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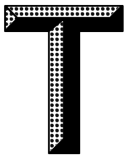

T/CNPPA 3023—2023

Application guide for moist heat sterilization bag for pharmaceutical packaging materials

药包材用湿热灭菌包装袋应用指南

（*English Translation*）

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Contents

Foreword

This standard is drafted in accordance with the rules given in the GB/T 1.1—2020.

This standard was proposed by China Pharmaceutical Packaging Association.

Introduction

Moist heat sterilization bag for pharmaceutical packaging materials is suitable for packaging, in-process transferring, transportation, and articles awaiting moist heat sterilization (including pre-filled syringe components, rubber stoppers, aluminum caps and their assembly, etc.) used or produced by chemical pharmaceutical, biopharmaceutical, pharmaceutical packaging materials and other manufactures. Moist heat sterilization bag is a functional packaging material used in the production process for ready-to-use/ ready-to-sterilize (RTU/RTS) pharmaceutical packaging materials to be sterilized.

With the increasing requirements for drug quality, the state started to classify and control pharmaceutical packaging materials since 2000. As a new format of pharmaceutical packaging, ready-to-use/ ready-to-sterilize pharmaceutical packaging materials have emerged and are growing rapidly as they are convenient to use with simplified operations, waste reduction and additional flexibility for multi-variety and small-batch of special drugs. This document has been developed for moist heat sterilization bag as there is no standard that can be applied to such product amongst current packaging standards for pharmaceutical packaging materials.

This document is used to guide manufacturers of ready-to-use/ ready-to-sterilize pharmaceutical packaging material 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 it may be appropriately adjusted as regulations & standards continue to evolve and science & technology continue to develop. It does not include administrative matters involved in registration approval and is not enforceable as a regulation. This document shall be used in compliance with relevant regulations.

Application guide for moist heat sterilization bag for pharmaceutical packaging materials

1 Scope

This document provides guidance on technical requirements, test methods, packaging, labels, signs and storage, etc. for moist heat sterilizable bag (hereinafter referred to as the bag) for pharmaceutical packaging materials.

This standard applies to packaging bags for pharmaceutical packaging materials (including pre-filled syringe components, rubber stoppers, aluminum caps and their assembly, etc.) that can be sterilized by moist heat.

2 Normative references

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

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 6673—2001, *Determination of length and width of plastics film and sheeting*

GB/T 12914—2018，*Paper and board—Determination of tensile properties—Constant rate of elongation method*（20 mm/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*

YY/T 0287—2017，*Medical devices—Quality management systems—Requirements for regulatory purposes*

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*

T/CNPPA 3017—2021，*Guidelines for self-stability of plastic and rubber pharmaceutical packaging materials*

Chinese Pharmacopoeia（2020）

3 Terms and definitions

For the purposes of this document，the following terms and definitions apply.

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

4 Technical requirements

4.1 General requirements for materials

The bag is made of a layer of porous material and a layer of impermeable material melting sealed. And the materials used shall meet the requirements of 5.1.1－5.1.7 and 5.1.9 in GB/T 19633.1—2015.

4.2 Porous material

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

Table 1—Porous material properties, specifications and testing methods

Property		Technical specification
Basis weight		shall be within ±7% of the nominal value stated by the manufacturer
Air permeance		≥1 μm/(Pa • s) at an air pressure of 1.47 kPa
Delamination		≥1 N/25.4 mm
Resistance to water penetration (hydrostatic head)		≥1 000 mm
Mechanical strength	Tensile strength (MD & CD)	≥4.8 kN/m (MD) & 5.0 kN/m (CD)
	Internal tearing resistance (MD & CD)	≥1 000 mN (MD & CD)
	Bursting strength	≥800 kPa
Microbial barrier		LRV (log reduction value) ≥4

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. The testing conditions and testing results 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 with following technical specifications specified in Table 2.

Table 2—Impermeable material properties, technical specifications

Properties		Technical specification
Thickness		shall be within ± 10% of the nominal value stated by the manufacturer
Opacity		≥40% measured at wavelength of 450 nm
Mechanical Strength	Tensile (MD & CD)	Average ≥20 MPa
	Elongation (MD & CD)	Average ≥300%
Ash content		≤0.2%

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. The testing conditions and testing results shall be documented. Data available from the manufacture may be used for that purpose.

4.4 Product extractable

4.4.1 Heavy metal: The level of heavy metals shall not exceed 1 part per million.

4.4.2 Readily oxidizable substances: The consumption of sodium thiosulfate titrant (0.01 mol/L) between test solution and control solution shall not exceed 1.5 mL.

4.4.3 pH value: The pH value shall be between 5.0 – 7.0.

