

## The Harmonization of USP <381> and Ph. Eur. 3.2.9

### I. Background

West has been producing and supplying elastomeric closures for injection to the healthcare market for over 85 years. West elastomeric formulations are developed and produced around the world. Traditionally, formulations have been developed to meet the requirements of their market. Today new West formulations are developed for the global market. Applicable standards are established by the United States Pharmacopeia (USP) and are written in General Chapter <381> *Elastomeric Closures for Injection*. Historically, physicochemical acceptance criteria associated with USP <381> did not exist; however, USP has implemented a revision to <381> to provide more definitive guidance regarding closure selection. This effort has produced the current revision USP <381> in which <381> has been harmonized with the European Pharmacopoeia (Ph. Eur.), Chapter 3.2.9 *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders*. The revision of USP <381> will take effect on May 1, 2009.

West has performed an assessment of all elastomeric formulations and has determined those which are in full compliance with the revision to USP <381>. Should you need to know if your formulation meets the new requirements, contact your Technical Customer Support Representative.

Formulations that do not comply with this revision are typically early generation formulations that have been used for many years with much success. Unfortunately, with this revision, USP has not included provisions to allow for the continued use of formulations that do not comply with the new standard for long-term contact with parenterals.

### II. Comparison of Compendia

The below table is a side-by-side comparison of the tests outlined in the Ph. Eur. and the revised USP. In order to provide the most comprehensive analysis of its elastomer formulations, West has adopted a combined protocol for testing, which is shown in the third column.

<b>Table 1: Comparison of Compendia Tests</b>		
<b>Ph. Eur. 3.2.9</b>	<b>USP &lt;381&gt; Revised</b>	<b>West Combined Protocol</b>
<b>Biological</b>	<b>Biological</b>	<b>Biological</b>
X	USP<87>	USP<87>
X	USP<88>	USP<88>
<b>Physicochemical</b>	<b>Physicochemical</b>	<b>Physicochemical</b>
Appearance (Opalescence and Color)	Turbidity and Color	Appearance (Opalescence and Color)
Acidity or Alkalinity	Acidity or Alkalinity	Acidity or Alkalinity
Absorbance	Absorbance	Absorbance
Reducing Substances	Reducing Substances	Reducing Substances
Ammonium	Ammonium	Ammonium
Extractable Zinc	Extractable Zinc	Extractable Zinc
Extractable Heavy Metals	Heavy Metals	Extractable Heavy Metals
Residue on Evaporation	X	Residue on Evaporation
Volatile Sulphides	Volatile Sulphides	Volatile Sulphides
<b>Physical</b>	<b>Physical</b>	<b>Physical</b>
Penetrability	Penetrability	Penetrability
Fragmentation	Fragmentation	Fragmentation
Self-Sealing	Self-Sealing Capacity	Self-Sealing

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The combined protocol satisfies both the Ph. Eur. and USP requirements for elastomeric closures for injection. The Ph. Eur. and USP chapters are nearly identical; however, where differences exist the procedures outlined in Ph. Eur. are used in the West combined protocol with the following justifications:

Residue on Evaporation Test – The revised USP has dropped this test; however, West will include it in the combined protocol in order to be compliant to both compendia.

Opalescence, Acidity or Alkalinity, Extractable Zinc Tests – The USP specifies to subtract the blank value where Ph. Eur. does not. However, blank values for these tests are generally negligible and subtraction of the blank value would have no significant impact on test results. The West combined protocol will follow Ph. Eur. and will not subtract the blank value to illustrate a worst case scenario.

Heavy Metals Test – Ph. Eur. 2.4.8 Heavy Metals Method (Limit Test A) will be used in the West combined testing protocol for the following reasons:

- ◆ USP method uses different solution volumes during a preparation step than Ph. Eur.; however, these solution volumes have no impact on test results.
- ◆ Ph. Eur. Limit Test A, which is equivalent to USP Method I, is used in all cases when testing aqueous closure extracts.
- ◆ Based on historical test results, sample extracts have always been found to be essentially clear and color-free solutions. Ph. Eur. Limit Test A has always been adequate for assessment of these solutions.
- ◆ An article published by the Pharmacopeial Forum, Vol. 34(2)[Mar.-Apr. 2008] cited reasons for not standardizing the USP Heavy Metals test with the Ph. Eur. method as essentially a counterproductive effort. In addition, this article presented data which illustrated that both methods produced equivalent test results.

### **III. Requirements of the New USP**

When performing testing per USP <381> on elastomeric closures for injection, two categories are specified: Type I or Type II. The following table outlines the requirements for both classifications, Type I and Type II.

