charles river

ENDOTOXIN: CONTROL, ANALYSIS & CLINICAL RELEVANCE

Dialysis

Alan Hoffmeister

Senior Global Technology & Market Development Manager



ENDOTOXIN

What & Why

What is Endotoxin:

Component from cell wall of GNB (gram-negative bacteria)

Measured in endotoxin units (EU)

Stable in presence of most disinfectants

LAL is official mandated assay method

Why Focus On Endotoxin:

It is extremely important to focus on endotoxin contamination control in parenteral manufacturing mainly due to the following:

It is extremely ubiquitous in nature.

It displays a more potent toxicity in comparison to other pyrogens.

It is very stable and can retain its endotoxic nature after being subject to extreme conditions (such as sterilisation).

Chemical Composition

Contains Three Distinct Regions:

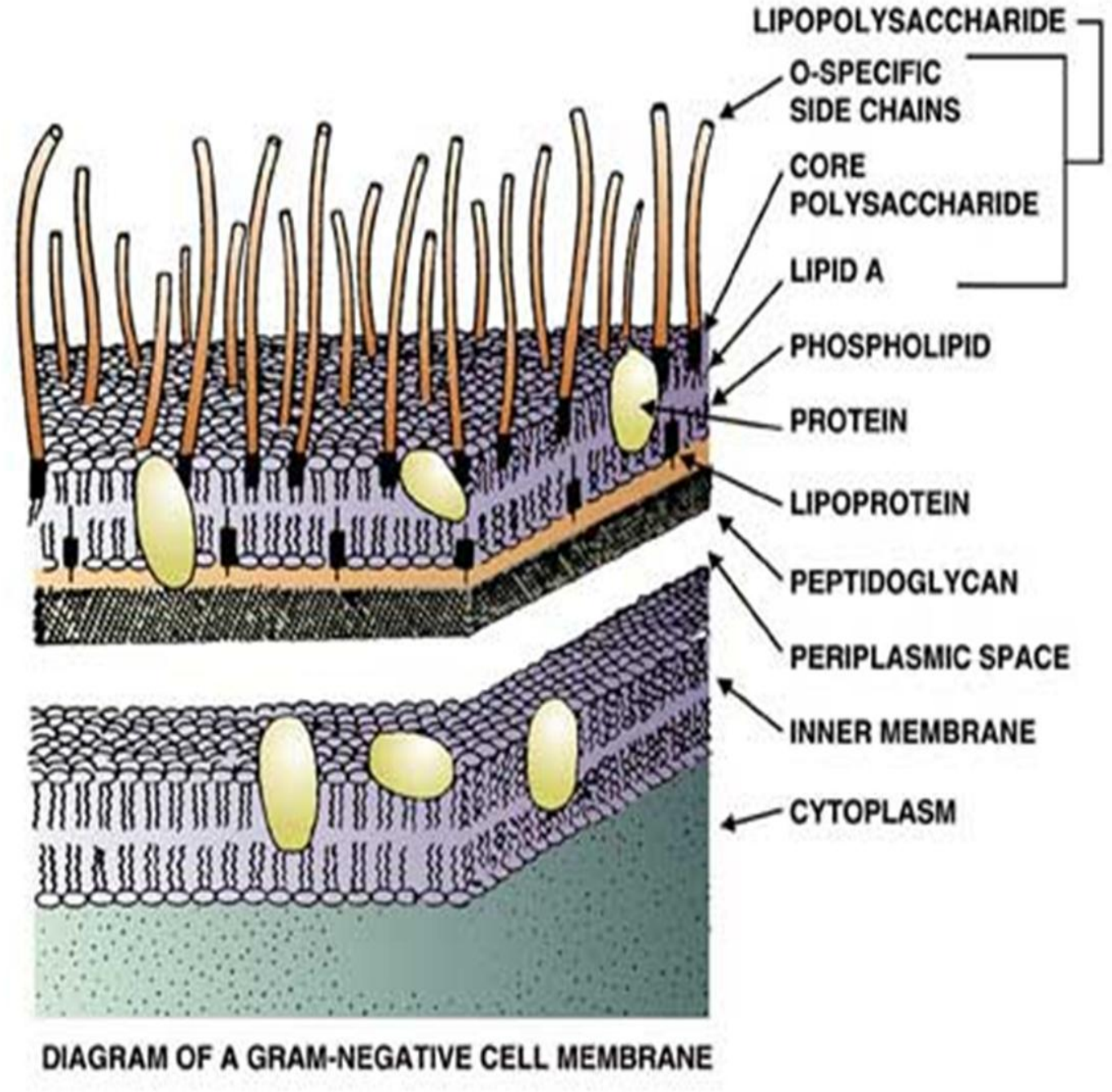
Region I: Lipid A

Region II: Core Polysaccharide. Highly conserved regions of acidic sugars that link O-Specific chain to Lipid A.

