Product Description: West Global Specification for **Halogenated Butyl Rubber Stopper for Small Volume Injection, China**

Control ID: **MSPEC: WPSCH-0009** Rev.: **9**

1 Scope

1.1 This Global Master Specification provides product acceptance criteria for the physical, microbiological and packaging properties of halogenated butyl laminated and non-laminated rubber stoppers for small volume injection supplied in China Market.

1.2 The specification applies to non-sterile and sterile components. Products are listed in VAL: E.00047.

1.3 The specification applies to laminated and non-laminated components.

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 method

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 YBB00042005-2015 Halogenated Butyl Rubber Stopper for Injection

2.11 YBB 00052005-2015 Halogenated Butyl Rubber Stopper for injectable sterile powder

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

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

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

2.15 YBB00262005-2015: Determination of Ash for Rubber

2.16 YBB00302004-2015: Determination of Volatile Sulfides

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

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

2.19 YBB00022003-2015: Test for Pyrogen

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

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

2.22 Inspection requirements: AQL GB/T 2828.1-2012

2.23 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.

2.24 MSPEC: WPSCH_INS-0009: Justification Document – Specification for Halogenated Butyl Rubber Stopper for Small Volume Injection, China

2.25 MSPEC: WPSCH_ATT-0009 Attachment for Halogenated Butyl Rubber Stopper for Small Volume Injection, China

2.26 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 4.14)
	Dimensions [2]	Complies (see 4.14)
	Functional Tests	
	Fragmentation	NMT 5 fragments
	Penetration Force	Test Method 2: Average force 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
	Chemical Test	
	Identification[3]	(i)Positive for $AGNO_3$ Test[9] (ii)Comply to Reference Spectrum
	Clarity and Color	Clarity: Intensity ≤ Number 2 turbidity standard solution Color: Intensity ≤ Number 5 yellow green standard solution.
	Volatile Sulfides[3]	NMT 50 µg Na_2S/20cm^2
	Ash YBB Ash limits to be followed for all formulation with the exceptions as listed below:	≤ 45%
	Ash PH 21/50 Grey Ash 4023/50 Grey Ash 4432/50 Grey Ash 4405/50 Grey Ash 4416/50 Grey	≤ 48.0% ≤ 48.4% ≤ 48.6% ≤ 45.2% ≤ 49.5 %
	pH Change[4]	NMT 1.0

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Absorbance (wavelength 220 to 360nm)	NMT 0.1 AU
Oxidizable Substance	NMT 3.0 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
Biological Tests	
Pyrogen[3]	Non pyrogenic response is observed
Hemolysis[3]	< 5%
Acute systemic toxicity test[3]	No acute systemic toxic response is observed
Particulate Tests	
Insoluble Particles[4; 8]	Particles size ≥ 10 µm; Max. 30 particles/mL Particles size ≥ 25 µm; Max. 3 particles/mL
Tests for Ready to Use (RU) products	
Bacterial Endotoxin [5]	≤ 1 EU/Piece (BIO-22)
F_0 Lethality[6]	≥ 35.0 (minutes)
Dosimeter [7]	Stopper Dose range 10-40 kGy (Cobalt 60)

Notes:

[1] For product registration and stability testing, appearance is performed according to YBB0042005-2015.

VAL: E.00078 justifies that Dimensions do not have to be performed for registration and 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-0009.

[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. Chemical and particulate 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] 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.

[6] 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.

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

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

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

4 NMPA Test Methods

4.1 Appearance

4.1.1 Product Registration

Collect several samples and visually inspect these samples according to paragraph 4.12. and 4.13 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-0009.

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 10 mL of water, dissolve and filter. In a test tube, place 1.5 mL of filtrate, acidify with nitric acid and add 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 stopper, 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.

4.3 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 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)

4.4 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 out at 121±2°C.

4.5 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.

4.6 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.

4.7 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.

4.8 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 30 particles with size ≥10 µm; not more than 3 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 30 particles with size ≥10 µm; not more than 3 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 >.

4.9 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:

4.9.1 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.

4.9.2 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.

4.9.3 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 0.1.

4.9.4 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 3.0 mL.

4.9.5 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.

4.9.6 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.

4.9.7 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%).

4.9.8 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 100 mL). 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%).

4.9.9 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.

4.10 Biological Tests

4.10.1 Pyrogen

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 YBB00022003-2015 (Tests for Pyrogen), the result should comply with the stated requirements.

4.10.2 Hemolysis

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

4.10.3 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.

4.11 Microbiological Tests

4.11.1 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.

4.11.2 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 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**.**

4.11.3 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.

4.12 Sampling requirements

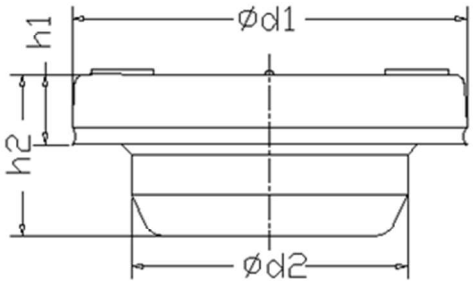
Conduct the sampling procedure Part I: AQL limits based on the sampling plan (GB/T2828.1 -2012). The closures should comply in accordance to the tabulated table below.

4.13 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.

4.14 Dimension for stopper to comply with Diagram & Table

4.14.1 Dimension and Design of Stopper Diagram



4.14.2 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 ESOP-8105. Full inspection may be carried out if needed.

