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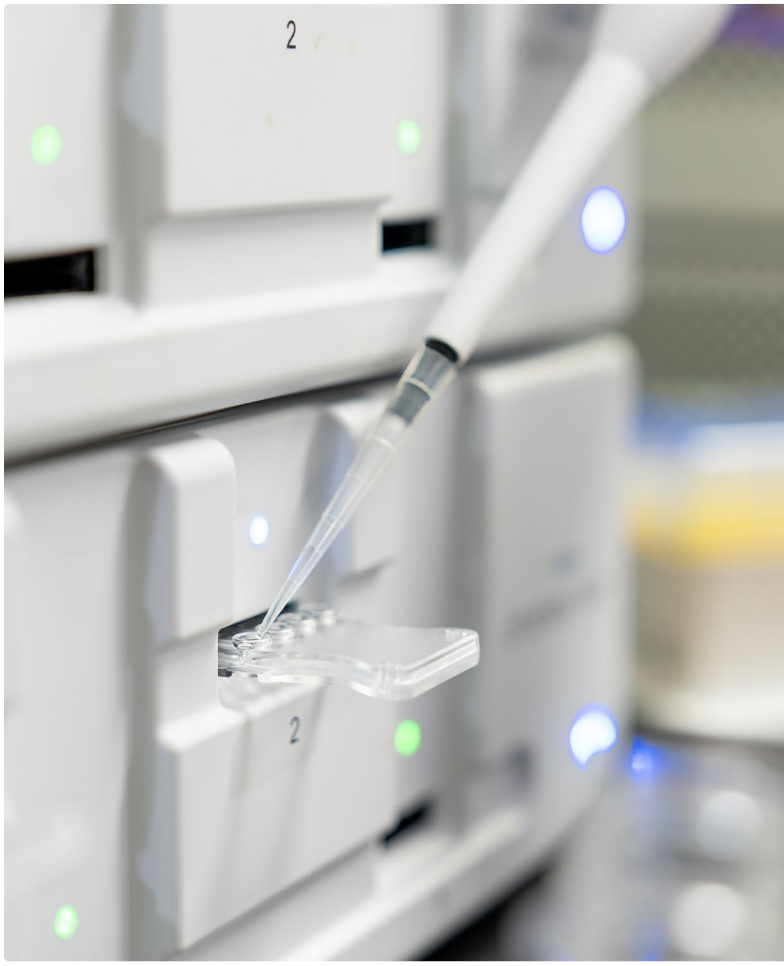
Validating BET Methods for Ultrapure and Critical Water

U.S. Micro-Solution's Side-by-Side Study of Endosafe® nexgen-MCS™ and Sievers Eclipse



