Product Description: West Global Specification for **Halogenated Butyl Rubber Stopper for Lyophilized Injectable Drug Products , China**

Control ID: **MSPEC: WPSCH-0010** Rev.: 12

1 Scope

1.1 This Global Master Specification provides product acceptance criteria for the physical, microbiological and packaging properties of halogenated butyl rubber stoppers for lyophilized injectable drug products supplied for the China Market.

1.2 The specification applies to both laminated and non-laminated components.

1.3 The specification applies to non-sterile and sterile components. Products will be listed in VAL: E.00047.

1.4 The process operates under applicable cGMPs.

1.5 All tests in this Master Specification are required for releasing product to China Market, as applicable.

2 Reference Documents: (Current Versions)

2.1 Policy on Change Notification of Process/Material Changes

A copy may be obtained on West's website, www.westpharma.com; (Support/Quality Assurance Support/Global Change Policy)

2.2 ESOP-8105: Change Control

2.3 EPD-7001: Testing and Release Policy – China Market

2.4 EPD-7002: Product Grouping for Chinese Pharmacopeia and YBB methods

2.5 EPD-7003: Fragmentation Testing of Stoppers and Liners for Pen-Injectors (in accordance with YBB/ChP as applicable)

2.6 EPD-7008 Justification for Compendial Test Methods

2.7 ESOP-3133: YBB Stability Studies for China

2.8 VAL:E.00047 China Registration Bracket

2.9 VAL:E.00078 Justification Report: Registration and Stability testing T0 of Dimensional characteristics aligned with YBB Requirements

2.10 YBB00052005-2015: Halogenated Butyl Rubber Stopper for Injectable Sterile Powder

2.11 Chinese Pharmacopeia (2020 Edition): 4002 Test for Infrared Spectrum of Packaging Materials

2.12 Chinese Pharmacopeia (2020 Edition): 4016 Test for Fragmentation of Injection Closures

2.13 Chinese Pharmacopeia (2020 Edition): 4015 Test for Penetration Force of Injection Closure

2.14 YBB00262005-2015: Determination of Ash for Rubber

2.15 YBB00302004-2015: Determination of Volatile Sulfides

2.16 YBB00272004-2015: Test for Insoluble Particulate Matter of Packaging Materials

2.17 Chinese Pharmacopoeia 2020, Vol. IV General Rule 0401, 0631, 0821, 0901, 0902

2.18 YBB00022003-2015: Test for Pyrogen

2.19 Chinese Pharmacopeia (2020 Edition): 4013 Test for Hemolysis of Packaging Materials

2.20 Chinese Pharmacopeia (2020 Edition): 4011Test for Acute Systematic Toxicity of Packaging Materials

2.21 Inspection requirements: AQL GB/T 2828.1-2012

2.22 Chinese Pharmacopeia (2020 Edition): 1143 Method for Bacterial Endotoxin Test in accordance with harmonized BIO-22: Quantification of Endotoxins on Elastomeric Closures and Westar Lined Seal.

2.23 MSPEC: WPSCH_INS-0010: Justification Document – Specification for Halogenated Butyl Rubber Stopper for Lyophilized Injectable Drug Products, China

2.24 MSPEC: WPSCH_ATT-0010: Attachment Document – Specification for Halogenated Butyl Rubber Stopper for Lyophilized Injectable Drug Products, China

2.25 ISO 11137: Sterilization of health care products – Radiation

3 Specification Table

	Test	Acceptance Criteria
National Medical Products Administration (NMPA)	**Visual Inspection and Dimension**	
	Appearance (YBB) [1]	Complies (see 4.1.1)
	Appearance [2]	Complies (see 4.1.2)
	Dimensions (YBB) [1]	Complies (see 4.15)
	Dimensions [2]	Complies (see 4.15)
	Functional Tests	
	Fragmentation	NMT 5 fragments
	Penetration Force	Test Method 2: Average force shall not exceed 10 N. The maximum force for each rubber stopper should not exceed. 10 N.
	Closure-Vial Compatibility	No traces of Methylene Blue inside the vials
	Resealability	No traces of Methylene Blue inside the vials
	Biological Tests	
	Pyrogen [3]	No pyrogenic response is observed
	Hemolysis [3]	< 5%
	Acute systemic toxicity test [3]	No acute systemic toxic response is observed
	Particulate Tests	
	Insoluble particles[4;11]	Particles size ≥10 µm; Max. 60 particles/mL Particles size ≥25 µm; Max. 6 particles/mL
	Chemical Tests	
	Identification[3]	(i)Positive for $AGNO_3$ Test[10] (ii)Comply to Reference Spectrum
	Clarity and color	Clarity: Intensity ≤Number 2 turbidity standard solution Color: Intensity ≤Number 5 yellow green standard solution.

