

1 Purpose

The purpose of this Guideline is to provide a general guideline for endotoxin testing. The guideline should aid in assuring that the products manufactured at any of the company sites as well as by a contract manufacturer meet the appropriate regulatory and company requirements and that there is a harmonized, company-wide approach to the concept of endotoxin testing.

2 Scope and Applicability

This Guideline applies specifically to endotoxin testing as it is carried out at Any manufacturing site, as well as at third party testing labs.

The guideline applies, where applicable, to raw material (including water), components, in-process material and drug products, and well as to validation of dry heat sterilization procedures.

In addition to the guideline, the following items should also be in place.

2.1 Standard Operation Procedures (SOPs)

SOPs shall be developed to provide clear direction for the execution of the testing procedures, material preparation, data analysis, and the development of the documentation referred to in this guideline.

2.2 Validation Protocols

Validation protocols shall be generated to verify and document that the methods used to perform endotoxin testing can reliably and consistently detect endotoxins that may be present in units being tested, and that the equipment does not interact with the endotoxin testing. These protocols, the data generated and the associated summary reports should provide documentation of the acceptability of these methods and equipment for their intended use.

3 Definitions

3.1 Endotoxin

Toxic lipopolysaccharides originating from the outer cell wall of Gram-negative bacteria.

3.2 Bacterial Endotoxin Test (BET)

A test used to detect or quantify endotoxins of Gram-negative origin.

3.3 Endotoxin Limit

- Endotoxin testing should be carried out in a solution that is at a neutral pH (6.0-8.0) and has a balance of divalent cations.
- The sensitivity claimed of each batch of the LAL reagent should be verified.
- The absence of interference should be established for each test item by performing Inhibition/Enhancement validation studies.
- Endotoxin test methods should be validated and demonstrated to be appropriate for their intended use.
- Appropriate preventative maintenance procedures for critical equipment and systems should be approved and in place.
- Critical instruments and equipment should be calibrated and included in the routine calibration program.
- Endotoxin elimination (depyrogenation) cycles for internal processes, supplies, equipment and materials should be validated.
- Endotoxin test analysts or technicians should have appropriate training and documentation of that training should be on file and available for review.
- Endotoxin test methods and/or procedures should be approved, current and available for use by the analysts or technicians.
- Endotoxin limits and MVD or MVC should be established for each test item.
- Inhibition/Enhancement testing should be performed on each raw material, packaging component, in-process material and drug product requiring a BET specification. Ideally three separate batches or individual shipments of the item should be used for this testing.
- Product test assays shall be validated before being used to release final product.
- Revalidation shall be performed as prescribed by Pharmacopoeia (e.g. at product reformulation, changes in concentration, change in drug substance or drug product).

5.2.2 **Methods & Procedures**

The following items or issues should be addressed in approved methods and/or procedures:

- Validation and Revalidation of Endotoxin Test Methods.
- Sample Collection, Transport and Storage.
- Endotoxin Test Methods.
- Preparation, Testing, Approval and Storage of Endotoxin Test Reagent and