4.4.4 Absorbance: The maximum absorbance at wavelength range of 220 nm – 240 nm shall not exceed 0.08. The maximum absorbance at wavelength range of 241 nm – 350 nm shall not exceed 0.05.

4.4.5 Nonvolatile matter: The difference between test solution and control solution shall not exceed 30.0 mg.

4.5 Product design

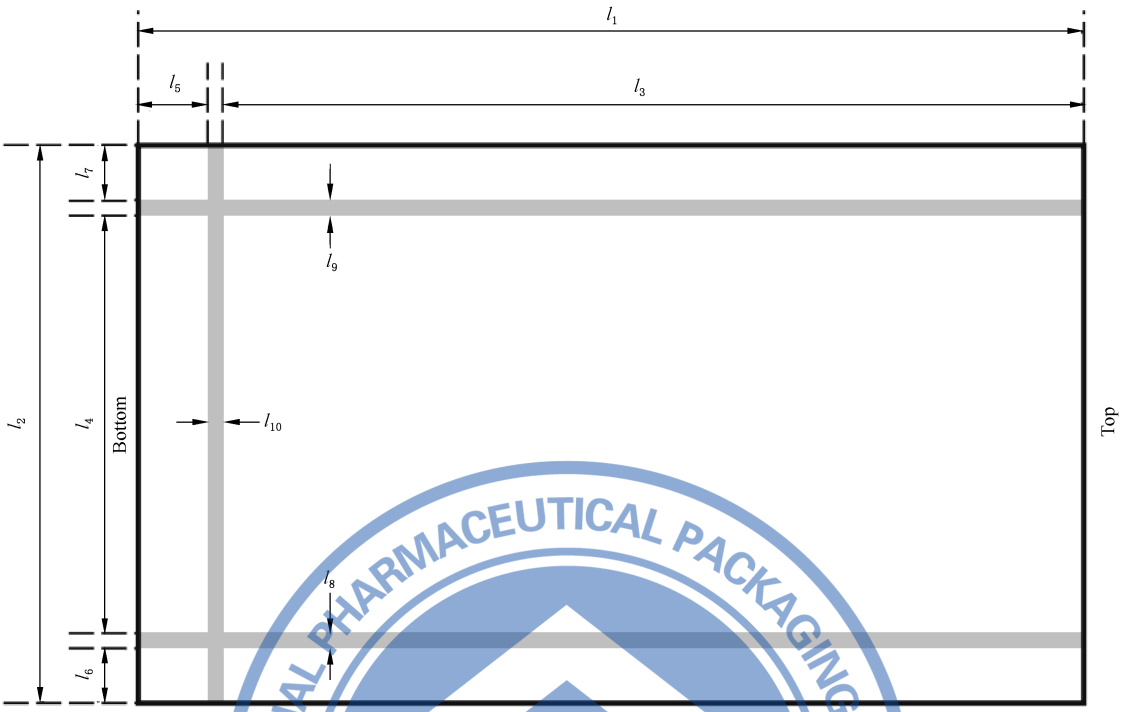
4.5.1 Appearance: The packaging bag for pharmaceutical packaging materials shall be odorless, free of holes, cracks, tears, creases or localized thickening and/or thinning sufficient to impair functioning. The printing shall be clear with evenly distributed ink, and the location of the printing shall meet the design requirements.

4.5.2 Dimension: The maximum acceptable variation in dimensions of the bag shall be within ±1% for both length and width for package dimension > 400 mm. For package dimension ≤ 400 mm, the maximum acceptable variation in dimensions of the bag shall be within 4 mm.

4.6 Welded seal

4.6.1 Product seal shall be a 3-side welded seal (l_8-right seal in Figure 1/l_9-left seal in Figure 1; l_{10}-bottom seal in Figure 1) 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.

In millimeter



Key:

l_1 Length
l_2 Width
l_3 Inner length
l_4 Inner width
l_5 Bottom skirt
l_6 Right skirt
l_7 Left skirt
l_8 Right seal
l_9 Left seal
l_{10} Bottom seal

Figure 1—Product schematic design

4.6.2 Seal strength shall not be lower than 15 N/15 mm.

4.6.3 Seal integrity: No channel shall be detected in the test.

4.7 Product cleanliness requirements

4.7.1 Subvisible particles: Particle counts shall not exceed 100 counts/mL, 20 counts/mL, 2 counts/mL for particle diameter ≥5 μm, 10 μm, 25 μm, respectively.

4.7.2 Visible particles: Particle counts shall not exceed 0.05 counts/10 cm^2 for 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: The technical requirements are shown in Table 3.

Table 3—Bioburden limit

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

4.8 Sterilization validation

4.8.1 Sterilization condition

After moist heat sterilization at temperature of (123±2)℃ for 30 min, the following testing requirements shall be met.

