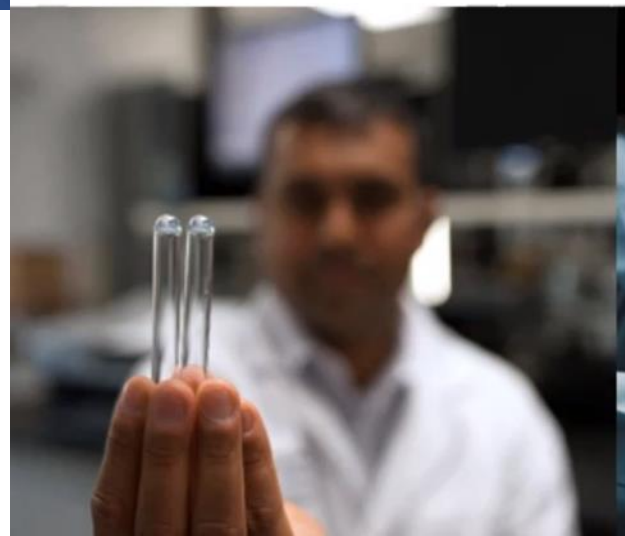
GEL CLOT
VS
CARTRIDGE TECHNOLOGY

Gel-Clot	Traditional Kinetic Assays	Rapid Testing: Endosafe® nexgen-PTS™ & MCS™	Automated Robotics: Endosafe® Nexus™



DATA INTEGRITY RISK ANALYSIS

High Or Low Risk?

Gel Clot

Labour Intensive Setup

Manual Read of Results

Hand Written Documentation

Subjective Result Analysis

Easy Results Deletion and Alteration

No Audit Trail

Zero Proof of Assay Completion

No Date or Time Stamp

Cartridge Technology

Minimal User Setup

Automated Results

Hardcopy Printout

Suitability Criteria Given

Result Cannot be Deleted or Altered

Full Audit Trail

Automatic Saving of Data File

Automatic Date and Time Stamp

Assuring data integrity in microbiological test data is fundamental and significant to drug product quality and patient safety.

DATA INTEGRITY RISK ANALYSIS

High Or Low Risk?

Gel Clot

Labour Intensive Setup

Manual Read of Result

Hand Written Documentation

Subjective Result Analysis

Easy Result Deletion and Alteration

No Audit Trail

Zero Proof of Assay Completion

No Date or Time Stamp

HIGH RISK

Cartridge Technology

Minimal User Setup

Automated Results

Hardcopy Printout

Suitability Criteria Given

Result Cannot be Deleted or Altered

Full Audit Trail

Automatic Saving of Data File

Automatic Date and Time Stamp

LOW RISK

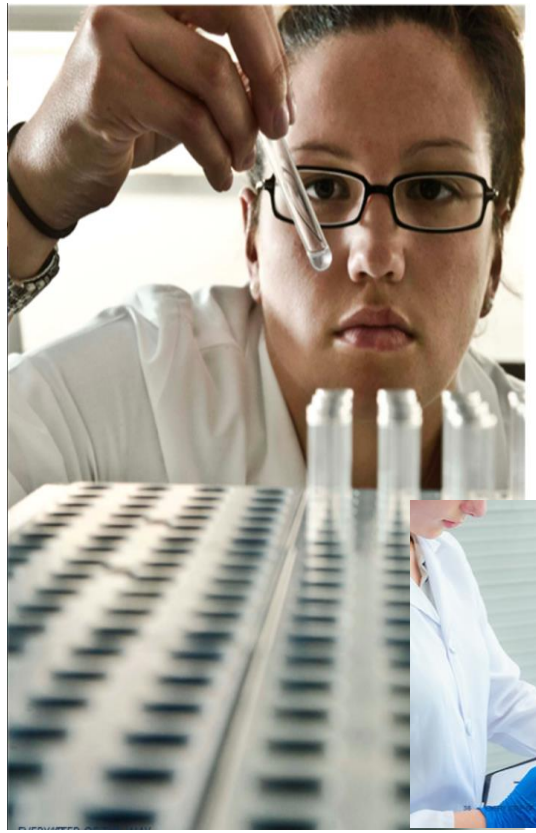
Assuring data integrity in microbiological test data is fundamental and significant to drug product quality and patient safety.

