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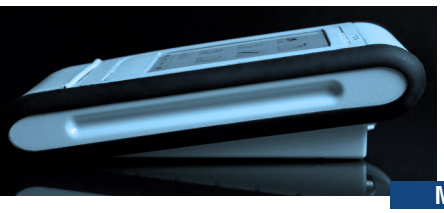

MICROBIAL SOLUTIONS

A comparison study of conventional bacterial endotoxin testing and the Endosafe® Cartridge Technology

Key Points:

- FDA Licensed Cartridges
- Wide range of sensitivities from 10-0.005 EU/mL
- Results within approx. 15 minutes
- Reduction in analyst-analyst assay errors due to no standard curve preparation

Introduction

The bacterial endotoxins test (BET) is a mandatory quality control (QC) release test for injectable drug products, which utilizes the Limulus ameboyte Lysate (LAL) assay, the gold standard for endotoxin testing. Guidelines for the BET and monographs with endotoxin limits are included in major pharmacopoeias.

Today, the US FDA recommends that Process Analytical Technology (PAT) be implemented as part of pharmaceutical manufacturing, which involves risk-based management at every step of the process. More companies are implementing in-line, on-line or at-line tools to provide them with real-time analysis on the manufacturing floor to build quality into the process.

In-Process Testing

During the manufacturing process, both production and QC are involved in the collection and testing of raw materials, in process and final product samples. Often, the results of the LAL test are not available to production staff within the short time frame required to proceed with downstream processing (e.g., endotoxin levels for in-process buffer solutions and water for production). A rapid turnaround of LAL test results is required to determine whether the endotoxin levels of in-process samples are within in-house limits before proceeding to the next step of the manufacturing process.

Case Study and Benefit Analysis

A Six Sigma analysis was conducted by an objective third party consultant to analyze LAL test efficiency at a biotech company. The study analyzed the sample process, flow, and turnaround time (TAT) for two sets of in-process buffer samples. One set was performed by experienced QC technicians using their current method of LAL testing, the kinetic chromogenic assay, in the central microbiology lab (Method 1 – see Figures 1a and 1b). The other set was performed using an Endosafe®-PTS™ reader with FDA-licensed LAL cartridges on the manufacturing floor (Method 2 – see Figures 2a and 2b). This testing was performed by manufacturing technicians after minimal training. A benefit analysis was performed taking productivity, quality and financial implications into consideration.

Productivity

Method 2 was shown to reduce total TAT by 1.25 hours per set of samples as compared to the company's traditional method. The efficiency was achieved by optimizing sample testing at the point of collection and obtaining results in 15 minutes. Method 1 required extensive sample transportation, detailed chain of custody documentation and preparation of a standard series (the PTS™ utilizes an archived standard curve). Batching of samples was utilized in Method 1, which also caused delays. In some stat situations, a buffer sample would need to be run alone on the microplate, while the remaining LAL in the vial was wasted.

Testing utilizing Method 2 was performed by manufacturing technicians after a one-day training period. The company typically allowed QC technicians to begin release testing with the traditional LAL method after a two-week training program.

Quality

Analyst-to-analyst and lab-to-lab variations were minimized in Method 2 because results from the PTS™ were not based on a standard curve prepared by an analyst. If a retest was required, it could be performed immediately, eliminating the 2.5-hour downtime of manufacturing technicians that occurred with the traditional test method. In addition, the PTS™ platform allowed technicians to simplify OOS investigations because fewer reagents and accessories were required.

Financials

Implementation of Method 2 resulted in several employee efficiencies for the company, and they were able to reassign two third-shift full-time employees to other roles. With the PTS™, the company was able to reduce one hour from its manufacturing cycle time, allowing for improved capacity and the ability to produce two additional lots of product per year. In summary, with the more efficient PTS™ method, the company reduced scrap and employee downtime, eliminated waste, and decreased cycle times.

Method 1

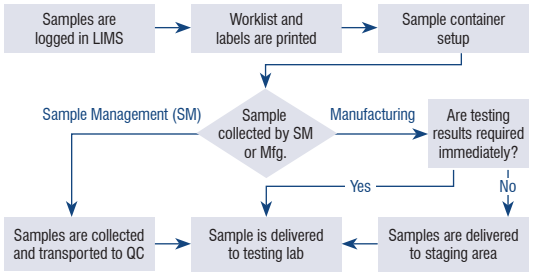

Figure 1a: BET flow chart for in-process buffer samples sent to QC lab using kinetic assays/microplate reader

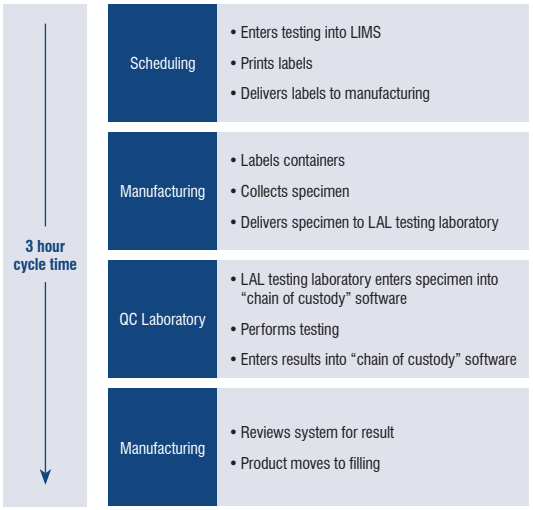

Figure 1b: TAT for BET using kinetic assay/microplate reader

Method 2

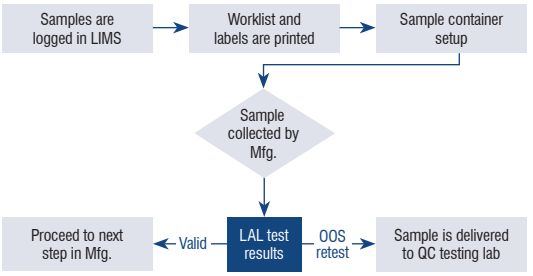

Figure 2a: BET flow chart for in-process buffer samples using the LAL Cartridge/PTS™ at point of use

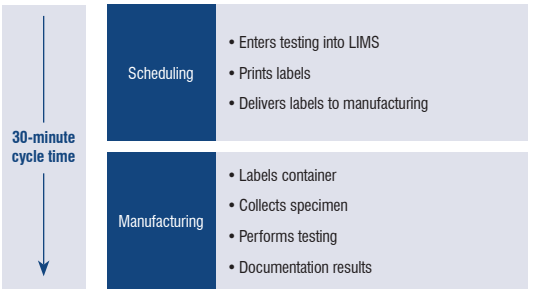

Figure 2b: TAT for BET using LAL cartridges/PTS™

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