4.8.2 Indicator

4.8.2.1 Moist 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 ±1% for both length and width for package dimension >400 mm. For package dimension ≤400 mm, the maximum acceptable variation in dimensions of the bag shall be within 4 mm.

4.8.3.2 Seal strength & seal integrity post sterilization: The bag shall meet the requirements of 4.6.2 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 shelf life of raw materials shall be no less than shelf life of the product and the shelf life of the product shall be no less than 2 years.

5 Testing methods

5.1 General requirements for materials

The materials used shall meet the requirements of 5.1.1－5.1.7 and 5.1.9 in GB/T 19633.1—2015.

5.2 Porous material

Porous material shall be tested according to testing methods listed in Table 4.

Table 4—Testing methods for porous material

Property		Test method
Basis weight		GB/T 451.2—2002
Air permeance		GB/T 458—2008
Delamination		*Chinese Pharmacopoeia*(2020), Part 4-4004
Resistance to water penetration (hydrostatic head)		GB/T 4744—2013
Mechanical strength	Tensile strength (MD & CD)	GB/T 12914—2018
	Internal tearing resistance (MD & CD)	GB/T 455—2002
	Bursting strength	GB/T 454—2020
Microbial barrier		YY/T 0681.10—2011

5.3 Impermeable material

The impermeable material shall be tested according to testing methods specified in Table 5.

Table 5—Tesing methods for impermeable material

Properties		Test methods
Thickness		GB/T 6672—2001
Opacity		GB/T 2410—2008
Mechanical Strength	Tensile (MD & CD)	*Chinese Pharmacopoeia*(2020), Part 4-4005
	Elongation (MD & CD)	
Ash content		*Chinese Pharmacopoeia*(2020), Part 4-0841

5.4 Product extractable

5.4.1 Sample preparation: Take an appropriate amount of the product and prepare three samples. Each sample shall have a single-layer surface area of 300 cm^2 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 a dimension of 5 mm × 50 mm and the small pieces are

put into a stoppered Erlenmeyer flask. Each Sample with small pieces is soaked in 200 mL water (70±2)℃ for 2 h respectively. Then the samples are taken out and the extractions are cooled to room temperature and filled to 200 mL with the same batch of soaking water. The same batch of water is used as control for below tests.

5.4.2 Testing methods

5.4.2.1 Heavy metal: Heavy metal shall be tested according to *Chinese Pharmacopoeia* (2020), Part 4-0821.

5.4.2.2 Readily oxidizable substances: 20 mL of potassium permanganate titrating solution (0.002 mol/L) and 1 mL of diluted sulfuric acid are added into 20 mL test solution precisely. The mixture is heated to boil for 3 min, and then cooled to room temperature immediately. 0.1 g potassium iodide is added to the solution and placed in a dark environment for 5 min. The solution is then titrated with sodium thiosulfate titrant (0.01 mol/L). When close to the end, 5 drops of starch indicator solution are added to continue titrating until it becomes colorless. The control experiment shall be carried out with the water as control solution.

5.4.2.3 pH value: The pH value shall be tested according to *Chinese Pharmacopoeia* (2020), Part 4-0631.

5.4.2.4 Absorbance: The absorbance shall be tested according to *Chinese Pharmacopoeia* (2020), Part 4-0401.

5.4.2.5 Nonvolatile matter: Take 100 mL of the test solution and 100 mL of the control solution, respectively and then place them in an evaporating dish with constant weight. Then the solutions are evaporated to dryness in a water bath, and dry at 105 ℃ to a constant weight.

5.5 Product design

5.5.1 Appearance: The bag shall be visually inspected under bright natural light, and the printing part shall be inspected with a steel ruler with an accuracy of 0.5 mm.

5.5.2 Dimension: The length and width shall be tested according to Clause 3 in GB/T 6673—2001.

5.6 Welded seal

5.6.1 Welded seal: Welded seal shall be tested according to 5.6.2 and 5.6.3.

5.6.2 Seal strength: Samples are taken from welded seal part. Seal strength shall be measured according to *Chinese Pharmacopoeia* (2020) Part 4-4008.

5.6.3 Seal integrity: Seal integrity shall be tested according to Method A in YY/T 0681.4—2021.

5.7 Product cleanliness requirements

5.7.1 Subvisible particles

5.7.1.1 Sample preparation: The bag is filled with an appropriate amount of particle-free water (the ratio between milliliters of particle-free water and the square centimeters of the bag area to be tested shall be 1∶6, e.g.: for a 320 mm × 450 mm bag, the corresponding particle-free water used shall be 480 mL). The bag is then sealed following with stirring for 20 s [horizontal circular rotation with a frequency of (250 ± 10) r/min]. Open the bag with caution and pour out part of the test solution to rinse the opening part and the sampling bottle first. The rest of the test solution is then poured into the sampling bottle and allowed standing for 15 min. The solution is then stirred slowly to ensure homogeneity (or degas the solution directly without stirring).