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Volatile Sulfides[3]	NMT 50 µg Na_2S/20 cm^2
Ash content [5] YBB Ash limits to be followed for all formulation with the exceptions as listed below:	≤ 50%
Ash 1816 grey	⩽ 50.2%
pH Change[4]	NMT 1.0
Absorbance (wavelength 220 to 360nm)	NMT 0.2 AU
Oxidizable Substance	NMT 7.0 mL of 0.01 M $Na_2S_2O_3$
Non-volatile Matter	NMT 4.0 mg
Heavy Metals	NMT 1 ppm
Extractable Ammonium	NMT 0.0002%
Extractable Zinc	NMT 0.0003%
Conductivity[4]	NMT 40.0 µS/cm
Moisture Content[6]	NMT 0.5%
Tests for Ready to Use (RU) products	
Bacterial Endotoxin [7]	≤ 1 EU/Piece (BIO-22)
F_0 Lethality[8]	≥ 35.0 (minutes)
Dosimeter [9]	Stopper Dose range 10-40 kGy (Cobalt 60)

Notes:

[1] For product registration and stability testing, appearance is performed according to YBB0052005-2015.

VAL: E.00078 justifies that Dimensions do not have to be performed for registration testing stability T0 testing.

[2] For release testing, appearance and dimension checks are done according to West's procedures and inspection plan as stated in MSPEC: WPSCH_INS-0010.

[3] Tests performed for product registration only. Not required for release testing except in events as described in EPD -7001.

[4] Not required for standard washed product. Tests are for pharmaceutical washed products only and not for soft/purified water rinsed products that have not undergone pharmaceutical washing. For West Standard items, the final washing is done by the customer.

[5] Ash limit acceptance criteria for products previously registered under JBB License J20140043 and J20140022 is to be obtained from the Formulation Characteristics.

[6] Moisture will only be required for products previously released under J20140043 and J20140022.

[7] Applies to Ready to Use (RU) components only. Results will be extracted from release batch testing, by the method BIO-22: Quantification of Endotoxins on Elastomeric Closures and Westar Lined Seal.

[8] Applies to Ready to Use (RU) steam sterilized components only. Sterilization achievement will be determined using the parametric review of critical process parameters and achieved F_0 Lethality during the autoclave cycle.

[9] Applies to Ready to Use (RU) gamma sterilized components only.

[10] This test is not required for Non-halogenated Butyl Rubber products.

[11] West internal limit is more stringent with ≥, whereas the YBB standard refers to >.

4 NMPA Test Methods

4.1 Appearance

4.1.1 Product Registration

Collect several samples and visually inspect these samples according to paragraph 4.14. The closures should comply with the requirement.

4.1.2 Routine Release

Collect several samples and visually inspect these samples according to West's procedures and inspection as stated in MSPEC: WPSCH_INS-0010.

4.2 Identification (See Appendix 1 for Reference Spectrum)

4.2.1 Silver Nitrate Method

Cut sufficient samples into small pieces. Weigh 2.0 g and place in a crucible, add 2.0 g of sodium bicarbonate and cover with a lid. Heat gently in an electric burner, until the sample is thoroughly charred. Allow to cool, place in a high temperature furnace and heat at 300°C until completely reduced to ash. Allow to cool, add approximately 10mL of water, dissolve and filter. In a test tube, place 1.5 mL of filtrate, acidify with nitric acid and silver nitrate solution dropwise until a precipitate is formed. A pale yellow (bromobutyl) or white (chlorobutyl) precipitate should appear.

4.2.2 Infrared Spectrum Method

For rubber, take sufficient samples, test as per Chinese Pharmacopoeia 2020 Edition 4002 Test for Infrared Spectrum of Packaging Materials, ATR Method. The spectrum should comply with the reference spectrum provided in Appendix 1.

West is using a Diamond ATR Crystal instead of Zinc Selenide.

If laminated, take sufficient samples, test the laminated side of the product contact side of the component as per Chinese Pharmacopoeia 2020 Edition 4002 Test for Infrared Spectrum of Packaging Materials, ATR Method. The spectrum should comply with the reference spectrum Appendix 1. West is using a Diamond ATR Crystal instead of Zinc Selenide.

4.3 Moisture Content

Moisture will only be required for J20140043 and J20140022

List of products to be tested for moisture content are registered under JBB License J20140043 and J20140022:

1. J20140043: Singapore- 4432/50 Grey, PH 701/45 C Black
2. J20140022: Singapore- 4405/50 Grey, 1816 Grey, 4023/50 Grey

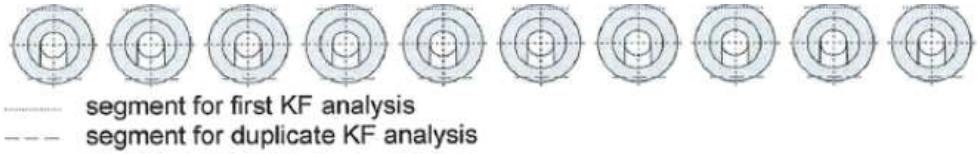
Pre-treatment

The autoclaving shall be performed under conditions of 121°C for 30 minutes. Place twelve stoppers in a beaker (or suitable receptacle) and autoclave them as-is. Upon completion of autoclave cycle, the samples shall be cooled in a desiccator for 30 minutes. The autoclaved, cooled stoppers shall be put into the drying oven, previously conditioned at 105°C, and dried for four hours at 105°C. After the requisite drying period, the stoppers shall be tested without undue delay.