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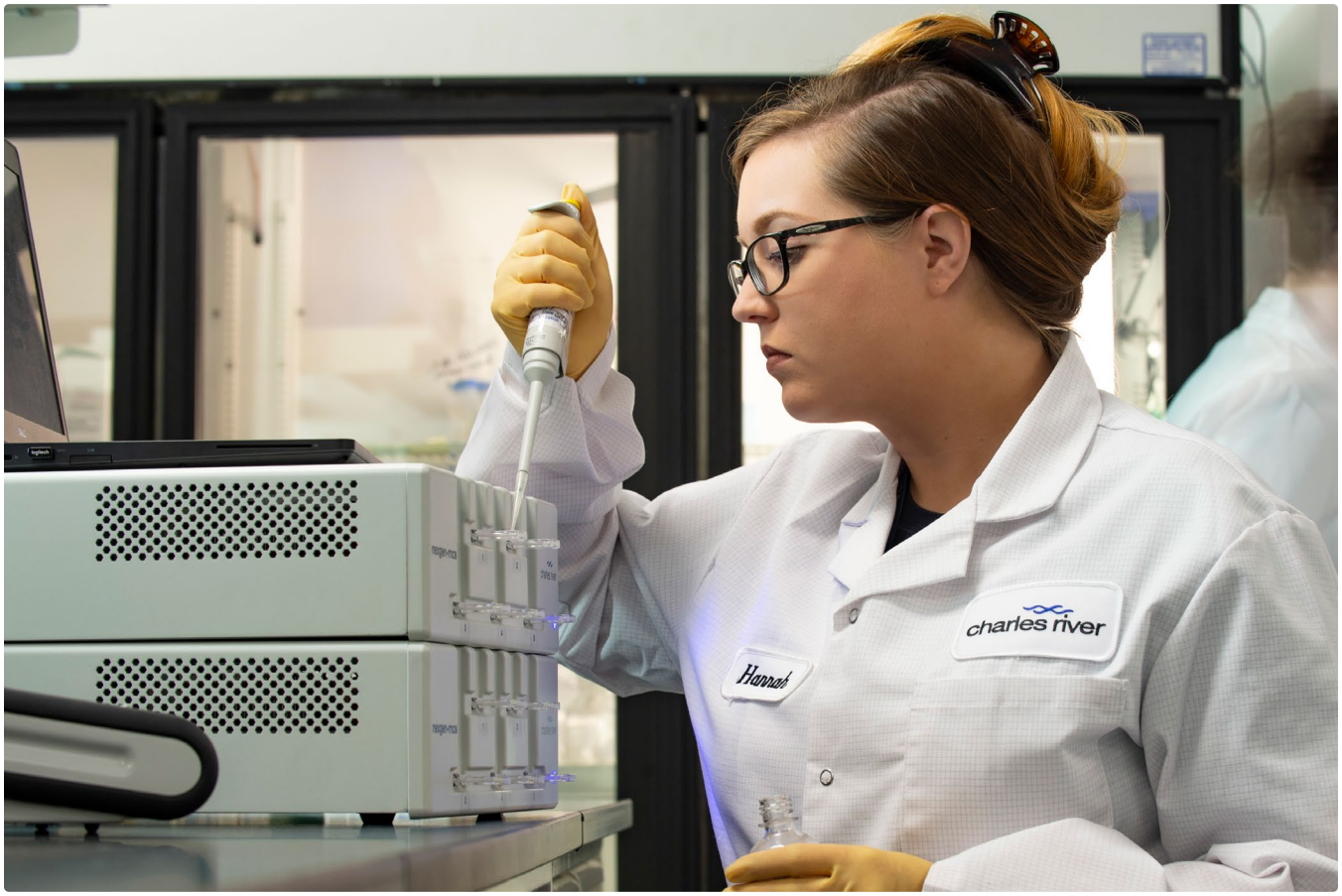
U.S. Micro-Solutions Inc. (US Micro), a contract laboratory serving medical device and pharmaceutical manufacturers, conducted a side-by-side evaluation of the Endosafe® Multi-Cartridge Endotoxin Testing System (nexgen-MCS™) and Sievers Eclipse endotoxin detection platforms. The study was initially designed to demonstrate equivalency between the two systems to support their interchangeable use. Post-study, US Micro displayed a preference for cartridge-based systems and found that cartridges performed better overall. Testing 120 water samples spiked with low and medium levels of endotoxin, they determined that the Endosafe nexgen-MCS cartridge-based benchtop platform was easier to use, delivered faster results, and proved more accurate at low concentrations.

Overview

Accurate endotoxin quantification is crucial for ensuring the safety of water used for medical device processing (ANSI/AAMI ST108), preparation of hemodialysis fluids (ANSI/AAMI/ISO 23500-3:2019; preparation and quality management of fluids for haemodialysis and related therapies), and preparation of pharmaceutical products (USP 1231 - Water For Pharmaceutical Purposes). Laboratories and service providers supporting these sectors must now demonstrate not only compliance but agility, delivering fast, accurate, and reproducible results across diverse settings.

In this study, US Micro tested the Endosafe nexgen-MCS, a benchtop system that houses five individual cartridge bays and enables multiple tests to be run in parallel. Its configuration was well-suited for the study's sample volume and test structure. For smaller testing volumes or point-of-use applications, the same cartridge technology is also available in the portable Endosafe nexgen-PTS™.

Contract labs, like US Micro, sit at the nexus of this transition. Their clients demand validated data, short turnaround times, and testing methods aligned with harmonized pharmacopeia standards such as USP <85>, and EP 2.6.14. In this environment, labs must assess whether their current instrumentation can meet both operational needs and evolving regulatory demands.