Region III: O-specific Chain.

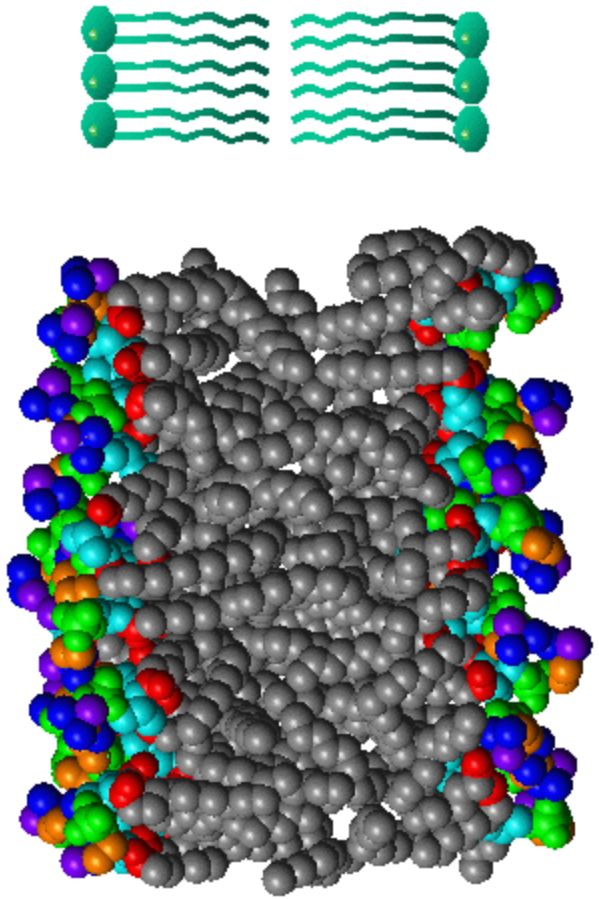
Whisker like projections that make up the somatic antigens for Gram Negative bacteria.

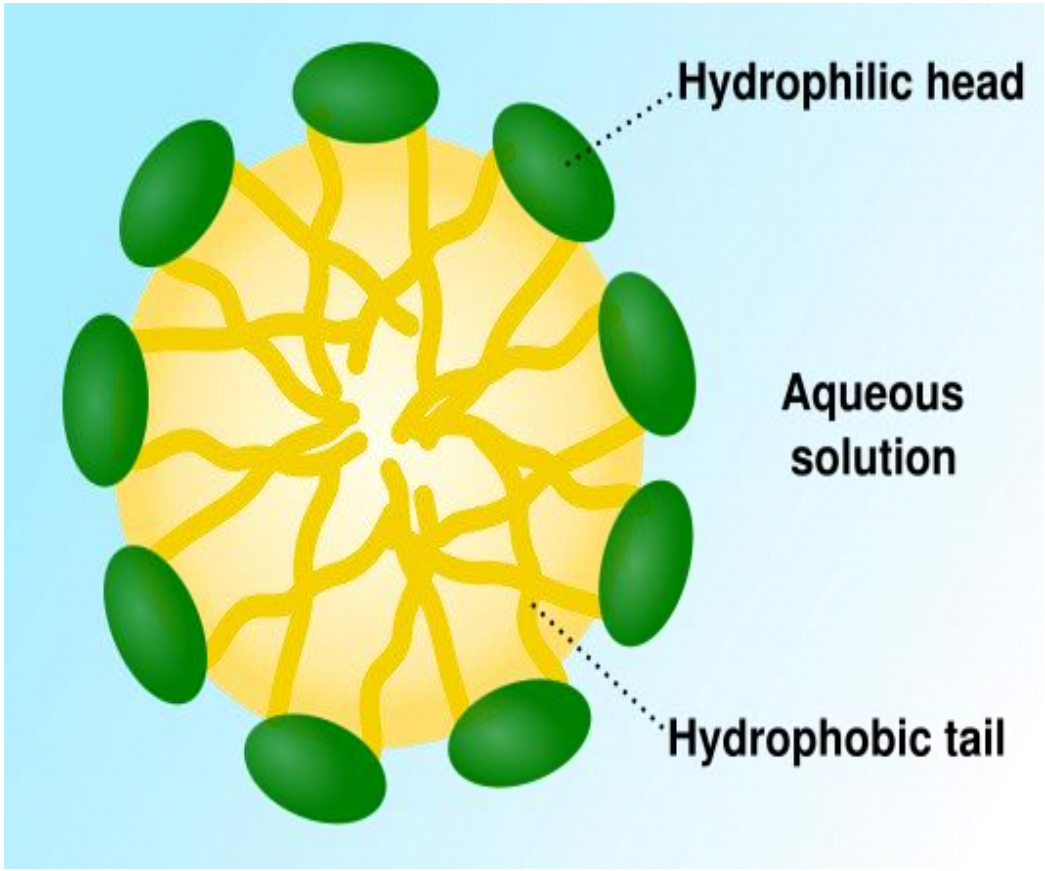
Highly variable.