Sample Preparation

Perform the sample preparation in a suitably dry environment (23±2°C, 50±5 %RH).

Use pincers and disposable gloves to handle the closures. Collect at least ten closures (from twelve listed earlier). From each closure, cut one segment from the top flange along a perpendicular plane such that the segment length is 4-7 mm. There should be ten segments from ten different closures, making a total mass of approximately 100 mg (100 mg for a 13 mm stopper, 100-200 mg for a 20 mm stopper). Weigh the segments in a weighing boat and transfer to the vial to be crimped for the analysis. Cut another segment in a location diametrically opposite, for the duplicate analysis.



If there are delays due to sample queue, the cut segments should be placed in crimped vials until the analysis set-up is ready. Retain the cut closures in suitable air-tight vessels (previously dried at 105°C for 2 hours), until all analysis is complete.

Coulometric KF analysis

Set up the apparatus in accordance to the equipment manual. Adjust the drying pistol to 140±2°C. Check the apparatus for drift and determine the suitability of the test condition using a certified water standard. This should be at least performed daily, and whenever required.

Place the cut segments (in the vial) into the heater and start the analysis until endpoint is reached. Perform the duplicate analysis. The data should be reported as sample weight and % water. The moisture content should not exceed 0.5%.

4.4 Fragmentation

Take sufficient samples, in alignment with Chinese Pharmacopeia (2020 Edition): 4016 Test for Fragmentation of Injection Closures Method II, reference method, the total number of fragments should not exceed 5.

Fragmentation testing will be carried out using the method as described in Chinese Pharmacopeia (2020 Edition): 4016 Test for Fragmentation of Injection Closures, without the testing of the reference samples alongside the test samples. (Reference EPD-7003)

4.5 Penetration Force

Take 10 samples, test as per Chinese Pharmacopeia (2020 Edition): 4015 Test for Penetration Force of Injection Closures, Method II. The maximum penetration force for each stopper should not exceed 10 N. Autoclaving of the samples will be carried at 121±2°C.

4.6 Closure-Vial Compatibility

Place 10 samples into a beaker, add water and boil for 5 minutes, remove and dry the stoppers at 70°C for 60 minutes. Fit the samples onto 10 vials filled with nominal volume of water, crimp and autoclave at 121±2°C over 30 minutes, remove the vials and stand for 24 hours. Invert the vials and immerse in 0.1 % Methylene Blue solution and reduce the pressure by 25 kPa for 30 minutes. Restore to atmospheric pressure and allow to stand for another 30 minutes. Rinse the exterior of the vials and inspect, there should be no traces of Methylene Blue inside the vials.

4.7 Resealability

Take samples as described in Closure-Vial Compatibility, pierce each stopper thrice with a hypodermic needle described in Chinese Pharmacopeia (2020 Edition): 4015 Test for Penetration Force of Injection Closures, Method II, change the needle after tenth pierce. Submerge the vials inverted in 0.1 % Methylene Blue solution and reduce the pressure by 25 kPa for 30 minutes. Restore to atmospheric pressure and allow to stand for another 30 minutes. Rinse the exterior of the vials and inspect the vials, there should be no traces of Methylene Blue inside the vials.

4.8 Ash Content

Weigh 1.0 g of sample, test as per YBB00262005-2015 “Determination of Ash for Rubber.” The mass of the residue should meet the applicable product ash limit in the Specification Table.

Ash limits from formulation characteristics are required for the following products previously registered under JBB License J20140043 and J20140022:

1. J20140043: Singapore- 4432/50 Grey, PH 701/45 C Black
2. J20140022: Singapore- 4405/50 Grey, 1816 Grey, 4023/50 Grey

4.9 Volatile Sulfides

Use samples corresponding to 20±2 cm^2, cut the sample if necessary. Test as per YBB00302004-2015 “Determination of Volatile Sulfides.” The test results obtained should comply with the outlined requirements.

4.10 Insoluble Particulates

Testing is performed using the Light Obscuration Method as detailed in YBB00272004-2015 “Insoluble Particulate Matter Test for Packaging Materials”. For every mL, there should not be more than 60 particles with size ≥10 µm; not more than 6 particles with size ≥25 µm.

If the result obtained using the Light Obscuration Method does not meet the specification, the test is repeated using the Membrane Method as detailed in YBB00272004-2015. For every mL, there should not be more than 60 particles with size ≥10 µm; not more than 6 particles with size ≥25 µm. The Membrane Method result is used for disposition.
West internal limit is more stringent with ≥, whereas the YBB standard refers to >.