GEL CLOT VERSUS CARTRIDGE TECHNOLOGY

Risk Analysis

Test Type	Samples	Impact To Drug Product (DP) Quality	Risk Of Human Error In Final Results Reading	Overall Risk To Patient Safety	What's Needed To Lessen Risk	Impact Concerns
Gel Clot	Final Drug Product	High	Medium/High	High	Four-eye Principal Plus Data Review And Verification	Patient Safety
	In-process	Medium	Medium/High	Medium/High		DP Quality
	Raw Materials	Low/Medium	Medium/High	Medium/High		In-process Samples
Cartridges	Final Drug Product	High	Low	Low	Data Review And Verification	Patient Safety
	In-process	Medium	Low	Low		DP Quality
	Raw Materials	Low/Medium	Low	Low		In-process Samples

The modern way to avoid data integrity risk in microbiological tests is to implement validated rapid methods that are automated



Types of data

Visual example

GEL CLOT
Report Form

Metadata

Technician name: ANNA LYST
Date of test: MAY 04 2020
Product EL: 0.5EU/mL MVC:
MVD: 1:4
Lysate Lot #: M4661L Sensitivity: 0.125 Expiry date: SEP 2023
Endotoxin Lot #: EX93223 Expiry date: NOV 2022
LRW Lot #: 34118004 Expiry date: DEC 2021

Standard Curve:

Replicate	2λ	λ	0.5λ	0.25λ
1	+	+	−	−
2	+	+	−	−

Raw Data

Sample Results:

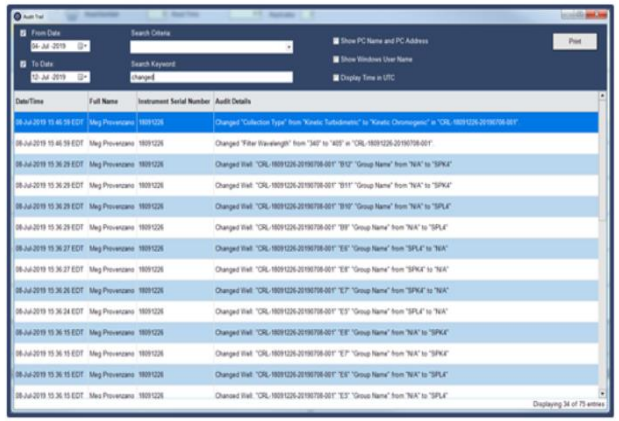
Conc/Dilution	Sample Negative		PPC at 2λ	
1:1	−	−	+	+
Water Negative Controls			−	−

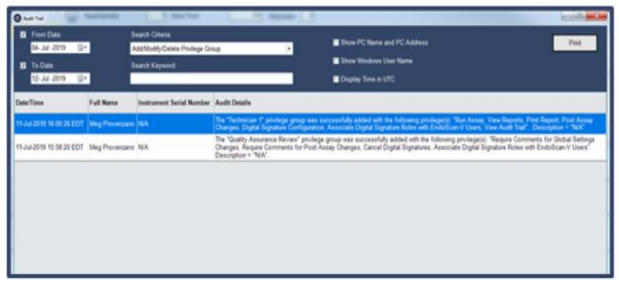
SOFTWARE

EXAMPLE OF ENDOTOXIN TESTING SOFTWARE DESIGNED TO FULFILL DI EXPECTATIONS

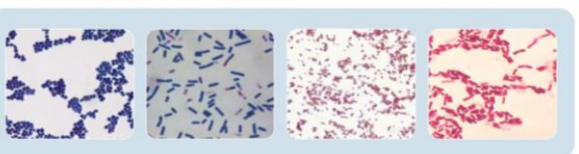
Audit Trail Searchable

- Electronic records that allow for the reconstruction of events relating to the creation, modification, or deletion of a record.
- They should be:
  - Secure
  - Computer-generated
  - Time-stamped
  - User relatable
- The should follow a chronology; who, what, when, and sometimes why.