The Challenge

US Micro had historically relied on the Sievers Eclipse BET platform from Veolia, which supports 21-sample runs using a 5-point standard curve. While effective for high-throughput applications, Eclipse presented key limitations:

- **Time-to-result:** Each run required approximately 2 hours.
- **Inefficiency for small batches**: Running a full disc with a standard curve for just a few samples was not cost-effective. Once the disc is used, even for a single sample, it cannot be reused, so maximum efficiency is only achieved when all 21 wells are filled.
- **Operational complexity:** Eclipse requires users to manage multiple vendors, one for instruments and discs, and another for reagents, resulting in dual vendor qualifications and potential support gaps.
- **Manual preparation steps:** The system also requires users to reconstitute and vortex LAL reagents and perform multiple pipetting steps, adding hands-on time and opportunities for variability.

> The challenge was to determine whether the Endosafe nexgen-MCS could match or exceed Eclipse in accuracy while reducing complexity and test time.

Decision-Making Criteria

US Micro's evaluation was structured around three key priorities:

- **Measurement sensitivity:** Especially at lower endotoxin concentrations (<0.1 EU/mL), which are commonly encountered in ultrapure and critical water testing.
- **Operational efficiency:** Including reagent prep, analyst time, and SOP simplicity.
- **Regulatory and business alignment:** Instruments had to be compatible with existing validated processes and allow for strategic expansion into additional ultrapure and critical water services.

The Endosafe nexgen-MCS instrument was selected for the comparison study based on its use of FDA-licensed cartridges, which include a built-in standard curve and positive product controls. The system delivers quantitative results in approximately 15 minutes with minimal preparation and hands-on steps.

The Solution

Study Objective

To evaluate equivalency between the Endosafe nexgen-MCS (5-bay cartridge platform) and the Eclipse platform in measuring bacterial endotoxins in spiked water samples.

Dates

Start: December 16, 2024
Completion: December 18, 2024

Acceptance Criteria

- Endotoxin recoveries between 50-200% of the expected EU concentration.
- Unspiked samples do not reach the mean onset time.
- Statistics performed by EpiClear Consulting, LLC.

Materials Used

- LAL reagent: Associates of Cape Cod Lot#: 337093, Exp: 02-02-27
- LAL reagent water (LRW): Cape Cod Cat# W0051-10, Lot#: 314-4359, Exp: 10-18-26
- Reference standard endotoxin (10,000 EU): Charles River Cat# E150, Lot#: H0K354, Exp: 11-22-27
- Glass tubes: Charles River, Cat# TL700, Lot#: 41011C, Exp: 04-2027
- Eclipse microplate: Veolia, Lot#: KI128713, Exp: 10-25-25
- Endosafe cartridges (0.01 EU/mL): Charles River Cat# PTS2001F, Lot#: 4559130, Exp: 02-2026

Statistical analysis performed using multivariate regression with adjustments for test day and sample concentration

Procedure Summary

1. Add 5 mL of LRW to the reference standard endotoxin vial to reconstitute. Vortex for 30 minutes. Final concentration is 2000 EU/mL. Store at 2-8 °C for up to 14 days.
2. Dilute the standard in glass tubes as follows:
    a. Tube 1 - 1:10 dilution = 300 *u*l standard in 2700 *u*l of LRW (EU = 200 EU/mL). Vortex.
    b. Tube 2 - 1:100 dilution = 300 *u*l tube 1 in 2700 *u*l of LRW (EU = 20 EU/mL). Vortex.
    c. Tube 3 - 1:1000 dilution = 300 *u*l tube 2 in 2700 *u*l of LRW (EU = 2 EU/ mL) Vortex.
3. Prepare water samples in glass tubes as follows:
    a. 0.25 EU/mL = 375 *u*l of tube 3 in 2625 *u*l LRW (MED)
    b. 0.05 EU/mL = 75 *u*l of tube 3 in 2925 *u*l LRW (LOW)
    c. For each day/sample type, use 550 *u*l (10 x 55 *u*l) for Eclipse and 1 ml (10 x 100 *u*l) for Endosafe.
4. Day 1 - test all 10 low concentration samples and 10 medium concentration samples as per MIC 61 and MIC 62. Vortex samples for 1 minute prior to pipetting into the microplate or cartridge.
5. Repeat steps 2-4 on days 2 and 3.