4.11 Chemical Characteristics

Test solution: Place uncut samples corresponding to a surface area of about 200 cm^2 into a beaker. Add water corresponding to a ratio of 1:2 (Surface Area: Water) and boil for 5 minutes. Rinse 5 times, each time using the same amount of water. Transfer the washed samples to a conical flask, add the same amount of water and autoclave by raising the temperature to 121±2 °C over 30 minutes. Maintain the temperature for another 30 minutes. Then, cool to room temperature in 20-30 minutes. Separate the closures to obtain the extract.

Blank: Prepare a blank in same manner. Carry out the following tests:

4.11.1 Clarity and Color

Obtain 10 mL of test solution, test as per (Chinese Pharmacopoeia 2020, Vol. IV General Rule 0902, 0901), the test solution should be clear and colorless. If it appears turbid, compare with No.2 turbidity reference solution, the solution should not be more turbid than the reference. If it appears colored, compare with Yellow-Green No. 5 standard solution, the color of the test solution should not be more intense than the reference.

4.11.2 pH Change

Obtain 20 mL of test solution and blank solution. Add 1 mL of potassium chloride solution (1 → 1000) to each and test as per (Chinese Pharmacopoeia 2020, Vol. IV General Rule 0631). The pH difference between the two should not exceed 1.0.

4.11.3 UV Absorbance

Obtain sufficient test solution, using the blank solution as reference, test as per (Chinese Pharmacopoeia 2020, Vol. IV General Rule 0401). Measure the absorbance at wavelength of 220-360 nm, the greatest absorbance should not exceed 0.2.

4.11.4 Oxidizable Substances

Add 20.0 mL of 0.002 mol/L potassium permanganate and 2 mL dilute sulfuric acid to 20.0 mL test solution. Boil for 3 minutes and cool rapidly. Add 0.1 g potassium iodide and leave in the dark for 5 minutes. Titrate with 0.01 mol/L sodium thiosulfate solution until light brown. Add 5 drops of starch indicator solution and titrate until colorless. Carry out a titration using the blank. The titration volume difference between the two should not exceed 7.0 mL.

4.11.5 Non-volatile Matter

Measure 100 mL of test solution and place in an evaporating dish weighed to constant mass. Evaporate to dryness by placing the samples in an oven at 105 °C for 16 hours. Repeat for 100 mL of blank solution. The weight difference between the two should not exceed 4.0 mg.

4.11.6 Heavy Metals

Add 2 mL of acetate buffer solution (pH 3.5) to 10 mL of test solution and test as per (Chinese Pharmacopoeia 2020, Vol. IV General Rule 0821, Method One). The heavy metal level should not exceed 1 ppm.

4.11.7 Extractable Ammonium

Add 2 mL of Nessler's reagent to 10 mL of test solution and allow to stand for 15 minutes. The sample solution should remain colorless. If color appears, prepare a reference solution by adding 2.0 mL of ammonium chloride solution (dissolve 31.5 mg of ammonium chloride with ammonium-free water and dilute to 1000.0 mL) to 8 mL of blank and 2 mL of Nessler's reagent. The test solution shall not be darker than the reference (0.0002 %).

4.11.8 Extractable Zinc

Filter the test solution through a 0.45 μm filter. Collect 10 mL of filtrate and add 1 mL of 2 mol/L hydrochloric acid and 3 drops of freshly prepared potassium hexacyanoferrate solution (dissolve 4.2 g of potassium hexacyanoferrate trihydrate in water and dilute to 100mL). The solution should be freshly prepared. The sample solution should remain colorless. If color appears, prepare a reference by adding 3.0 mL of zinc standard solution (dissolve 44.0 mg of zinc sulfate heptahydrate in cooled freshly boiled water and dilute to 1000.0 mL, the solution should be freshly prepared), 7 mL of blank solution, 1 mL of 2 mol/L hydrochloric acid, and 3 drops of potassium hexacyanoferrate. The test solution should not be darker than the reference (0.0003%).

4.11.9 Conductivity

Perform the test within 5 hours of test solution preparation: The conductivity of the blank solution should not exceed 3.0 μS/cm at 20±1°C. The conductivity of the sample should not exceed 40.0 μS/cm at 20±1°C, adjustments should be made if the measurement is not done under conditions of 20±1°C.

4.12 Biological Tests

4.12.1 Pyrogen

Take sufficient samples, add sodium chloride injection in the ratio of 0.2 g/mL and place it in an autoclave oven at 115±2°C for 30 minutes. Test the extraction solution as per YBB00022003-2015 “Tests for Pyrogen”; the result should comply with the stated requirements.

4.12.2 Hemolysis

Test per as per Chinese Pharmacopoeia 2020 Edition 4013 Test for Hemolysis of Packaging Materials. The results should comply with the stated requirement.