Concept of Lipopolysaccharide Micelle

Aggregation

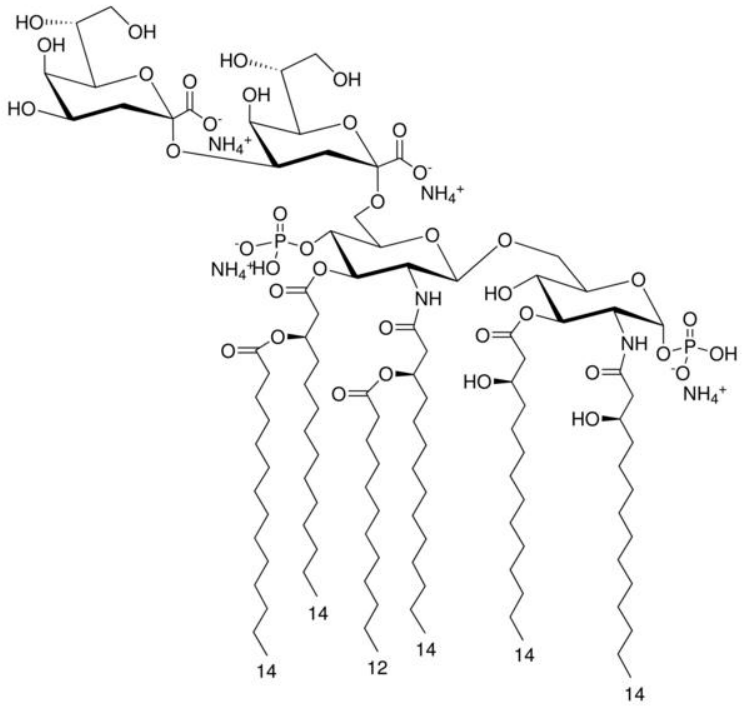


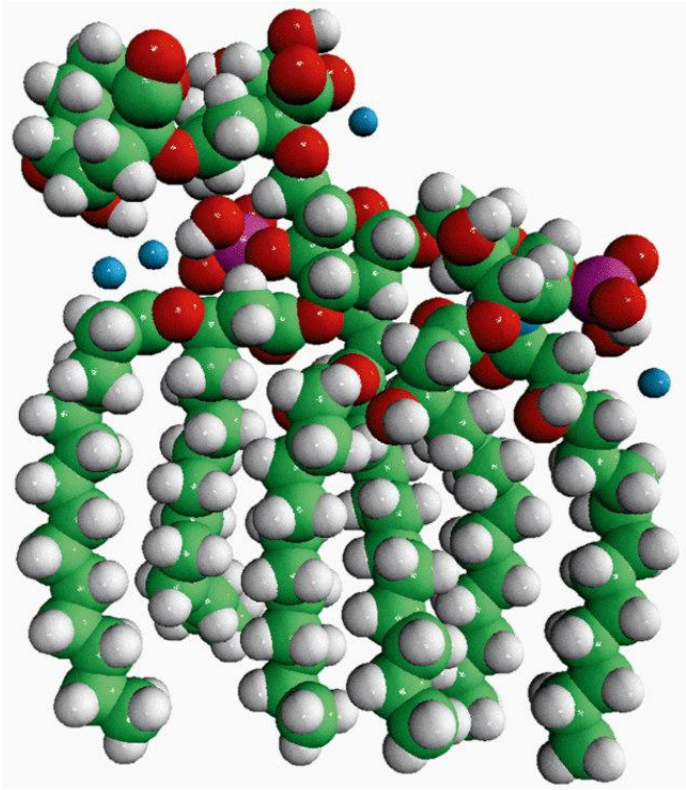


Lipid A

Consists of:

- Disaccharide glucosamine backbone
- Highly substituted with Amide-linked and Ester-linked long chain fatty acids
- Responsible for all of the biological activity of LPS





charles river

Lipid A

Biological Activity

- Pyrogenicity
- Leukopenia
- Leukocytosis
- Local Shwartzman Reaction
- Bone Marrow Necrosis
- Complement Activation
- Platelet Aggregation
- Hageman Factor Activation
- Induction Of Plasminogen Activator
- Adjuvant Activity
- Tumor Necrotic Activity
- Induction Of Colony Stimulating Factor
- Induction Of Interferon Production
- LAL Activation

Mammalian Response to Endotoxin
How Much is Needed?

Produces profound alterations in ORGAN FUNCTION in vivo when endogenous pyrogens are activated

Diffuse illness from ng doses:

- Fever, mild hypotension and inflammation

Septic Shock from µg doses:

- Hypotension & disseminated intravascular coagulation, which can lead to death
- Edema in lungs can lead to suffocation

Sources of Endotoxin

Bioburden

Parenteral Industries:

- Water systems and containers
- Ion-exchange columns
- Starting materials of biological origin
- Any source of bioburden

Compounding Pharmacies & Sterile Supplies:

- Wet devices, glassware and plastic ware
- Non-sterile components & solutions

NO MICROBES, NO ENDOTOXIN PYROGEN

What are safe levels of endotoxin?

The Lower The Better

Safety is stated in terms of endotoxin units per body weight, generally 5 EU/kg

An EU is measured by LAL tests and referenced to pyrogenicity of an international reference endotoxin standard

Safety varies with the route of administration/injection, with intraspinal being the most sensitive

‘Pyrogen-free’ means that article contains less than the endotoxin limit not zero

Introduction to LAL



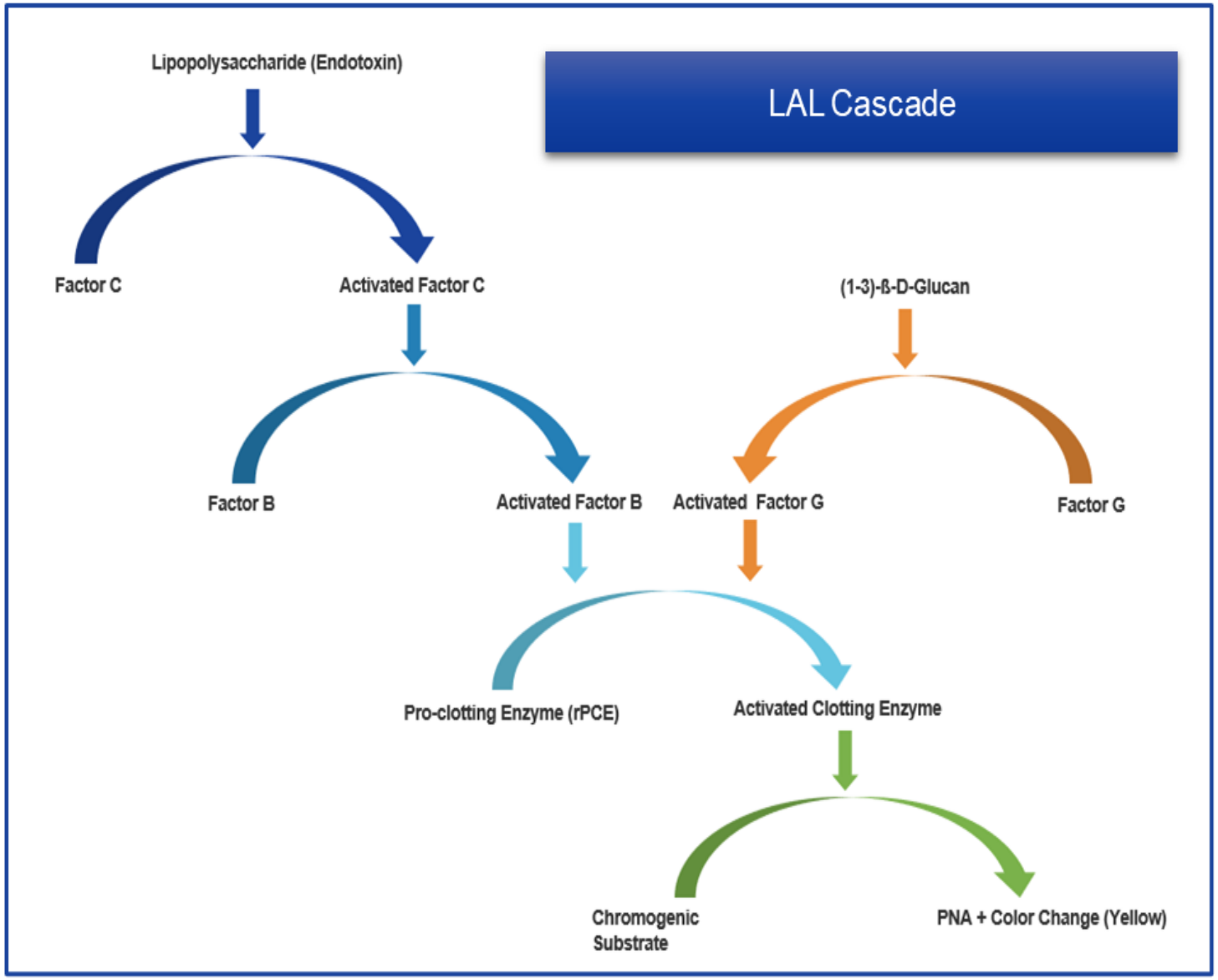
WHAT IS LAL?

