

**Reference Guide**  
**Regulatory Requirements for the Preparation of Parenteral Packaging Components**

Reference	Bioburden	Pyroburden	Particulate	Silicone	Revalidation	Cleaning
21 CFR 211	211.160(b)(1)(2), 211.80(b)	211.94(c)(d), 211.160(b)(1)(2), 211.80(b), 211.167(a)	211.160(b)(1)(2), 211.80(b)	211.63, 211.65, 211.67, 211.11(c), 211.160(b)(1)(2), 211.182, 211.80(b)		211.63, 211.65(a), 211.67, 211.182, 211.80(b)
Sterilization Process Guidance	Section VI.A. and VII	Section VI.A., VI.B.1 and VII		Section VI.B.1	Section VI.B.1	Section VII
Sterilization Process Validation Guidance	II.C,1,2(pp 5,6); II.D (p 7); II.H (p 8)	II.D(p7); II.F & II.H (p 8); IV.C (p 12)				
USP		<85>	<788>			
LAL Guideline		Entire Document				
1991 Munsun Paper		2, 10, 11,				
1994 Munsun Paper		#1, #3				

**References (Applicable Sections)**

21 CFR	Code of Federal Regulations Title 21, Chapter I - Food and Drug Administration, Department of Health and Human Services, Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals
Guidance for Industry Sterile Drug Products Produced by Aseptic Processing	Guideline for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA); September 2004
Guidance for Industry Documentation for Sterilization Process Validation	Guidance for Industry - for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. Center for Drug Evaluation and Research; Center for Veterinary Medicine; November 1994.
USP	U.S. Pharmacopeia / National Formulary 27, United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852. Official from January 1, 2004
LAL Guideline	Guideline on Validation of the Limulus Ameobocyte Lysate (LAL) Test as an End-Product Endotoxin Test For Human and Animal Parenteral Drugs, Biological Products, and Medical Devices; U.S. Department of Health and Human Services, Public Health services, Food and Drug Administration (CDER, CBER, CVM, CDRH); December 1987.
'91 Munsun Paper *	Department of Health and Human Services Letter to LAL Users Group, c/o Karen McCullough, 7 Latourette Rd, Whitehouse Station, NJ, dated February 5, 1991; from Terry E. Munsun, Chief, Sterile Drugs Branch, HFD-322, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research.
'94 Munsun Paper *	Department of Health and Human Services Letter to LAL Users Group, c/o Karen McCullough, 7 Latourette Rd, Whitehouse Station, NJ, dated January 27, 1994; from Terry E. Munsun, Chief, Sterile Drugs Branch, Center for Drug Evaluation and Research.
Note * on Munsun Papers	These are not guidance documents or standards but rather responses to questions raised by the LAL Users Group during several meetings and question and answer periods where Mr. Munsun was asked to attend. Mr. Munsun, while at FDA, was actively involved in the development and issuance of the <i>Guideline on Validation of the Limulus Ameobocyte Lysate Test As An End-Product Endotoxin Test For Human and Animal Parenteral Drugs, Biological Products and Medical Devices</i> , December 1987. This Guideline is currently enforced and, as with many guidance documents, is general in nature. Many early users of LAL had questions related to substituting LAL for the rabbit pyrogen test (USP <151>) and, as a result, had asked Mr. Munsun questions regarding its interpretation and use. Many of these comments are still referred to today as valid. You may use these at your discretion.

## Bioburden

### Issue:

Bioburden on stoppers can lead to contamination of drug products. Maintaining microbiologically clean components is critical to preventing contamination and preserving drug product integrity during storage, shipping and handling.

### Why it is important:

Knowledge of bioburden is essential in assessing whether the sterilization process is adequate. An unvalidated level of bioburden on stoppers raises questions about the assurance level of the validation of the stopper sterilization process.

Sterility failure of drug products could lead to a recall.

Unknown and uncontrolled bioburden levels can have a dramatic impact on pyrogen/endotoxin levels (pyroburden).

### West's approach:

West has characterized the types of bioburden that may be present in its controlled manufacturing environment.

West has established a specification for bioburden of less than or equal to 5 colony forming units (CFU) per 100 square centimeters of stopper surface area.

West validates products to this specification and tests pre- and post-wash samples during the validation.

West tests every wash load and includes the results on the Certificate of Analysis.

West periodically monitors bioburden levels on stoppers before they are washed.

West has implemented controls for bioburden in the processing and preparation areas stoppers pass through prior to Westar® processing.

West tests and controls the environment where the Westar® processing occurs.

West packs Westar® processed stoppers in clean, validated packaging to preserve and protect product against environmental and biological contamination.

West has validated the sealing process for the SterilizeableBag™ which is the primary package for the components.

### Regulatory and Industry Guidances, Regulations and Trends:

Reference	Bioburden
21 CFR 211	211.160 (b)(1)(2), 211.80 (b)
Sterilization Process Guidance	Section VI.A. and VII
Sterilization Process Validation Guidance	II.C,1,2 (pp 5,6); II.D (p 7); II.H (p 8)

See Reference Tab for full details.

## Endotoxin (Pyroburden)

**Issue:**

Pyroburden (levels of biological endotoxin) on stoppers can contaminate and compromise the drug product.

**Why it is important:**

Parenteral products are intended to be non-pyrogenic.  
 Pyrogens on stoppers can contaminate drug products and may be the cause of a product recall.  
 Maintaining microbiologically clean components after they are washed is critical for preventing contamination during storage, shipping and handling.  
 The manufacturing steps used to assure that packaging components are non-pyrogenic is typically included in the respective drug application when filed with the FDA.