4.12.3 Acute Systemic Toxicity

Take sufficient samples, add sodium chloride injection in the ratio of 0.2 g/mL and place it in autoclave oven at 115±2°C for 30 minutes. Test the extraction solution as per Chinese Pharmacopoeia 2020 Edition 4011Test for Acute Systematic Toxicity of Packaging Materials. The result should comply with the stated requirements.

4.13 Microbiological Tests

4.13.1 Bacterial Endotoxin*

Transfer 10 stoppers to a depyrogenated flask, add LAL reagent water with Tween 80 and shake at approximately 350 RPM for 1 hour at room temperature. A fixed volume of resulting solution is tested in duplicate. Test sample preparation as per US Pharmacopoeia: <85>Bacterial Endotoxins, European Pharmacopoeia 2.6.14 Bacterial Endotoxins and Chinese Pharmacopoeia (2020 Edition) : 1143 Method for Bacterial Endotoxin Test.

The specification as per globally aligned BIO-22 Test Method is ≤ 1 EU/Piece.

4.13.2 Biological Indicators+

Use standard biological indicators (BI). This method is applicable for qualification production sterilization cycles. Following sterilization, the biological indicators are removed from the sterilizer load and forwarded to the lab for testing. Under appropriate environmental conditions, each BI is transferred to a Tryptic Soy Broth (TSB) jar. A positive and negative control is tested per autoclave cycle. Samples are incubated and monitored: BI's not less than 7 days

Results are reported as follows:
N = No Growth
P = Growth

For results to be valid, the positive control must show growth.
All biological indicators subjected to the sterilization cycle should not have any growth. The specification is 0 positive.
The sterilization achievement for release testing will be determined using the parametric review of critical process parameters and achieved F_0 Lethality during the autoclave cycle.
The specification is F_0 Lethality calculation ≥ 35.0 minutes**.**
Use standard biological indicators (BI). This method is applicable for qualification production sterilization cycles. Following sterilization, the biological indicators are removed from the sterilizer load and forwarded to the lab for testing. Under appropriate environmental conditions, each BI is transferred to a Tryptic Soy Broth (TSB) jar. A positive and negative control is tested per autoclave cycle. Samples are incubated and monitored: BI's not less than 7 days at 55-60°C.

Results are reported as follows:
N = No Growth
P = Growth

For results to be valid, the positive control must show growth.
All biological indicators subjected to the sterilization cycle should not have any growth. The specification is 0 positive.
The sterilization achievement for release testing will be determined using the parametric review of critical process parameters and achieved F_0 Lethality during the autoclave cycle.
The specification is F_0 Lethality calculation ≥ 35.0 minutes**.**

4.13.3 Dosimeter#

During exposure, the contract sterilizer will place dosimeters within the load using locations identified during qualification. The dosimeters will collect exposure amounts and the contract

sterilizer will certify the minimum and maximum dose on a certificate at the time product is released back to West. The minimum and maximum dose results will appear on the West provided certificate.

Acceptable dose range is between 10 and 40 kGy.

* Applies to Ready to Use product only.

+ Applies to Ready to Use steam sterilized product only.

Applies to Ready to Use gamma sterilized product only.

4.14 Sampling requirements

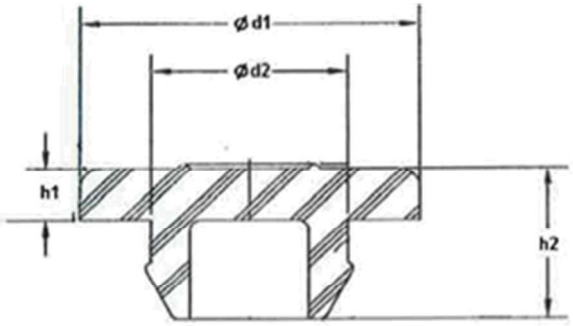
Conduct the sampling procedure Part I: AQL limits based on the sampling plan (GB/T2828.1 -2012). The closures should comply in accordance to the tabulated table below.

4.14.1 Inspection Level and Acceptable Quality Limits (AQL) Table

Inspection Item	Appearance		
Inspection Level	General Inspection Level I		
AQL	0.4	1.5	6.5
Non-Conformance	Type A	Type B	Type C
	Spots or contamination (≥0.2 mm^2) within target ring or on the surface that is in contact with drug. Air bubble or crack within target ring or seal area.	Spots, contamination (≥0.2 mm^2), rubber trash, rubber particles, sponge, fringe on closure surface. Rough surface or non-fill on closure plug area.	Defects caused by trimming, mold marks and color variations.