Remarkable Blue Blood

An Aqueous Extract Obtained From The Horseshoe Crabs Single Blood Cell – The Amebocyte.

LAL Is An Enzyme Clotting System:

The Amebocyte Clotting Enzymes Represents A Simple Defensive Mechanism For The Crab.



charles river

Discovery of LAL

Historical LAL Background

1953: F. Bang's Landmark Study

Origin of the LAL test is traced to Dr. Frederik Bang:

Discovered that endotoxins from *Vibrio* caused massive intravascular coagulation and death in *Limuli*.

While studying HSC passive immunity, saw infection produce intravascular clotting.

Gram Neg. Bacteria and a heat-stable extract of these bacteria were equally effective in producing coagulation.

Gram-positive bacteria failed to promote a response.

A product of the blood cells produced a gel *in vitro* when exposed to the GNB extract.

1963: LAL Discoveries by Bang and Levin

Dr. Jack Levin: A hematologist interested in a clinical assay for diagnosing endotoxemia

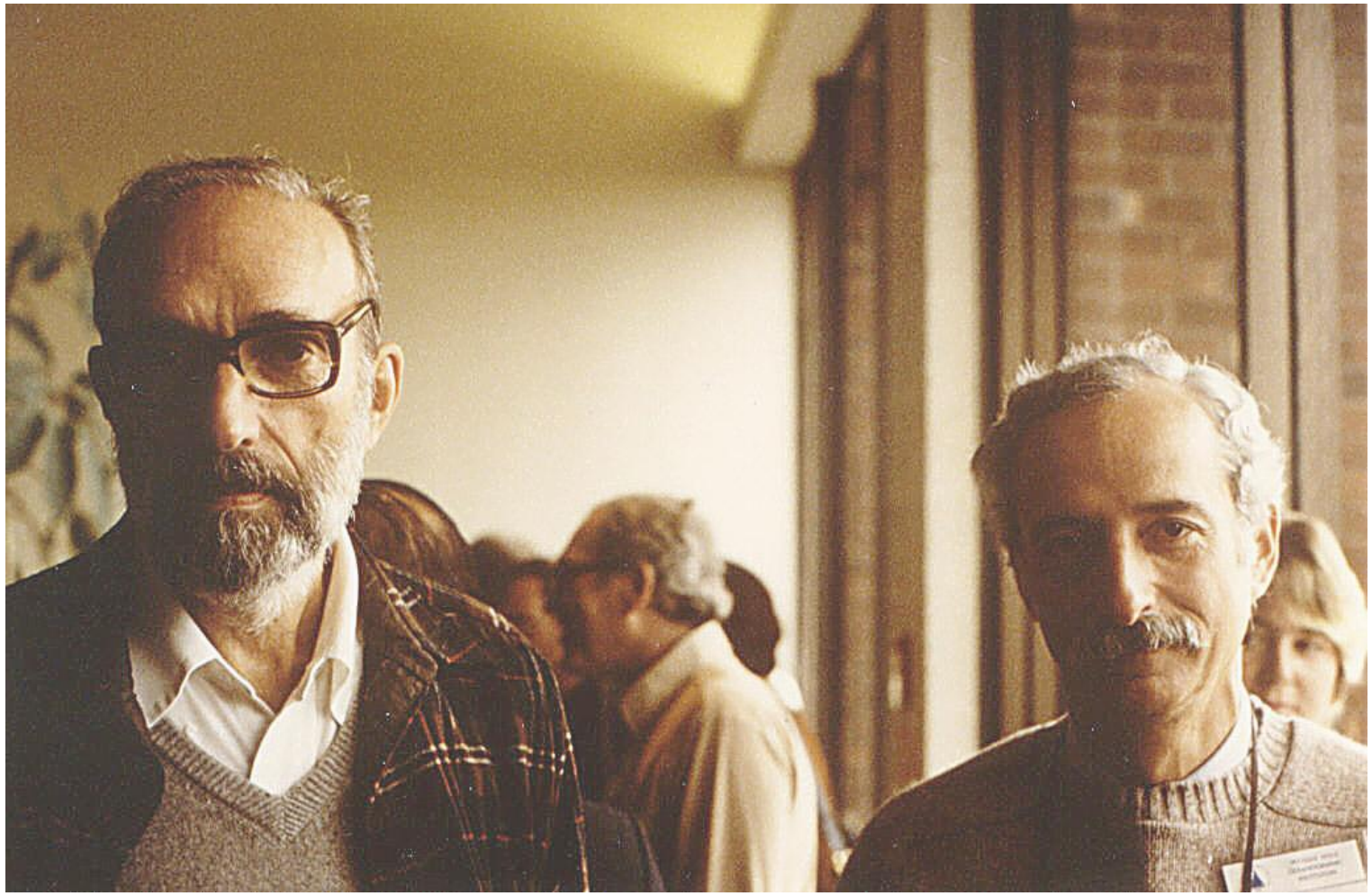
Bang and Levin collaboration, both of Johns Hopkins Univ., began in 1963.

Described role of endotoxin in coagulation of *Limulus* blood; all clotting factors were in amebocytes.

PREPARED ENDOTOXIN-RESPONSIVE cell lysate from AMEBOCYTES (LAL).

