An Interview With...

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LAL is derived from the blood of the horseshoe crab. What makes this natural resource so successful in detecting endotoxin?

In one word: sensitivity. From blood coagulation systems to cellular signaling systems, there are a number of cascading enzymatic systems whose mechanisms have been elucidated. Among these systems, the horseshoe crab coagulation system, mediated by bacterial endotoxins, is unique. Through its distinct biological amplification facility, it can detect bacterial endotoxin concentrations to less than 1 part per trillion.

What is the outlook for horseshoe crab populations and what steps has Charles River taken to support sustainability?

The Limulus polyphemus species has been subjected to stress associated with baiting for eel and whelk fisheries. Charles River recognized the significance of this resource 22 years ago when Dr. James Cooper (Endosafe® company founder) wrote draft legislation calling for the management and regulation of horseshoe crab fisheries. This resulted in South Carolina laws that limit horseshoe crab use to biomedical applications and marine biological research and prohibit use as bait. Today, Charles River further supports this legislation by exclusively employing fishermen licensed by the Department of Natural Resources to hand-harvest horseshoe crabs (as opposed to trawling) and return them to the wild within 24 hours. As a result, horseshoe crabs are more protected in South Carolina than anywhere else in the world.

Over the years, concerns about long-term sustainability of horseshoe crab populations have prompted the development of alternative methods for LAL testing. Do you see alternative methods eventually replacing the traditional endotoxin test?

With 50 years as the most sensitive, reliable and popular method for testing for bacterial endotoxin, the LAL test has a very healthy future. As an FDA-regulated product, it comes with the knowledge that manufacturers of LAL are the focus of stringent FDA oversight and cGMP compliance. Synthetic alternative methods are not subjected to this standard and require time and funding to specially validate use. The future for the LAL test, therefore, lies with traditional compendia-compliant reagents, packaged and used in novel systems similar to the Endosafe®-PTS™.

When your PTS™ cartridge system first came onto the market, many questioned whether its use was in compliance with USP BET regulations. Is this still an issue you face today?

The PTS™ was licensed by the FDA for all BET testing uses, including end product release, back in 2006, so there has never been any question of its compliance with USP BET. Additionally, in 2007, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the executive body of the European Pharmacopoeia, described the cartridge system as a "demonstrably suitable technique" for which "no further elaboration to the harmonised BET text was considered necessary".

The FDA made it clear at the September 2012 Bacterial Endotoxin Summit that, like any other LAL BET method, the cartridge system can meet the USP BET requirements.

Which industries have benefited most from your rapid test systems?

The rapid test system has been widely adopted within the healthcare industry. In drug production, it has provided a near real-time at-line method for in-process control, ensuring QbD processes can be implemented, and has improved product quality and laboratory efficiencies. Our systems have also streamlined testing by minimizing training needs, decreasing test variability and reducing the need for subsequent investigations.

What is low endotoxin recovery (LER), and what steps are being taken in the industry to address it?

LER is a hot topic among biopharmaceuticals regarding "hold times", or the intervals between when a sample has been drawn to the time it's tested. The FDA's question is whether the endotoxin concentration at the time of sampling is the same at time of testing. It has been shown that certain biological formulations actually lead to endotoxin degradation (and possible under-detection). Are these data real or is this an artifact associated with the use of purified endotoxin standards? Charles River is actively pursuing the answer to this question by studying a variety of purified and native endotoxin preparations utilizing all available in vitro techniques and the traditional in vivo model (rabbit testing).