4.15 Dimension for stopper to comply with Diagram & Table

4.15.1 Dimension and Design of Stopper Diagram



4.15.2 Dimension of Stoppers (Unit: mm) Table

Size (mm)	Φ d_1	Φ d_2	h_1	h_2

13	See applicable West drawing for dimension requirements
20	See applicable West drawing for dimension requirements

Based on the rationales described in Val: E 00078 Justification Report: Registration and Stability testing T0 of Dimensional characteristics aligned with YBB Requirements, West justifies therein that it is not necessary to test dimensional characteristics for registrations and stability T0.

5 Testing Program

5.1 **The testing as outlined in this Master Specification:**

The batch release criteria in accordance with EPD-7001

The stability testing plan in accordance with ESOP-3133

The registration testing plan in accordance with EPD-7002

Testing will be carried out per applicable Chinese Pharmacopoeia and YBB standards in accordance with EPD 7008.

5.2 Changes impacting the product will be evaluated in accordance with West's change control procedure. Full inspection may be carried out if needed.

6 Revision History

Revision 12:

- The release criteria on Ready-to-Use (RU) steam sterilized components will change according to CC # 200040017. The parametric release replaces biological indicator (BI) specification and results with the F0, Lethality specification and results. There is no product impact from removing the BIs from the production sterilization cycles. The autoclave cycles have been validated to achieve a sterility assurance level of 10^{-6}. This leads to the following updates:
- Section 1 removal of ChP reference Biological Indicator Section 3
- Section 3 Specification Table updated Biological Indicator to F_0 Lethality$^{8} \geqslant$ 35.0 (minutes) and the related footnote accordingly,
- Section 4.13.2 Biological Indicators^{+} updated the wording to reflect the F_0 Lethality calculation. Removal of the self-contained indicators (SCBI) in the method as West does not use SCBIs.

Revision 11:

- Section 4.15.2 Dimension of Stoppers (Unit: mm) Table, deleted 28 mm reference as per CC 200022691 to exclude the groups 96 and 110 from this document.

Revision 10:

- Section 2 updated VAL: E.00078 title, reference CC # 200002279

- Section 3 Specification Table amended stability T0 to footnote 1 VAL: E.00078 and updated the title, reference CC # 200002279
- Section 4.15.2 Dimension of Stoppers (Unit: mm) Table, updated wording to include stability T0 and updated the VAL: E.00078 title, reference CC # 200002279.

Revision 9:

- Reworded 4.7 Resealability and exchanged previous YBB0032204-2015 reference to Chinese Pharmacopeia 2020: 4015. The related Change Control # is 435342.

Revision 8:

- Section 2 Reference Documents exchanged the pervious YBB references to Chinese Pharmacopoeia 2020 Edition 4002, 4011, 4013, 4015 and 4016 as the Chinese Pharmacopoeia superseded the YBB standards for the aforementioned methods. The related Change Control # is 435342. Added Chinese Pharmacopoeia Reference General Rule 0401, 0631, 0821, 0901, 0902 and VAL: E.00047 and VAL: E.00078 to the section. Updated title of EPD 7008. Revision 2 of EDP 7003 leads to the update of the title to Fragmentation Testing of Stoppers and Liners for Pen-Injectors (in accordance with YBB/ChP as applicable). Deleted BIO-05 reference.
- Section 3 Specification Table added to footnote 1 VAL: E.00078 justifies that Dimensions do not have to be performed for registration testing. Endotoxin: Deleted the BIO-05 reference, as BIO 22 is implemented now and supersedes Bio-05.
- Updated the Chinese Pharmacopeia 2015 references where applicable to Chinese Pharmacopeia 2020, the related Change Control # is 435342.
- Incorporated to Infrared Spectrum Method 4.2.2 the Chinese Pharmacopeia 2020 Edition 4002 and deleted the previous YBB references, as the Chinese Pharmacopoeia superseded the YBB standards for the aforementioned method. The related Change Control # is 435342.
- 4.4 Fragmentation Exchanged the previous YBB 00332004 (2015) reference on Fragmentation to Chinese Pharmacopeia (2020 Edition): 4016 Test for Fragmentation of Injection Closures Method II, reference method. The related Change Control # is 435342.
- 4.5 Penetration Force Exchanged the previous YBB 00322004 (2015) reference on Penetration force to Chinese Pharmacopeia (2020 Edition): 4015 Test for Penetration Force of Injection Closures Method II, reference method. The related Change Control # is 435342
- Added to Acute Systemic Toxicity Test 4.12.3 and Hemolysis 4.12.2 the applicable Chinese Pharmacopoeia 2020 Edition 4011 and 4013 and deleted the previous YBB references as the Chinese Pharmacopoeia superseded the YBB standards for the aforementioned methods. The related Change Control # is 435342.
- Added to Dimension of Rubber Plunger (Unit: mm) Table 4.15.2 “Based on the rationales described in Val: E 00078 Justification Report: Registration of Dimensional characteristics aligned with YBB Requirements, West justifies therein that it is not necessary to test dimensional characteristics for registrations.”
- 4.13.1 Bacterial Endotoxin, reworded the method description, deleted BIO-05 reference and included USP and EP reference as BIO -022 is applicable to all Pharmacopoeias. Added Tween 80 detergence in alignment with the BIO-022 method.
- Section 5 Testing Program: introduced EPD 7008 to this section to enable to delete the previous redundant references to EDP 7008 within the NMPA Test methods of Section 4. Reworded “Full testing may be carried out per applicable YBB standards” to “Testing will be carried out per applicable Chinese Pharmacopoeia and YBB standards in accordance with EPD 7008.”