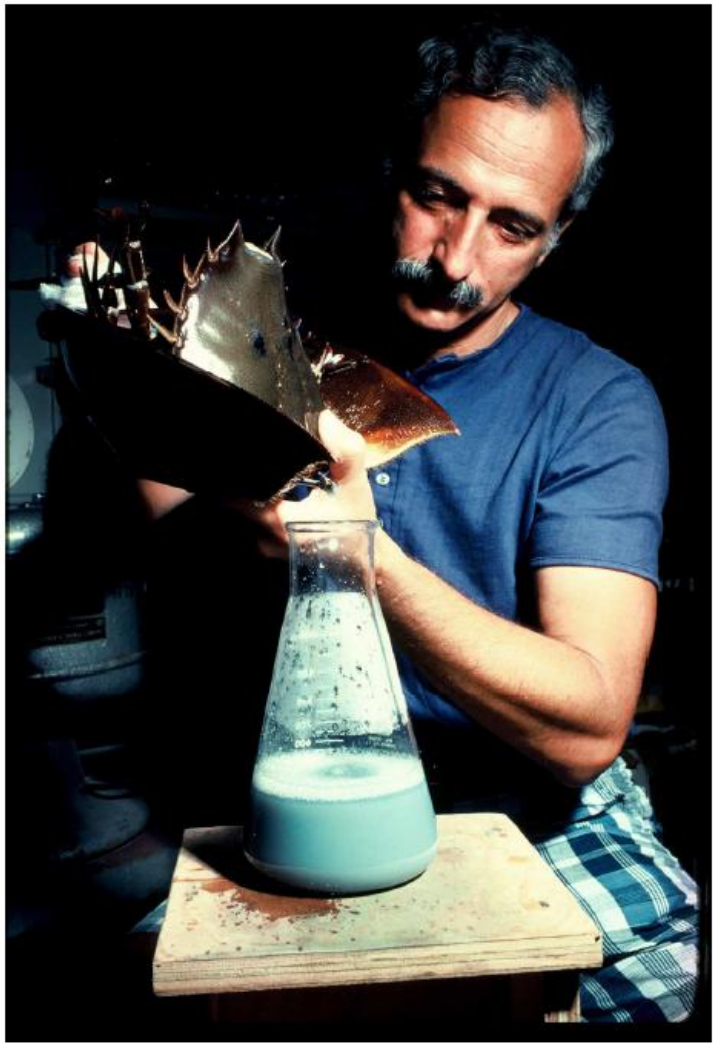
The Founders of the LAL Test

Dr Frederik Bang and Dr Jack Levin (1980)



charles river





Photo’s by kind permission of Dr Jack Levin

charles river

Why is it called LAL?

Limulus Amebocyte Lysate (LAL)

Limulus

- Genus of horseshoe crab

Amebocyte

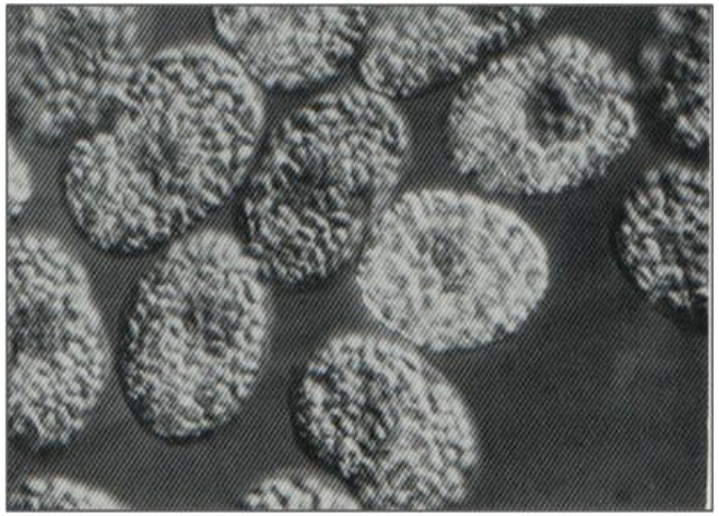
- Horseshoe crab blood cells

