delamination	≥1 N/25.4 mm	ChP 2020-4004
Resistance to water penetration (hydrostatic head)	≥1000 mm	GB/T 4744-2013

Mechanical strength	(MD & CD) Tensile strength, (MD & CD)	≥4,8 kN/m (MD) & 5,0 kN/m (CD)	GB/T 12914-2018
	(MD & CD) Internal tearing resistance (MD & CD)	≥1 000 mN (MD & CD)	GB/T 455-2002
	Bursting strength	≥ 800 kPa	GB/T 454-2020
Microbial barrier		The LRV (log reduction value) not less than 4	YY/T 0681.10

4.2.2 The mechanical strength and microbial barrier property of the porous materials used shall also be tested after moist heat sterilization and aging based on the claimed shelf life of the product at appropriate time intervals; following test results and test conditions shall be documented. Data available from the manufacture may be used for that purpose.

4.3 Impermeable material

4.3.1 The impermeable material shall be high-density polyethylene film, its characteristics shall meet the technical specifications listed in Table 2 according to the test method specified in Table 2.

Table 2 Impermeable Material Properties, Technical Specifications and Test Methods

Properties		**Technical Specification**	**Test Methods**
Thickness		±10%	GB/T 6672-2001
Opacity		not less than 40%	GB/T 2410-2008
Mechanical Strength	Tensile (MD & CD)	>20MPa	ChP 2020-4005
	Elongation (MD & CD)	>300%	
Ash content		less than 0.2%	YBB00102005-2015

4.3.2 The mechanical strength properties of the impermeable materials used shall also be tested after moist heat sterilization and aging based on the claimed shelf life of the bag at appropriate time intervals; following test results and test conditions shall be documented. Data available from the manufacture may be used for that purpose.

4.4 Product Extractable

4.4.1 Sample preparation: Take an appropriate amount of this product and prepare three samples. Each sample shall have a one-layer surface area of 300 cm2 containing top material, bottom material, and the welded seal part (The top and bottom material shall have the same surface area). Each sample is cut into small pieces with dimension of 5 cm long × 0.5cm wide and put into a stoppered Erlenmeyer flask.

4.4.2 Testing method: Product extractables are tested according to <YBB00132002-2015 General Requirement for Laminated Films and Pouches for Pharmaceutical Packaging>.

4.4.3 Technical requirements

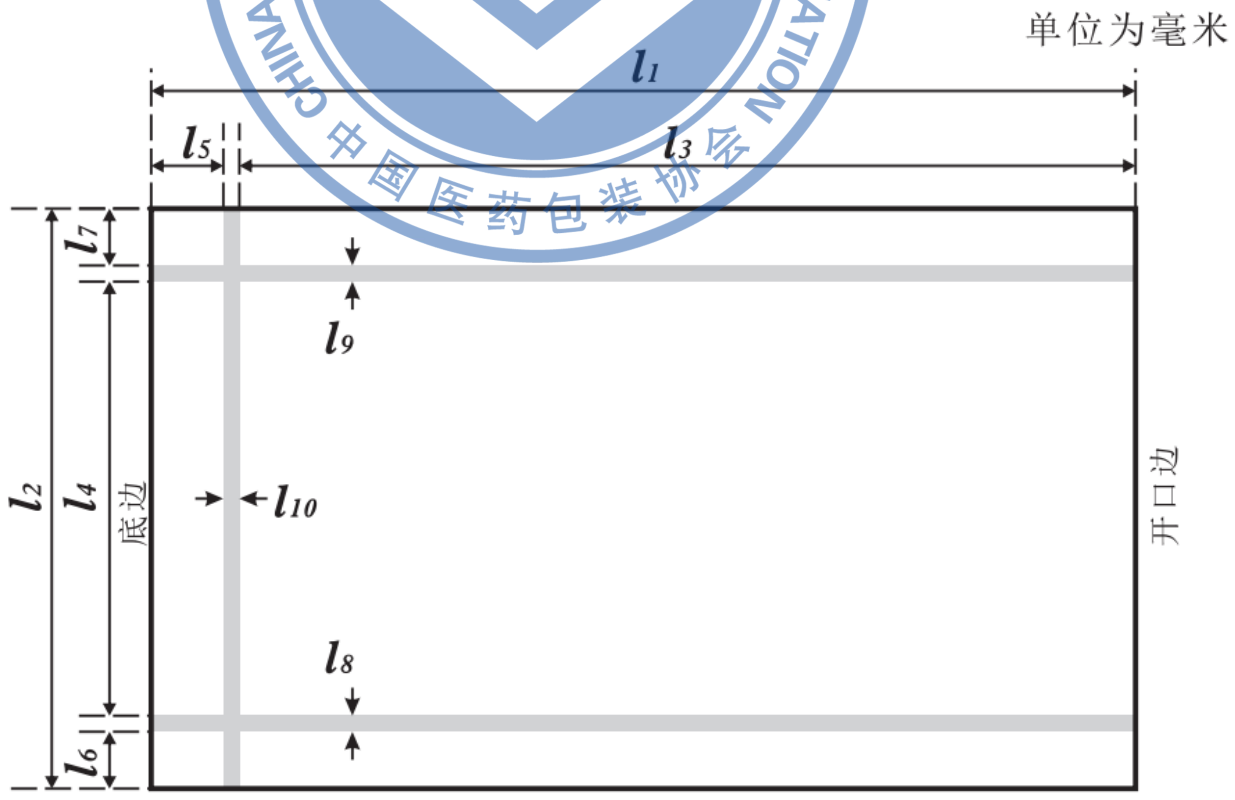
4.4.3.1 Heavy metal: the amount of heavy metals shall not exceed 1 part per million.
4.4.3.2 Readily oxidizable substances: The consumption of sodium thiosulfate titrant (0.01mol/L) between the solution and the control solution shall not exceed 1.5 mL.
4.4.3.3 pH value: The pH value shall be 5.0-7.0.
4.4.3.4 Absorbance: The maximum absorbance value in the range of 220-240nm shall not exceed 0.08; the maximum absorbance value in the range of 241-350nm shall not exceed 0.05.
4.4.3.5 Nonvolatile matter: The difference between test solution and control solution shall not exceed 30.0 mg.