Revision 7

- Added to Section 2 Reference Documents 2.6 EPD 7008 2.19 BIO-22: Quantification of Endotoxins on Elastomeric Closures and Westar Lined Seal
- Incorporated BIO-22 method to the Section 3 Specification Table Bacterial Endotoxin test, added acceptance criteria ≤ 1 EU/Piece (BIO-22) and rephrased footnote 7 for the transition period. In 4.13.1 Bacterial Endotoxin* deleted the words "100 mL of", as the amount of LAL reagent water vary, and added "The specification is during transition period either ≤ 0.10 EU/mL/10 plungers (BIO-05) or ≤ 1EU/Piece (BIO-22)".
- Added to Insoluble Particulates in Specification table footnote 11 and to 4.10 Insoluble Particulates: West internal limit is more stringent with ≥, whereas the YBB standard refers to > . Quality record reference is 404198.
- Added Footnote 10 to the Specification table [10] This test is not required for Non-halogenated Butyl Rubber products. For non-halogenated butyl rubber, the silver nitrate testing is not possible, no precipitate can be formed.
- Corrected Section 4.2.1 Silver Nitrate, the silver nitrate solution is now added dropwise until a precipitate is formed, as referenced in EPD 7008, instead of one drop.
- Build into Section 4.2.2 Infrared Spectrum Method the sentence "Reference EPD 7008 West is using a Diamond ATR Crystal instead of Zinc Selenide".
- Added to Section 3 Specification table into Penetration force column the maximum force for each rubber stopper should not exceed 10 N corrected the wording in 4.4. and deleted average, exchanged maximum. The maximum penetration force for each stopper should not exceed 10 N in alignment with YBB YBB00052005-2015.
- Added to 4.5 Penetration force "Autoclaving of the samples will be carried at 121±2°C. (Reference EPD 7008)"The autoclaves cannot be qualified to 121 +/- 1°C, therefore we had to implement the wider range 121+/- 2°C.
- Correction in Section 4.6 Closure-Vial Compatibility and 4.7 Resealability10 % to 0.1 % Methylene Blue solution (Reference EPD 7008).
- In Section 4.11.5 Non-volatile Matter deleted "waterbath" and detailed that the samples are placed in an oven at 105 °C for 16 hours (reference EPD 7008).

Revision 6:

- Corrected Section 4.2.1 Identification text. The word "Into" should be read "of", canary exchanged to pale, based on a translation error from Chinese to English. The sentence "Let the mixture stand for five minutes" was deleted, as it is not referenced in YBB.
- Implemented EPD 7003 which was made effective 25 February 2020
- Included Footnote 5 Ash limits from formulation characteristics are required for the following products previously registered under JBB License J20140043 and J20140022, which include J20140043: Singapore- 4432/50 Grey, PH 701/45 C Black and J20140022: Singapore- 4405/50 Grey, 1816 Grey, 4023/50 Grey. The inclusion required a renumeration of the footnotes
- Added to 4.8 Ash Content "Ash limits from formulation characteristics are required for the following products previously registered under JBB License J20140043 and J20140022.
  J20140043: Singapore- 4432/50 Grey, PH 701/45 C Black
  J20140022: Singapore- 4405/50 Grey, 1816 Grey, 4023/50 Grey".
- Added 28 Dimension of Stoppers (Unit: mm) into Table 4.15.2 to include further registrations.

Revision 5:

- The overarching MSPEC change: ESW 2019-138: YBB Master Spec Change, required an update of all existing MSPECs including several changes as listed below:
- Deleted the sentence "Products will be listed in Appendix 2" in 1.3 as Appendix 2 will be removed from the Attachment according to VAL: E.00047. Therefore added "Products are listed in VAL: E00047
- Added EPD-7002 Product Grouping for Chinese Pharmacopeia and YBB methods and EPD-7001: Testing and Release Policy – China Market and ESOP-3133: YBB Stability Studies for China MSPEC: WPSCH_ATT-0010: Attachment Document – Specification for Halogenated Butyl Rubber Stopper for Lyophilized Injectable Drug Products, China to the Reference Documents.
- Deleted columns R and RT in the table
- Divided the test within the Specification table into Particulate, Chemical, Functional, Biological tests, Visual Inspection and Dimension and Tests for Ready to Use (RU) products in alignment with the YBB Standard
- Deleted ≤ for Section 3 Specification table to Biological Indicator[6] 0 Positive as the ≤ was not applicable.
- Added 4.3 and footnote in specification table: Moisture Content Moisture will only be required for J20140043 and J20140022
  List of products to be tested for moisture content are registered under JBB License J20140043 and J20140022:
  J20140043: Singapore- 4432/50 Grey, PH701/45 C Black
  J20140022: Singapore- 4405/50 Grey, 1816 Grey, 4023/50 Grey
- Exchanged CFDA to NMPA
- Added mL to Particles size ≥10 µm; Max. 60 particles/mL within Specification table
- Deleted biological in footnote 3 and added following tests Identification[3] and Volatile Sulfides[3]
- Deleted [4] For individual ash limits, refer to respective formulation characteristic. The deletion then requires a renumeration of the footnotes.
- Added footnote 4 into the Specification Table of Section 3 "[4] Not required for standard washed product. Tests are for pharmaceutical washed products only and not for soft/purified water rinsed products that have not undergone pharmaceutical washing. For West Standard items, the final washing is done by the customer".
- Added footnote 4 to the following tests: Insoluble particles[4], pH Change[4], and Conductivity[4]
- Regrouped the footnotes accordingly.
- Extended the Dosimeter to 10-40 kGy in Specification table and 4.13.3, added the word "range"
- Re-phrased Fragmentation to test "in alignment" as per 200017978 Change control for fragmentation for stoppers
- Added additional space between number and Si units except for % and °C.
- Renamed min into minutes, hr into hours, min to minimum and max to maximum.
- Corrected small and capital letters.
- Rephrased Section 4.10 Insoluble Particulates; Membrane Method is used in incidences when LO methods fails.
- Added "The solution should be freshly prepared" to Extractable Zinc to Section 4.11.8.
- Rephrased Section 5 deleted the testing listed in this Master Specification may be subject to a reduced testing program in accordance with West procedures, as applicable. And added EPD-

7001, 7002 and ESOP-3133, added Full testing may be carried out as per applicable YBB standards.

Revision 4:

- Added MSPEC: WPSCH_INS-0010 to Reference Documents of Section 2.
- Added Appearance (YBB) and Dimension (YBB) to Specification Table of Section 3
- Added footnote [1] to Appearance (YBB) and Dimension (YBB) to Specification Table of Section 3
- Changed acceptance criteria of pH Change from "NMT 1" to "NMT 1.0" in section 3
- Changed acceptance criteria of Hemolysis from "NMT 5%" to "<5%" in section 3
- Re-phrased footnote[1] to explain the appearance and dimension inspection requirement for product registration and stability testing
- Added footnote [6] for release testing requirement for Appearance and Dimension tests to Specification Table of Section 3.
- Added footnote [7] for dosimeter requirement
- Re-phrased paragraph 4.1 to state the requirements for appearance and dimension checks for product registration and routine release.
- Change "reduce the pressure to 25kPa" to "reduce the pressure by 25kPa" in section 4.6 and 4.7.
- Deleted "Testing shall be initiated within 4 hours of processing" from section 4.13.2.
- Added Dosimeter test to section 4.13.3.

Revision 3:

- Added Biological Indicator reference to paragraph 2.15
- 3 Specification Table – Changed the symbol from ">" to "≥" for Insoluble Particles size of Insoluble Particles test to align with YBB standards.
- 3 Specification Table – Added Biological Indicator acceptance criteria and footnote [5].
- Added paragraph 4.13.2 and note "+".

Revision 2:

- 2.1 – Minor change on sentence description and update on the link to global change policy.
- 3 Specification Table – Added a footnote [4] to indicate Ash limits to refer to respective Formulation Characteristic.

Revision 1:

- Replaced the terms “Ammonium Extractable” and “Zinc Extractable” with “Extractable Ammonium” and “Extractable Zinc” respectively to align the description in the YBB standards.
- 4.11.7 – Changed chloride-free water to ammonium-free water to align the description in the YBB standards.
- 4.12.1 and 4.12.3 – Changed sodium chloride solution to sodium chloride injection and re-phrased the paragraphs to align the description in the YBB standards.

Signature Manifest

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Approve MSPEC-0010

Author Approval

Name/Signature	Title	Date	Meaning/Reason
Jeanette Hampe (HAMPEJ)	Sr. Specialist, QA	05 Mar 2024, 06:54:51 AM	Approved

Approval

Name/Signature	Title	Date	Meaning/Reason
Cecile Guyot (GUYOTC)	Sr Director, QA Ops, HVP	07 Mar 2024, 10:53:53 AM	Approved
Jenny Wong (WONGJ02)	Dir, Global Reg Affairs	08 Mar 2024, 04:46:25 PM	Approved
Laura Simpson (SIMPSONL)	Sr. Specialist, Quality System	13 Mar 2024, 07:37:38 PM	Approved
Lucia Ino (INOL)	Sr Dir, Quality Ops, Core	19 Mar 2024, 11:57:43 AM	Approved