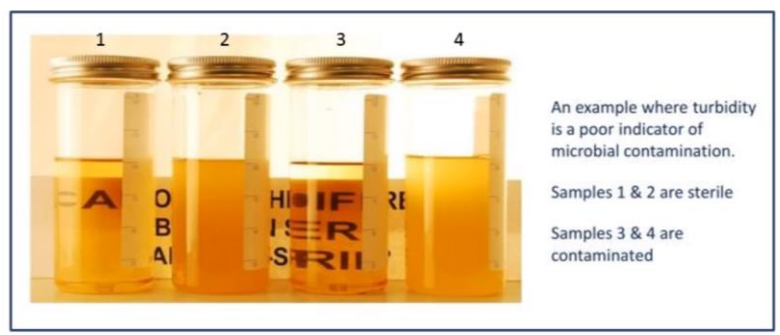


GRAM STAIN – ERRORS IN INTERPRETATION IN THE LAB



Gram positive cocci	Gram positive rod	Gram negative cocci	Gram negative rod

STERILITY - TURBIDITY ERRORS IN THE LAB



PATIENT SAFETY

Patient Safety is the most important factor!

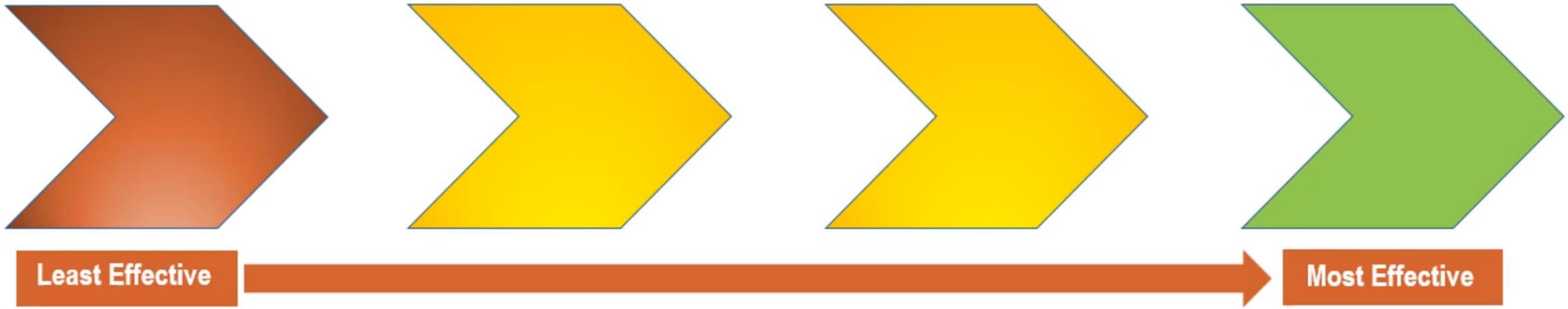
Why do I (quality control or manufacturing professional) care about data integrity?

- **The answer to this is also simple; because it's the right thing to do for the safety of the patient!**
  - Compliant and integral data allows us to make efficient, effective, and scientific based decisions about the quality and safety of the products we manufacture.
  - This ensures that we put the safety of the patient first above all else.
  - These decisions directly impact patients and customers in the industries that we serve:
    - Pharmaceutical Industry
    - Biotechnology Industry
    - Cosmetic industry
    - Food Industry
    - Nutraceutical Industry