Operational Benefits

Ease of Use

- The Endosafe nexgen-MCS required no reagent mixing or standard curve preparation.
- Self-contained cartridges minimized the risk of pipetting errors and ensured consistent technique.
- Reduced training burden: analysts required less time to become proficient on the Endosafe nexgen-MCS compared to Eclipse.

Time to Result

- The Endosafe nexgen-MCS delivered validated results in approximately 15 minutes, compared to Eclipse's 2-hour runtime.
- This speed enabled more agile batch release decisions and improved client service delivery.

Workflow Fit

Ideal for low to medium throughput sample testing, especially in scenarios where Eclipse's full-plate capacity is underutilized. While a single nexgen-MCS unit supports five samples per run, multiple systems can be networked through EndoScan-V™ software to scale throughput as needed. For point-of-use or lower-throughput testing, the Endosafe nexgen-PTS offers the same cartridge technology in a compact, portable format.

Business Impact

Statistical Findings

The 60 measurements yielded by each of the two instruments (total of 120 measurements) were analyzed using a multivariate regression model that controlled for variance associated with the testing date and the level of the expected EU concentration. While the initial model did not detect a statistically significant difference between the measurements yielded by the two instruments, the associated p-value of 0.059 indicates that a statistically significant difference would likely be detected with a larger sample size.

An additional model was then created to investigate the differences in measurements between the two instruments for each expected concentration (Low; Medium). The model created using the 60 Low Expected Concentration measurements detected a statistically significant difference between the measurements yielded by the two instruments, with an associated p-value of 0.016. While the model created with the 60 Medium Expected Concentration samples did not detect a statistically significant difference, the p-value of 0.096 indicates that a statistically significant difference would likely be detected with a larger sample size. In both cases, the Endosafe instrument consistently yielded higher measurements of endotoxin within the water samples. This was also seen with three pharmaceutical proficiency tests (PT) that were performed by their laboratory.

Assigned Value	Endosafe nexgen result (EU/mL)	Eclipse result (EU/mL)
0.527	0.532	0.332
0.220	0.242	0.073
0.170	0.170	0.0247

Regulatory Range Compliance

All but one sample fell within the 2-fold expected range (50-200%), validating both instruments' overall compliance. However, the Endosafe measurements were consistently closer to target values and less prone to under-reporting.

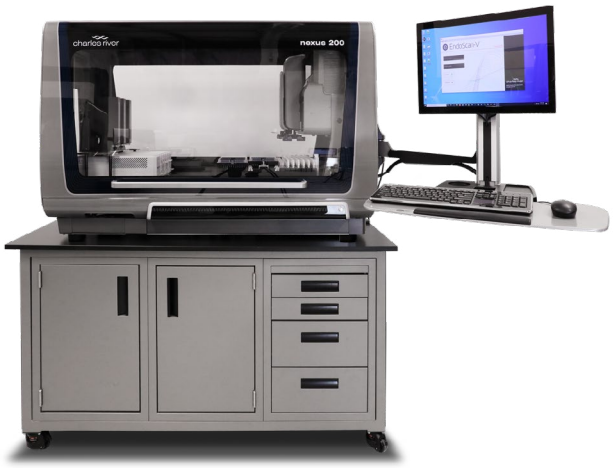
Conclusions

The study confirmed that while both instruments technically meet regulatory acceptability, they are not functionally interchangeable in all scenarios.

- The Endosafe cartridge technology excels in low-endotoxin water testing, rapid turnaround, and streamlined operations.
- The Eclipse may be effective for certain high-throughput applications when full batch capacity is achieved.

US Micro now applies a dual-platform strategy: Eclipse for large-scale runs, and Endosafe nexgen-MCS for agile, compliance testing. This flexibility enhances their ability to meet client needs across regulatory contexts. Their experience offers a replicable blueprint for other contract labs, hospitals, or service providers seeking to modernize their BET workflows without compromising scientific integrity.

Are you still using high-throughput systems for low-volume testing? Endosafe cartridge-based testing gives your lab the agility and accuracy required for today's regulatory landscape without rebuilding your infrastructure.



For labs ready to advance beyond mid-throughput systems, the Endosafe® Nexus 200™ represents the next step in cartridge technology, delivering large-scale, automated runs with full traceability and compliance. →

To learn more about cartridge-based technology, visit criver.com

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