5.7.1.2 Test method: Sub-visible particles shall be measured according to *Chinese Pharmacopoeia* (2020) Part 4-0903: subvisible particulates testing method.

5.7.2 Visible particles

5.7.2.1 Sample preparation: The bag is filled with an appropriate amount of particle-free water (the ratio between milliliters of particle-free water and the square centimeters of the bag area to be tested shall be 1∶6, e.g.: for a 320 mm × 450 mm bag, the corresponding particle-free water used shall be 480 mL). The bag is then sealed following with stirring for 20 s [horizontal circular rotation with a frequency of (250 ± 10) r/min]. Open the bag with caution and pour out the test solution into an appropriate container.

5.7.2.2 Test method: Visible particles are measured according to *Chinese Pharmacopoeia* (2020) Part 4-0904: visible particle testing method.

5.7.3 Bioburden

5.7.3.1 Sample preparation:

a) Extraction method: 100 mL buffered sodium chloride-peptone solution pH 7.0 is added to a clean bag and then sealed to make the inner surface area of 360 cm^2 (such as 13 cm × 14 cm). The test solution is obtained by stirring [horizontal circular rotation with a frequency of (250 ± 10) r/min]. for 20 s to ensure the complete contact between buffer solution and the inner surface of the test bag.

b) Wiping method: A sterile metal plate with an opening area of 25 cm^2 is placed on the inner side of the bag. A sterile cotton swab wetted with 0.9% sterile sodium chloride injection is used to wipe in the opening area for 5 times in one position and 5 more times in another position. Then a dry sterile cotton swap is used to wipe for 5 times in the first position and 5 more times in the

second position. Repeat this 4 times to cover a total area of 100 cm^2 on the inner side of the bag. After each cotton swab is used, the part that came in contact with hand is immediately removed, and the rest is placed into a test tube containing 10 mL of 0.9% sterile sodium chloride injection. The test solution is obtained after agitation [horizontal circular rotation with a frequency of (250±10) r/min] for 20 s.

c) If the extraction method is not suitable to prepare the test solution for bioburden test, the wiping method can be used.

5.7.3.2 Recovery of microorganisms in test samples: Membrane filtration is recommended for microbial recovery. If the wiping method is used to prepare the test solution following with membrane filtration, the sterile sodium chloride injection can be increased to 30 mL An Erlenmeyer flask is selected as the container.

5.7.3.3 Test method: Bioburden is tested according to *Chinese Pharmacopoeia* (2020) Part 4-1105: Bioburden testing for non-sterile products: enumeration of microorganisms.

5.8 Sterilization validation

5.8.1 Moist heat sterilization condition

Moist heat sterilization is controlled according to GB 18278.1—2015.

5.8.2 Indicator

Moist heat sterilization indicator, self-adhered & printed: Testing method is same with 5.5.1.

5.8.3 Sterilization compatibility

5.8.3.1 Bag dimension change: Testing method is same with 5.5.2.

5.8.3.2 Seal strength & seal integrity post sterilization: Testing method is same with 5.6.2 and 5.6.3 post sterilization.

5.8.3.3 Printing post sterilization: Testing method is same with 5.5.1.

5.9 Shelf life/Stability

The stability test shall be carried out according to the stability test requirements in T/CNPPA 3017—2021.

6 Packaging, labels, signs and storage

6.1 Inner packaging and label

The product shall be double 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:

a) Product name;

b) Product item number;

c) Product dimension;

d) Product material;

e) Quantity;

f) Batch number;

g) Production date;

h) Name of manufacturing company;

i) Product shelf life.

6.2 Outer packaging and label

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

a) Product name;

b) Product item number;

c) Product dimension;

d) Product material;

e) Quantity/box;

f) Batch number;

g) Production date;

h) Product shelf life;

i) Gross weight;

j) Packing staff;

k) Inspectors;

l) Box number;

m) Dimension of corrugated box (length × width × height);

n) Name and address of the manufacturing company;

o) Signs such as "Handle with care", "Keep dry" and etc. shall comply with the relevant requirements in YY/T 0313—2014.

6.3 Storage of product

Storage of product shall comply with requirements in 7.5.11 of YY/T 0287—2017 for regulatory purposes. The organization shall establish protective procedures to protect products during manufacturing, storage, handling, and transportation to meet product protection requirements. The 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.