charles river

DATA INTEGRITY

Strategic Risk Assessment

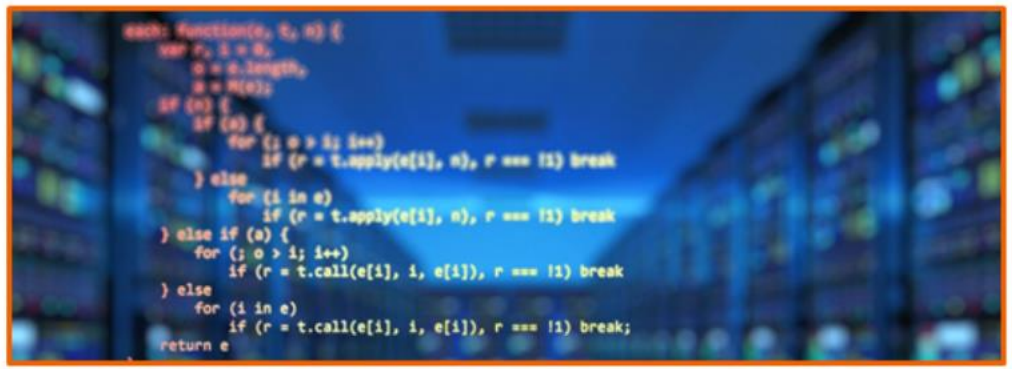


DUPLICATION	DETECT AND RECOVER	ERROR PREVENTION	ERROR PROOF
Repeating the same task or effort in order to identify or avoid error	Ability to find errors and get back to original state/minimize impact of error	Ability to use signals or devices to avoid error	Eliminating the possibility of making an error, its designed so human error is impossible

- Utilize an organized approach to assess the risk for human error in all of your laboratory processes.
- Take advantage of established six sigma/DMAIC methodologies to organize your investigations of your laboratory processes.
- Implement a human error risk ranking system for each one of your laboratory processes.
- Keep in mind that Detect and Recover and Duplication categories mean that human error is likely to occur again in the future.
- Measure and record the number of repeat events and the number of repeat root causes.

WHAT FACTORS IMPACT OUR DATA INTEGRITY COMPLIANCE?

EXAMPLE



HUMAN ERROR

Often overlooked factor in terms of Data Integrity.

SOFTWARE

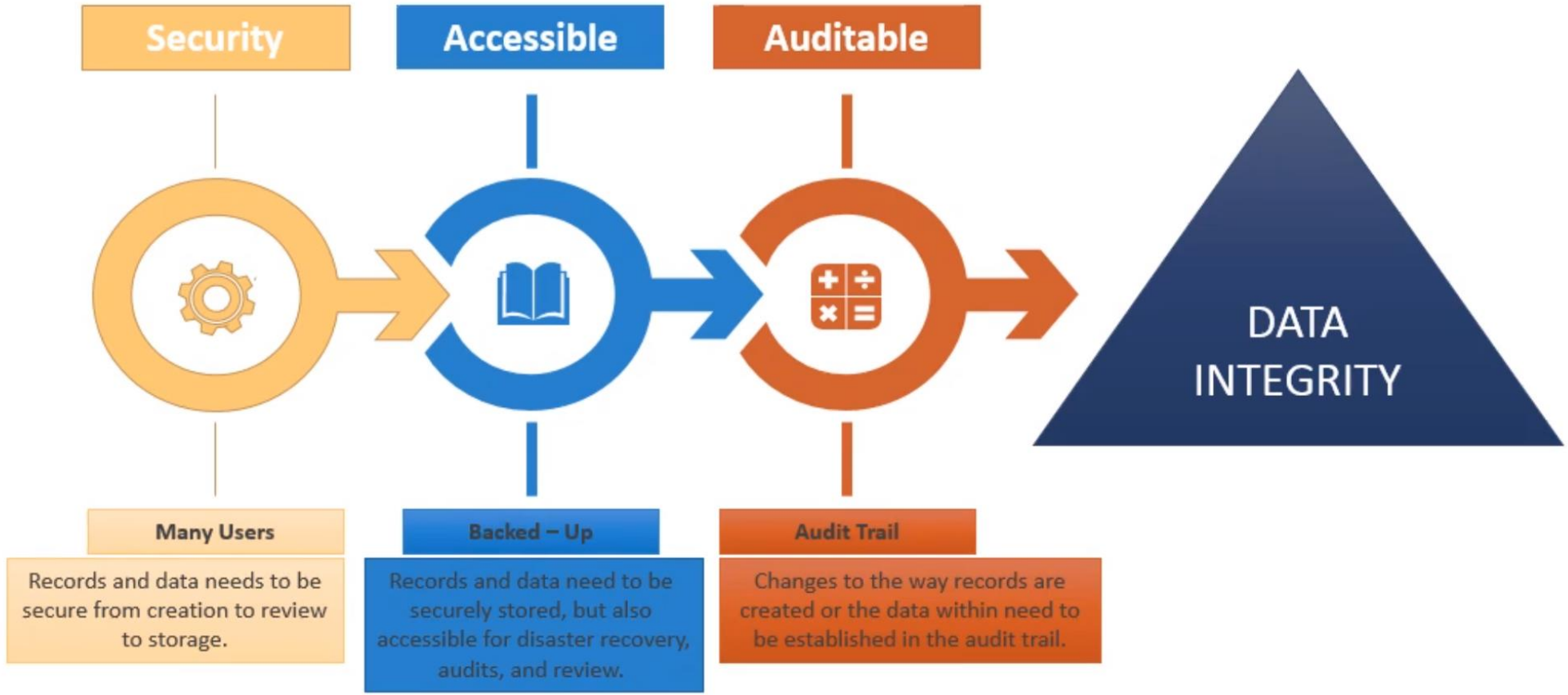
Poses challenges and risks for many organizations.