**West's approach:**

West validates a minimum 3-log reduction during initial product validations.  
 West has established a specification as part of its Westar® offering and provides validation to this specification by analyzing pre- and post-wash samples.  
 West tests every single wash load using validated equipment, procedures and methods and reports the results on the Certificate of Analysis.  
 West periodically tests pyroburden levels of stoppers before they are washed.  
 West has put many processes in place to control stopper preparation and routinely monitors its processes.  
 Following Westar® processing, the components are stored inside clean packages that prevent contamination.  
 West has studied and validated the packaging to assure that it maintains the specification integrity of the stoppers over their intended shelf life.  
 West has validated its pyrogen test method to meet industry and regulatory standards and requirements.  
 West has a Type V DMF on file with the FDA to support customer NDA/ANDA filings.

**Regulatory and Industry Guidances, Regulations and Trends:**

Reference	Pyroburden
21 CFR 211	211.94 (c)(d), 211.160 (b)(1)(2), 211.80 (b), 211.167 (a)
Sterilization Process Guidance	Section VI.A., VI.B.1 and VII
Sterilization Process Validation Guidance	II.D (p7); II.F & II.H (p 8); IV.C (p 12)
USP	<85>
LAL Guideline	Entire Document
1991 Munsun Paper	2, 10, 11,
1994 Munsun Paper	#1, #3

See Reference Tab for full details.

## Particulate

**Issue:**

Particulate matter on stoppers.

**Why it is important:**

Particulate on stoppers can be transferred to packaged drug products causing particles in the drug. This can lead to end-of-the-line rejects and could cause major problems for complex protein and peptide drug products.

Maintaining particulate-clean stoppers, once washed, is critical to preventing contamination during storage, shipping and handling of packaged drug products.

**West's approach:**

West has a product specification for particulate of less than or equal to 3.4 PCI (Proved Clean Index, a weighted average particle count by particle size).

West validates products to this specification, including testing of pre- and post-wash load samples to ensure particulate reduction is achieved by the process.

West tests every wash load.

West periodically tests pre-wash load particulate matter levels.

West monitors and controls its stopper preparation process and environment, including training of employees and special filtration for air handling equipment.

Following the Westar® wash process, stoppers are unloaded in a class 100 clean room and packed in clean packages to prevent environmental and biological contamination.

The quantity of stoppers per bag and carton is evaluated to help assure particles are not generated during shipping and storage.

Package material is not reused.

**Regulatory and Industry Guidances, Regulations and Trends:**

Reference	Particulate
21 CFR 211	211.160 (b)(1)(2), 211.80 (b)
USP	<788>

See Reference Tab for full details.

## Silicone

### Issue:

Silicone oil is often applied to stoppers to facilitate tracking in filling operations and insertion into the vial. The application process can have a high degree of variability.

### Why it is important:

Variability in the level of silicone oil on stoppers can result in erratic line performance and line stoppages.  
High levels of silicone oil can result in particulate in liquid drug products or cause hazing upon reconstitution of lyophilized drug products.  
Silicone oil is subject to the same raw material testing, certification and control as pharmaceutical ingredients.  
Silicone oil can contaminate other areas of a manufacturing facility.  
Silicone oil can be a safety hazard if left to accumulate on floors or if spilled.  
Silicone oil can have an adverse effect on the safety, quality or purity of a drug product.

### West's approach:

During the development of the Westar® process, West performed Statistical Process Control (SPC) studies to identify the family of variation (load to load, within load, day-to-day, etc.) and designed the process to reduce the variability of the silicone level on processed stoppers.  
West mechanically emulsifies pure silicone oil in Water For Injection (WFI) and has a process for adding the emulsion to the final rinse step of the wash process.  
West tests every wash load for silicone level and has establish statistically valid specifications for individual items over 27 wash loads.  
West has specifications and test methods for silicone oil.  
West has established validated cleaning methods to prevent cross contamination of product by silicone oil.

### Silicone-free Alternatives:

For a silicone-free alternative, West offers stoppers with FluroTec® film that provides lubricity and has barrier properties designed to minimize drug/closure interaction.

### Regulatory and Industry Guidances, Regulations and Trends:

Reference	Silicone
21 CFR 211	211.63, 211.65, 211.67, 211.11(c), 211.160(b)(1)(2), 211.182, 211.80(b)
Sterilization Process Guidance	Section VI.B.1

See Reference Tab for full details.

## Revalidation

**Issue:**

Periodic revalidation of processes critical to drug product quality, safety or purity is a requirement of CGMP.

**Why it is important:**

Processes can change over time and there should be no surprises where drug product quality and consistency are concerned.

Processes are required to be in a "state of control".

**West's approach:**

West performs annual Bacteria Endotoxin Reduction (BER) revalidation for all product families.

West performs BER revalidation based on change control procedures.

West tests every wash load for bioburden, endotoxin and particulate loads (and silicone level if applicable).

**Regulatory and Industry Guidances, Regulations and Trends:**

Reference	Revalidation
Sterilization Process Guidance	Section VI.B.1

See Reference Tab for full details.

## Cleaning

**Issue:**

Stopper washing equipment must have a validated cleaning process.

**Why it is important:**

A validated cleaning process prevents item-to-item contamination and process variability of silicone, particulate matter, bioburden and endotoxin.

**West's approach:**

West has established a validated clean in place (CIP) cycle for its washers. The process is validated for silicone removal, particulate matter removal, and assurance there is no residual detergent present, using validated test methods.

West runs a CIP on start-up every week.

West runs a CIP between unlike items.

West runs a CIP when silicone levels change (reducing the level).

West runs a CIP when using different viscosities of silicone oil.

**Regulatory and Industry Guidances, Regulations and Trends:**

Reference	Cleaning
21 CFR 211	211.63, 211.65(a), 211.67, 211.182, 211.80 (b)
Sterilization Process Guidance	Section VII

See Reference Tab for full details.