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Automation of Bacterial Endotoxins Testing (BET)

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To succeed and thrive in today's pharmaceutical manufacturing environment – particularly in the quality control (QC) lab where critical safety tests such as BET assays are performed – it is important to increase efficiency while maintaining compliance. The need to quickly and accurately test samples, review data, and release products drives innovation in analytical instrumentation and software, with the ultimate goal being to deliver medicines to patients safely and efficiently.

Since the 1980's, there have been nominal improvements for most QC labs when it comes to their everyday experiences with compendial endotoxin testing. While automation and robotics were introduced to reduce manual labor and streamline processes, most labs haven't fully adopted these technologies due to the complexity of the instrumentation, training, and validation practices that come with them. Unfortunately, many automated technologies and new software either don't meet the needs of users in the QC lab or cannot be implemented and validated without a significant amount of effort. As a result, labs are seeking automated solutions for BET that are easy to implement, fast to validate, and provide day-to-day advantages such as ease of use and decreased contamination.

What is microfluidic automation of BET assays?

Automation using a centripetal microfluidic platform is the simplest form of BET automation available to the market today. It leverages a network of microchannels to direct and mix fluids to automate endotoxin assays. This is achieved within a small, compact microplate that is analyzed using an incubating benchtop spectrophotometer similar in size and function to absorbance microplate readers used for traditional LAL assays.

Centripetal microfluidic automation simplifies endotoxin testing by offering a solution that is extremely easy to set up, use, and maintain. It enables labs to achieve the ease of use, ease of training, and high throughput they want, without having to be concerned about compliance, accuracy, complex validations, or footprint. Using the Sievers Eclipse BET Platform's microfluidic automation, fully compliant endotoxin assays can be set up in as little as nine minutes with a fraction of the

pipetting steps typically required.

- **Automation of standard curves and PPCs:** Preloaded standards and PPCs are used to automate standard curves and PPC spikes, saving labs significant amounts of time and reducing pipetting steps and opportunities for error. While time-savings are achieved, compliance is not compromised with the Eclipse. Like all compliant BET assays, users must construct at least a three-point standard curve in duplicate using standardized endotoxin, have duplicate negative controls, and run each sample in duplicate with a PPC, also in duplicate.
- **Automation of liquid handling:** With 200+ pipetting steps required to run a traditional LAL assay, it's no surprise that automation of liquid handling is a primary goal within endotoxin automation. With microfluidic liquid handling, the Eclipse technology minimizes the hands-on time needed to repeatedly and consistently deliver accurate measurement and dispersion of liquids. This greatly reduces potential human errors and the demands on analyst training and performance. In addition, because a closed microfluidic system is used, environmental contamination is reduced. A 1:1 sample to lysate ratio is precisely delivered using this consistent and reliable technology. Overall, with microfluidic automation, compendial endotoxin assays are performed effortlessly, quickly, and with fewer retests.
- **Data management & data integrity:** The importance of software's role in simplification can't be underestimated. It is an essential component of today's testing – including data review, sign off, and product release – and should be purpose-built for automated endotoxin testing. The Sievers Eclipse software meets the following criteria: adhere to current data integrity and compliance requirements, including 21 CFR Part 11 guidelines and ALCOA+; utilize client-server architecture for easy and remote data review and sign off; incorporate customization of permissions; integrate seamlessly with the BET automation platform; provide time-saving templates and features such as protocols for analyst qualification, product validation, and lysate qualification, plus libraries for easy customization; enable full assay-specific audit trail review.

By the numbers

With centripetal microfluidic automation using the Sievers Eclipse, fully compliant endotoxin assays are set up in as little as **9** minutes and **less than 30** pipetting steps, with **up to 21** samples and up to a **5-point** standard curve. Just **1 mL** of LAL is required.

Spotlight on ease of use

By drastically reducing pipetting steps, centripetal microfluidic automation decreases the complexity of assay setup and mitigates risks and opportunities for errors that lead to costly retests. In addition, microfluidic liquid handling precisely measures all liquids for the end user, which means that the precision typically required during the physical action of pipetting is reduced. With preloaded standards and PPCs, all the technician needs to do is pipette Water for BET, samples, and 1 mL LAL.

Ensuring successful validation of BET platforms

While validation of a new BET platform can be arduous if platforms are complex or suppliers do not provide support for the validation process, there are options available that are streamlined and keep labs functioning at the capacity needed, without disrupting or re-assigning analysts. Simplifying the process allows the QC lab to complete validation in-house or with the help of manufacturer. In an ideal validation scenario, QC labs experience the following:

- **IQ/OQ/PQ documentation that is clear, easy to follow, and comprehensive.** This enables an ideal platform to be fully validated in the lab within days. Users have confidence knowing that the instrument and software are fully qualified and validated per the regulations. Such robust qualification ensures that the instrument and software will function as designed, even at full capacity.
- **Option for validation to be performed on-site by a qualified and certified manufacturer's representative.** This allows the lab analysts and managers stay focused on other projects with minimal down time. Once validation is complete, a lab manager or validation engineer can simply review the documented results and sign off to support cGMP release of the equipment.
- **Software support and training.** Streamlining validation and integration of the platform in the lab can be achieved when a manufacturer's representative assists with steps such as configuring the software, training analysts how to use the platform, and pointing out helpful features and shortcuts, such as setting up assay templates, product libraries, validated products and user permissions.

Validation doesn't have to be a daunting task. There are options available to QC labs to speed up and simplify the process, ensuring a clear path to success. With an ideal platform, validation can be performed in just a few days, analysts can be fully trained during that time, and system validation is supported by the vendor's fully documented results for all seven guidelines outlined in USP <1225> and ICH Q2(R1).

Conclusion

There are often many goals associated with moving to an automated BET platform in the QC lab – time savings, simplification, fewer errors, process improvement, improved data management, data integrity, more efficient sign off, and others. Automation of endotoxin testing with microfluidics and the Sievers Eclipse BET Platform offers easier ways of working without compromising on compliance or accuracy. Pipetting, liquid handling, and mixing of reagents are all automated, along with preparation of standard curves and PPCs. Exploiting microfluidics for endotoxin testing reduces consumption of reagents and samples, decreases time setting up reactions, and increases sample throughput. Additionally, with the use of software that is purpose-built for endotoxin automation, QC labs are able to streamline testing, data review, and sign off in ways that meet today's needs and prepare for the future of pharmaceutical manufacturing.