4.5 Product design

The bag tested according to <YBB00132002-2015 General Requirement for Laminated Films and Pouches for Pharmaceutical Packaging> shall be odorless, free of holes, cracks, tears, creases or localized thickening and/or thinning sufficient to impair functioning.

The printing shall be clear with evenly distributed ink, and the location of the printing shall meet the design requirements.

The maximum acceptable variation in dimensions of the bag shall be within ±1% for both length and width.



Description of the index number:

l_1：Length
l_2：Width
l_3：Inner length
l_4：Inner width
l_5：Bottom skirt
l_6：Left skirt
l_7：Right skirt
l_8：Left seal part
l_9：Right seal part
l_{10}：Bottom seal part
Fig. 1: Product schematic design

4.6 Welded seal

4.6.1 Product seal shall be a 3-side welded seal (e-right seal; d-left seal, f-bottom seal) produced by the heat-sealing process. The heat-sealing process shall be validated to meet the seal strength, seal integrity and other requirements. The seal of the bag shall be flat and transparent according to <YBB00132002-2015 General Requirement for Laminated Films and Pouches for Pharmaceutical Packaging>.

4.6.2 Seal strength

4.6.2.1 Sample preparation: samples are taken from welded seal part.
4.6.2.2 Testing method: Seal strength is measured according to "China Pharmacopoeia" 2020 Part 4 general principles 4008.
4.6.2.3 Seal strength shall not be lower than 15N/15mm.

4.6.3 Seal integrity

4.6.3.1 Sample preparation: add toluidine blue test solution to test bag.
4.6.3.2: Test method: Seal integrity is tested according to "YY/T 0681.4-2021 Test Method for Sterile Medical Device Packaging " Part 4: Detecting seal leaks in porous packages by dye penetration".
4.6.3.3 Technical requirements: no channel shall be detected in the test.

4.7 Product Cleanliness requirements

4.7.1 subvisible particles

4.7.1.1 Sample preparation: Fill the bag with an appropriate amount of particulate inspection water (the ratio of the number of milliliters of particulate inspection water to the square centimeter of the area of the bag to be tested is 1:6, e.g.: for a 320×450 mm bag, the corresponding water used shall be 480 mL). Oscillate for 20 s in the oscillator after sealing the bag (horizontal circular rotation with a frequency of 250±10 rpm). Open the bag with caution and pour part of the test solution to rinse the opening port and sampling cup first. Then pour the rest of the test solution into the sampling cup and let the solution stand for 15 min or an appropriate time

period; then stirred slowly to ensure uniformity (or degas the solution directly without stirring).

4.7.1.2 Test method: Sub-visible particles are measured according to "China Pharmacopoeia" 2020 Part 4 general principles 0903：subvisible particulates testing method.

4.7.1.3 Technical requirements: Particle counts shall not exceed 100, 20, 2 /mL for particle diameter of 5, 10, 25μm, respectively.

4.7.2 visible particles

4.7.2.1 Sample preparation: Fill the bag with an appropriate amount of particulate inspection water (the ratio of the number of milliliters of particulate inspection water to the square centimeter of the area of the bag to be tested is 1:6, e.g.: for a 320×450 mm bag, the corresponding water used shall be 480 mL). Oscillate for 20 s in the oscillator after sealing the bag (horizontal circular rotation with a frequency of 250±10 rpm). Open the bag with caution and pour the test solution into appropriate container.

4.7.2.2 Test method: Visible particles are measured according to "China Pharmacopoeia" 2020 Part 4 general principles 0904：visible particle testing method.

4.7.2.3 Technical requirements: Particle counts shall not exceed 0.05/10 cm^2 for punctate visible particles with a size between 50 μm-2 mm and Particle counts shall not be detected for fiber-like visible particles with a size ≥2 mm.