6 Revision History

Revision 9:

- 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$^6 \geqslant$ 35 (minutes) and the related footnote accordingly,
- Section 4.11.2 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 8:

- Section 1 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 4.14.2 Dimension of Stoppers (Unit: mm) Table, updated wording to include stability T0 and updated the VAL: E.00078 title, reference CC # 200002279.

Revision 7:

- 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, as captured in Deviation 429473. Corrected Dimensions reference. Added Footnote 9 "[9]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. 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
- 4.3 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.

- 4.4 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 4.10.3 and Hemolysis 4.10.2 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 4.13.2 "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."
- 4.11.1 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 6:

- Added 2.5 EPD 7003, 2.6 EPD 7008, 2.9 YBB 00052005-2015 and 2.19 BIO-22 to Section 2 Reference Documents.
- Included Ash value for PH 21/50 Grey and 4416/50 Grey to Section 3 Specification table to include further registered formulations
- Corrected Section 4.2.1 Silver Nitrate Method. The word "Into" should be read "of", 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. Furthermore, 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".
- Implemented YBB 00052005-2015 Halogenated Butyl Rubber Stopper for injectable sterile powder and EPD 7003 which have been made effective 25 February 2020.
- 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 to the maximum. The maximum penetration force for each stopper should not exceed 10 N in alignment with YBB YBB00052005-2015.
- "Added to 4.4 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 4.5 Closure-Vial Compatibility 10 % to 0.1 % Methylene Blue solution (Reference EPD 7008).
- Added to Insoluble Particulates in Specification table footnote 8 and to 4.8 Insoluble Particulates: West internal limit is more stringent with ≥, whereas the YBB standard refers to >.Quality record reference is 404198.
- In Section 4.9.5 Non-volatile Matter deleted "waterbath" and detailed that the samples are placed in an oven at 105 °C for 16 hours (reference EPD 7008). Removed 'Continue heating at 105°C until constant mass' consequently

- Incorporated BIO-22 method to the Section 3 Specification Table Bacterial Endotoxin test, added acceptance criteria ≤ 1 EU/Piece (BIO-22) and rephrased footnote 5 for the transition period. In 4.11.1 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)".

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 1.2 as Appendix 2 will be removed from the Attachment according to VAL: E.00047. 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-0009 Attachment for Halogenated Butyl Rubber Stopper for Small Volume Injection, China to the Reference Documents
- Added additional columns to the Specification table in alignment to YBB and regrouped the required tests under the following columns: Particulate Test, Chemical Test, Functional Tests, Biological Tests, Visual Inspection and Dimension and Tests for Ready to Use (RU) products
- Deleted columns R and RT in the table
- Added "/mL" to Insoluble particles to 3. Specification Table
- Deleted "≤" for Section 3 Specification table to Biological Indicator[6] 0 Positive as the "≤" was not applicable
- Remove footnote 2 For individual ash limits, refer to respective formulation characteristic,
- Ash
  YBB Ash limits to be followed for all formulation with the exceptions as listed below
  Ash 4023/50G
  Ash 4432/50G
  Ash 4405/50G
- Reordered the footnotes, as footnote 2 was deleted
- Added footnote 4 into to Specification Table of Section 3 "[4] Not required for standard washed product. Chemical and particulate 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]
- Exchanged CFDA to NMPA
- Re-phrased Fragmentation to test "in alignment" as per 200017978 Change control for fragmentation for stoppers Fragmentation testing will be carried out using the method as described in YBB00332004-2015, but without the testing of the reference samples alongside the test samples.
- Added "The solution should be freshly prepared" to Extractable Zinc to Section 4.9.8.
- Rephrased section 5 Deleted the sentence "The testing listed in this Master Specification may be subject to a reduced testing program in accordance with West procedures, as applicable" Added "The testing as outlined in this Master Specification". Added EPD-7001, 7002 and ESOP-3133, added Full testing may be carried out as per applicable YBB standards, as determined by associated risk assessment.
- Rephrased insoluble particles method to detail that in case of failure on the light obscuration method the membrane method can be used.
- 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.
- Updated dosimeter specification.

Revision 4:

- Added MSPEC: WPSCH_INS-0009 to Reference Documents of Section 2.15
- 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
- Re-phrased footnote[1] to explain the appearance and dimension inspection requirement for product registration and stability testing
- Added dosimeter test and acceptance criteria to Specification Table of Section 3
- Added footnote [6] for release testing requirement for appearance and dimension tests
- Added footnote [7] for dosimeter requirement
- Re-phrased section 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 Closure-Vial Compatibility of section 4.5.
- Deleted "Testing shall be initiated within 4 hours of processing" from section 4.11.2.
- Added Dosimeter test to section 4.11.3.

Revision 3:

<u>Section 3.0 Specification Table</u>

- Included "Ash 4405/50G" and its acceptance criteria
- Added one decimal place to pH Change to align with YBB standard – changed from NMT 1 to NMT 1.0.
- Changed "NMT 5%" to "< 5%" for Hemolysis test.

Revision 2:

- Changed the symbol from ">" to "≥" in the Acceptance Criteria of Insoluble Particles in Specification Table (paragraph 3)
- Added biological indicator and footnote [5] to Specification Table (paragraph 3).
- Added paragraph 4.11.2 and note "+".

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.
- 4.9.7 – Changed chloride-free water to ammonium-free water to align the description in the YBB standards.
  4.10.1 and 4.10.3 – 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-0009

Author Approval

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Approval

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