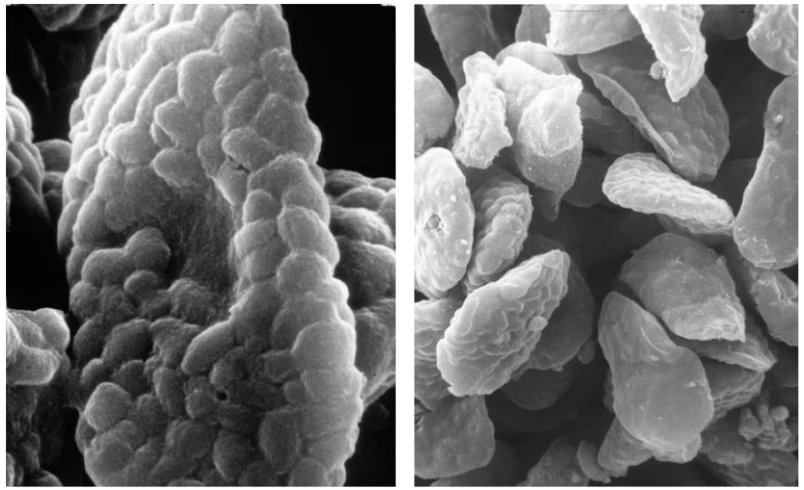
Lysate

- Lysing the cell to access the cell components

Hence The Acronym:

Limulus Amebocyte Lysate (LAL)





Photo's by kind permission of Dr Jack Levin

charles river

WHY USE LAL?

Sensitivity And Robustness Are Key

LAL Is Unequivocally Recognized As The Most Sensitive Method Available For The Detection Of Gram-Negative Endotoxins.