4.7.3 Bioburden

4.7.3.1 Sample preparation

4.7.3.1.1 Elution method: add 100 mL of pH 7.0 sodium chloride peptone buffer to a clean bag, seal to make the inner surface area of 360 cm^2 (such as 13 cm×14 cm). The test solution is obtained by placing the bag in an oscillator (horizontal circular rotation with a frequency of 250±10 rpm) for 20 s, and ensuring the pH 7.0 sodium chloride peptone buffer is in complete contact with the inner surface of the test bag.

4.7.3.1.2 Wiping method: put a sterile metal plate with an opening area of 25 cm^2 on the inner side of the bag, slightly moisten the sterile cotton swab with 0.9% sterile sodium chloride injection. The plate opening part is wiped 5 times in on position and 5 more times in the second position with rotation. Then wipe for another 5 times with a dry cotton swab in the first position and 5 more times in the second position 5, with a total of 100 cm^2 at 4 positions. After each cotton swab is wiped, immediately cut off the part that came in contact of the hand, put it into a test tube containing 10 mL of 0.9 % sterile sodium chloride injection; place it in a shaker (horizontal circular rotation with a frequency of 250±10 rpm) and shake for 20 seconds to obtain the test solution.

4.7.3.1.3 When it is not suitable to prepare the test solution for bioburden test using the elution method, the wiping method can be used.

4.7.3.2 Recovery of microorganisms in test samples: Membrane filtration is recommended for microbial

recovery. If the membrane filtration is used and the wiping method is used to prepare the test solution, the sterile sodium chloride injection can be increased to 30 mL. An Erlenmeyer flask is selected as the container.

4.7.3.3 Test method: bioburden is tested according to "China Pharmacopoeia" 2020 Part 4 general principles 1105.

4.7.3.4 Technical requirements: The test requirements are shown in Table 3.

Table 3 : Bioburden

Item	Total aerobic bacteria count （cfu/100cm^2）	Total combined molds and yeasts count （cfu/100cm^2）
Limit	100	10

4.8 Sterilization validation

4.8.1 Moist heat sterilization condition

Moist heat sterilization are controlled according to GB 18278.1-2015 Sterilization of health care products—Moist Heat—Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices. After moist heat sterilization under temperature of 123 ℃± 2 ℃ and time of 30 min, the following testing requirements shall be met.

4.8.2 Indicator

4.8.2.1Moist heat sterilization indicator，self-adhered

Moist heat sterilization indicator shall be adhered to the bottom of the bag. The adhesion shall be firm with obvious color change pre- and post-sterilization by visual check.

4.8.2.2 Moist heat sterilization indicator，-printed

Moist heat sterilization indicator shall be printed on the porous material surface side at the bottom of the bag. The color change shall be obvious pre- and post-sterilization by visual check.

4.8.3 Sterilization compatibility

4.8.3.1 Bag dimension change

The dimension change pre- and post-sterilization shall not exceed ± 3%.

4.8.3.2 Seal strength & seal integrity post sterilization

The bag shall meet the requirements of clauses 4.6.3 and 4.6.3 post sterilization.

4.8.3.3 Printing post sterilization

The printing shall be clear with no ink dissolved, no burrs, and no ink transfer to other sterilized items inside or outside the bag post sterilization.

4.9 Shelf life/Stability

The stability test shall be carried out according to the stability test requirements in T/CNPPA 3017-2021. Shelf life of raw materials shall not be less than shelf life of the product, Shelf life of the product shall not be less than 2 years.

5 Signs, labels, packaging

5.1 Inner packaging and label

The product shall be double-sealed and packaged with non-toxic materials to form an inner package. There shall be a label on the outside of the inner package, and the following information shall be included on the label:

1) Product name
2) Product item number
3) Product size
4) Product material
5) Product type
6) Quantity
7) Batch number
8) Production date
9) Name of manufacturing company
10) Product shelf life

5.2 Outside packaging and label

The inner packaging of the product shall be packed into the outside packaging of corrugated box. The following information shall be included on the label of the outside packaging:

1) Product name
2) Product item number
3) Product size
4) Quantity/box
5) Batch number
6) Production date
7) Gross weight
8) Packing staff
9) Inspectors
10) Box number
11) Dimension of corrugated box (length×width×height)
12) Name and address of the manufacturing company
13) Words or signs such as "Handle with care", "Keep dry", and the signs shall comply with the relevant requirements in YY/T 0313-2014.

5.3 Storage of product

Storage of product shall comply with requirements in Article 7.5.11 of YY/T 0287-2017 Medical

devices—Quality management systems—Requirements for regulatory purposes. The organization shall establish protective procedures to protect products during manufacturing, storage, handling, and transportation to meet product protection requirements；protection shall also be applied to components of the product.

The organization shall protect the product from alteration, contamination or damage when exposed to expected conditions and hazards during processing, storage, handling, and distribution by:

a) designing and constructing suitable packaging and shipping containers.

b) documenting requirements for special conditions needed if packaging alone cannot provide preservation.

If special conditions are required, they shall be controlled and recorded.

Reference

[1] Measures for the Administration of Materials and Containers for Pharmaceutical Packaging (Provisional) (Bureau Order No. 21), 2000.