charles river

SOFTWARE

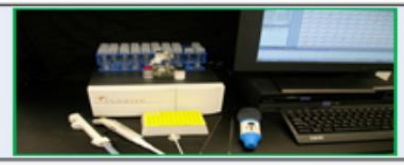
EXAMPLE OF ENDOTOXIN TESTING SOFTWARE DESIGNED TO FULFILL DI EXPECTATIONS

- new software applications have to be designed to cover and solve DI gaps



charles river

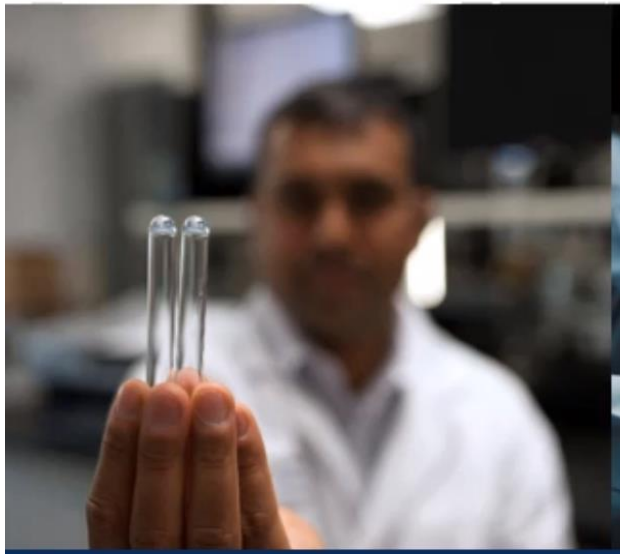
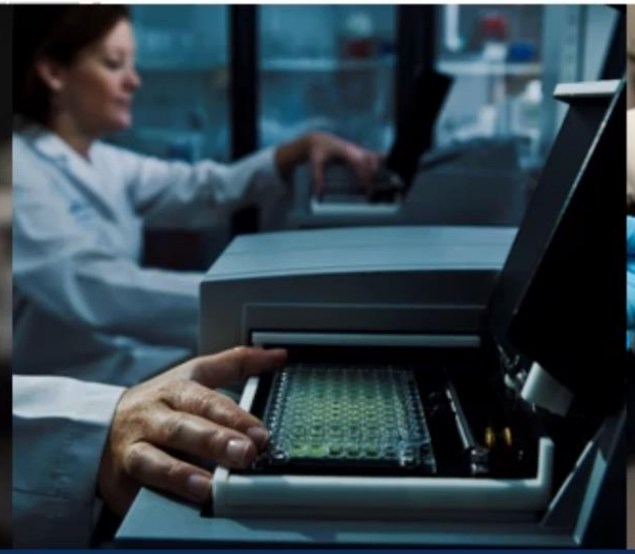
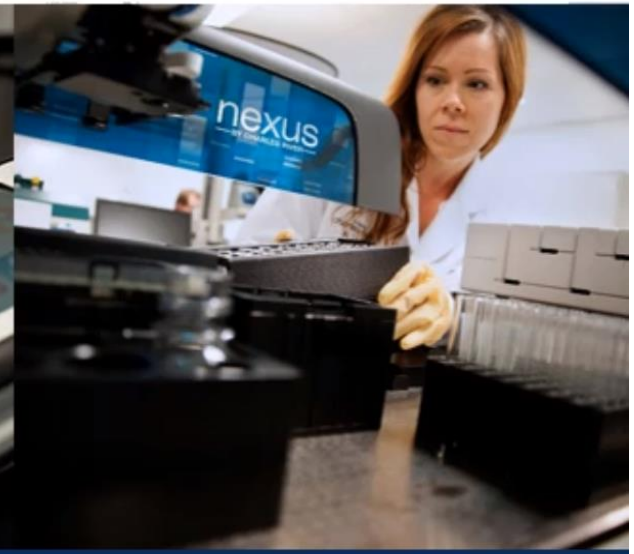
CRL PRODUCT COMPARISON

