



Dear Customer,

As anticipated, effective 12 July 2011, the U.S. Food and Drug Administration (FDA) has withdrawn the "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" that was issued in 1987 and its subsequent 1991 amendment "Interim Guidance for Human and Veterinary Drug Products and Biologicals, Kinetic LAL Techniques".

The FDA now refers drug manufacturers to the United States Pharmacopeia (USP) General Chapter <85> Bacterial Endotoxins Test (BET), which provides information on the performance and acceptance criteria for endotoxin testing.

**What does this mean to you?** You have an opportunity to update your procedures, and in some cases, make them more robust and/or simplified.

- **Regulation of LAL Reagents and LAL Testing Methods:** The FDA still has complete regulatory oversight of the LAL industry and CBER continues to approve LAL manufacturing facilities and all LAL reagents as well as to regulate product labeling for a reagent's intended use. Additionally, the USP BET requires only the use of LAL or TAL that is regulated by a competent authority for release of final product.

In the US, the competent authority is the FDA. Therefore, if you are using any of our FDA-licensed LAL reagents, including Endosafe® Gel-Clot, Endosafe® KTA, Endosafe® KTA2, Endochrome-K™ or Endosafe®-PTS™, and performing the test in accordance to the FDA-approved directions for use as indicated on the package insert, you meet cGMP expectations.

- **Regulated Document Considerations:** You should conduct a thorough review of all pertinent endotoxin testing documents, such as NDAs, BLAs, Quality Manuals, and SOPs. Any reference to the LAL Guideline should be removed. Those documents should be updated to reference only the USP and licensed LAL manufactures' package inserts. During this exercise, you have the opportunity to remove onerous procedures that do not add value to your testing protocols, like the "pass/fail cutoff".
- **Product Sampling Plans:** Recently, product sampling plans have come under scrutiny by regulatory authorities and you need to ensure that your sampling strategy is scientifically sound and statistically defensible.
- **Out-of-Specification Expectations:** Out-of-Specification (OOS) SOPs should reflect current FDA expectations, which can be found in the [OOS FDA Guidance](#) issued in October 2006.

For more information, please see the recent FDA notification by [clicking here](#) and scrolling down to questions 8 and 9. If you have any questions or concerns, please contact us at [askcharlesriver@crl.com](mailto:askcharlesriver@crl.com) or 1.800.762.7016.

Sincerely,

Alex Jelenevsky  
Sr. Director of Regulatory Compliance  
Charles River  
Endotoxin and Microbial Detection Division