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Table 2: Combined Protocol Requirements for Type I and II			
West Combined Protocol	USP Type I Requirements	USP Type II Requirements	Requirements are the same for Type I & II
<b>Biological</b>			
USP<87> Elution Cytotoxicity	Not greater than Grade 2 (mildly reactive)	Not greater than Grade 2 (mildly reactive)	Yes
USP<88> Acute Systemic Toxicity	No animals treated with sample extract show biological activity greater than animals treated with the blank	No animals treated with sample extract show biological activity greater than animals treated with the blank	Yes
USP<88> Intracutaneous Reactivity Toxicity	Difference between sample and blank mean score is 1.0 or less	Difference between sample and blank mean score is 1.0 or less	Yes
<b>Chemical</b>			
Appearance: Opalescence	Visual: No more opalescent than Suspension B	Visual: No more opalescent than Suspension C	<b>No</b>
	Instr: No more than 6 NTU	Instr: No more than 18 NTU	
Appearance: Color	Visual: Not more intense than Color Standard	Visual: Not more intense than Color Standard	Yes
Acidity or Alkalinity	Not more than 0.3 mL of 0.01N Sodium Hydroxide produces a blue color, OR not more than 0.8 mL of 0.01N hydrochloric acid produces a yellow color, OR no titration required	Not more than 0.3 mL of 0.01N Sodium Hydroxide produces a blue color, OR not more than 0.8 mL of 0.01N hydrochloric acid produces a yellow color, OR no titration required	Yes
Absorbance	Does not exceed 0.2	Does not exceed 4.0	<b>No</b>
Reducing Substances	Not greater than 3.0 mL	Not greater than 7.0 mL	<b>No</b>
Ammonium	No darker than the ammonium standard solution	No darker than the ammonium standard solution	Yes
Extractable Zinc	Contains not more than 5 ppm extractable zinc	Contains not more than 5 ppm extractable zinc	Yes
Extractable Heavy Metals	Contains not more than 2 ppm of heavy metals as lead	Contains not more than 2 ppm of heavy metals as lead	Yes
Residue on Evaporation	Not more than 2.0 mg	Not more than 4.0 mg	<b>No</b>
Volatile Sulphides	Not more intense than control	Not more intense than control	Yes
<b>Physical</b>			
Penetrability	No greater than 10N, accuracy +/- 0.25N	No greater than 10N, accuracy +/- 0.25N	Yes
Fragmentation	No more than 5 fragments	No more than 5 fragments	Yes
Self-Sealing	None contain any trace of blue solution	None contain any trace of blue solution	Yes

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### IV. Type I versus Type II Closures

Type I Closure – The closure meets the requirements listed under Type I. A Type I closure is defined by USP as that which is used for an aqueous preparation.

Type II Closure – The closure meets the requirements listed under Type II. A Type II closure is defined by USP as that which is typically intended for nonaqueous preparations and are those closures which, having properties optimized for special uses, may not meet all of the requirements listed under Type I because of their physical configuration, material of construction, or both. Type II closures have less strict requirements for turbidity, absorbance, reducing substances and residue on evaporation. For all other tests, the requirements are the same for Type I and Type II closures.

### V. Which Closure Type is the Right Choice For Your Application?

For aqueous preparations, a Type I closure must be used.

For non-aqueous preparations, a Type I or Type II closure can be used, but the closure must at least meet the requirements for Type II.

If the closure does not meet Type II requirements it is deemed noncompliant and should not be used for the long-term storage of a preparation.

If the preparation is a mixture of aqueous and non-aqueous solvents, contact the USP for support in determining which closure Type is best suited for the application. Questions to the USP may be directed to Desmond Hunt, M.S. PhD, Scientist, USP PPI EC Technical Liaison, USP Department of Standards Development, [dgh@usp.org](mailto:dgh@usp.org), Telephone: 301.816.8341, Facsimile: 301.816.8373

### VI. Testing Responsibility

It is the responsibility of both the closure manufacturer (supplier) and the end user to demonstrate applicable requirements are met. The monograph states that the closure must be tested before and after all processing to ensure the closure meets the requirements. The monograph does not specify the frequency at which the closures must be tested.

For the below discussion, the term entire test series includes biological, chemical and functional testing.

Siliconized or Unsiliconized Closures – The supplier and end user must demonstrate compliance for the entire test series. The testing may be performed using either siliconized or unsiliconized closures.

Closures with Lubricious Coating - The supplier and end user must demonstrate compliance for the entire test series. Testing must be performed on coated closures.

Lubricious Coating – Coating which is neither silicone nor a barrier coating or film e.g., Oxiglaze®, Purcoat®, TrakStar® and B2-Coating.

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Closures with Barrier Coating - The supplier and end user must demonstrate compliance for entire test series. Testing must be performed on coated/laminated closures.

Barrier Coating – That which provides a barrier between the rubber and drug e.g., FluroTec® and Teflon®.

NOTE: Supplier is responsible to demonstrate chemical compliance on uncoated/unlaminated closure.

NOTE: For biological testing, both the supplier and end user have the option to perform either testing on the coated/laminated closure only or testing on the uncoated/unlaminated closure and on the laminate/coating, reporting results for each separately.

### VII. West Product Offering

West provides closures to in the industry in various formats: bulk, Ready-to- Sterilize (Westar® RS) and Ready-to-Use (Westar RU). For all formats, compliance data is listed in the Formulation Characteristics sheets and stated on the product certificate. For Westar RU, compliance is demonstrated in the Formulation Characteristics package, product certificate and validation summary for sterile Ready-to-Use components.

West's products are sold on the basis that it is the customer's responsibility to evaluate and test the West product to determine its compatibility with other materials and fitness for any end use.

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Contact West's Technical Customer Support  
TCS.Americas@westpharma.com  
+1 800-231-3000  
TCS.Europe-AsiaPacific@westpharma.com  
+49 (2403) 7960