	Gel Clot	Cartridge Technology	KTA	KCA
Sensitivity	0.25, 0.125, 0.06, 0.03 or 0.015	0.005 (10 as upper limit)	0.005 (50 as upper limit)	0.001* (50 as upper limit)
Method	Gel	Kinetic Chromogenic	Kinetic Turbidimetric	Kinetic Chromogenic
Testing Time	60 min ± 2 mins	15 min	50 to 60 Minutes	45 to 75* Minutes
Prep Time	20 to 30 mins	3 to 5 mins	20 to 30 mins	20 to 30 mins
Licensing	FDA licensed			
Results	Qualitative or Semi-quantitative	Quantitative		
Reading	Manual	Automatic		
Validation Replicates	Quadruplicate	Duplicate		
Validation Endotoxin Conc.	2λ, λ, 0.5λ, 0.25λ	At or Near Mid point of Standard Curve		
Instrumentation	Heat block or Water bath	Nexgen-PTS, Nexgen-MCS or Nexus	BioTek ELx808IU	
Accessories Required				

* Reagent, reader and accessories dependent

HUMAN PERFORMANCE:

Categories of Preventing Human Error

Gel-Clot	Traditional Kinetic Assays	Rapid Testing: Endosafe® nexgen-PTS™ & MCS™	Automated Robotics: Endosafe® Nexus™
			
DUPLICATION Repeating the same task or effort in order to identify or avoid error	**DETECT AND RECOVER** Ability to find errors and get back to original state/minimize impact of error	**ERROR PREVENTION** Ability to use signals or devices to avoid human error	**ERROR PROOF** Eliminating the possibility of making an error, its designed so human error is impossible

Least Effective → **Most Effective**

charles river

TAKE ADVANTAGE OF THE CHANGE

Reagent Provider Change

INCREASE LAB EFFICENCY

Reduce the number of retests due to the assay complexity and give more time to the operators to perform value added tasks.

COMPETITIVE ADVANTAGE

Optimization of the time needed per test and validation that will allow your company to release product faster.

REDUCE TRAINING EFFORT

New technologies, and the cartridge technology in particular, reduce the training effort and the required knowledge to perform an endotoxin test.

EASE OF VALIDATION

Ease of validation for new products and ease of revalidation for existing products

SUMMARY

Utilize Laboratory Automation To Your Advantage!

Improve upon antiquated processes that rely a great deal on human input to generate subjective data:

- **Re-training is not effective** – analysts don't lack the knowledge, skill, or ability to perform a given task; but because many of our processes allow for error to occur in the first place.
- **Free up the human element** – utilize highly trained personnel to perform value-added laboratory tasks; *document creation and revision, LEAN activities, complex investigations, cross-training, method troubleshooting and validation*.
- **Examples tested by our industry** – Nexus™ Automated Endotoxin Testing System, Celsis rapid sterility and bioburden, Accugenix 16S sequencing and MALDI-TOF.
- **Be in control of the change** – Challenge your processes to identify DI gaps and define your own timeline to implement new technologies without waiting audit observations