Regulated biological product

100 times more sensitive, specific, and accurate than the rabbit pyrogen test

Sensitivity to <1 picogram

1 Endotoxin units (EU) = 1 International units (IU)



LAL

TEST SENSITIVITY

The LAL Test Can Detect Pyrogens to Less Than 1 Part per Trillion: 0.000000000001 Grams

1 Part per Trillion Is Equivalent To:

1 Second In 320 Centuries

1 Grain Of Sugar In An Olympic Size Swimming Pool

charles river

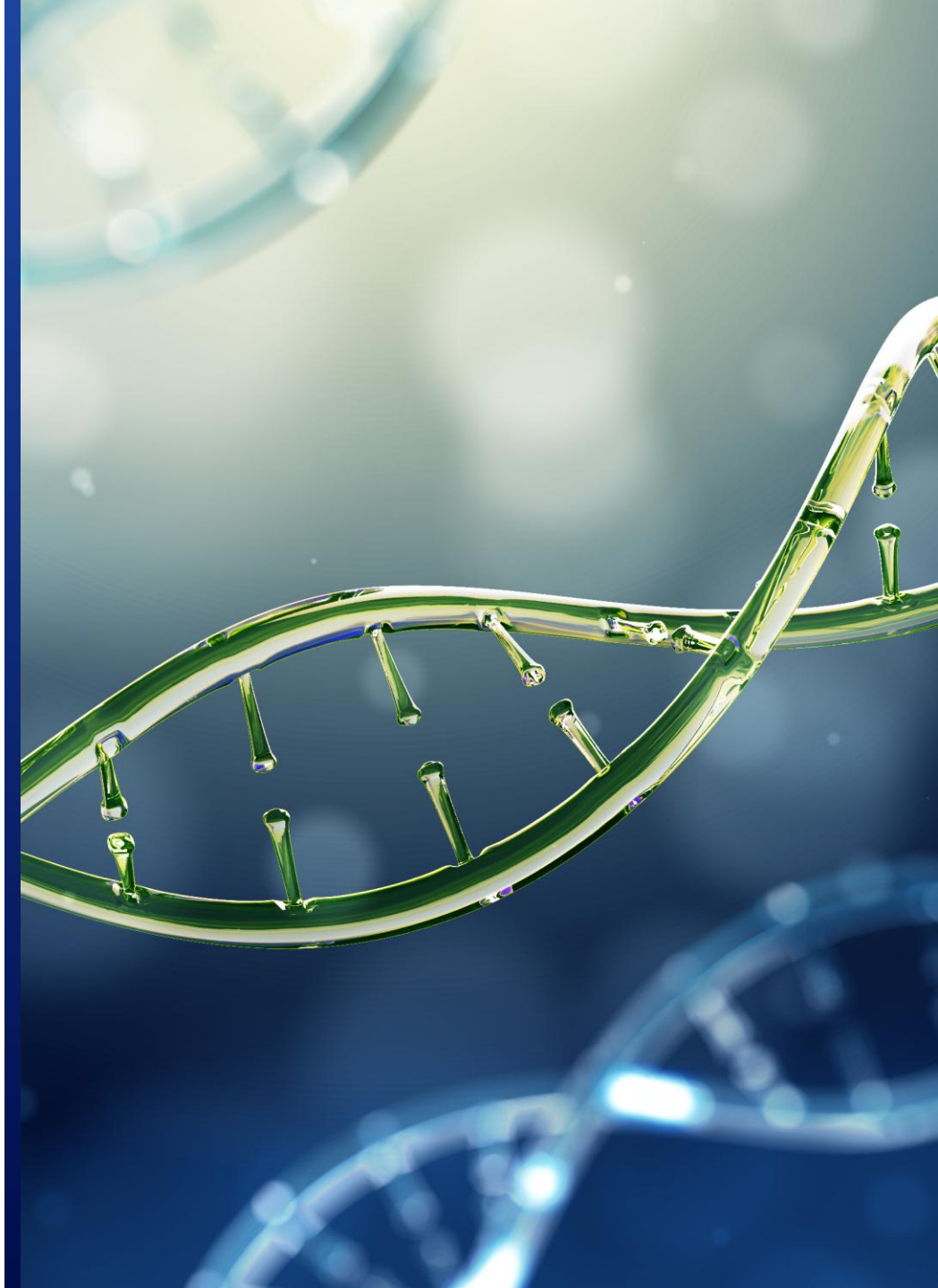
Introduction to Recombinant BET Reagents



What is a recombinant protein?

When recombinant DNA encoding a protein is introduced into a host organism to express foreign proteins.

Recombinant DNA: the combination of two DNA strands that are constructed artificially



Manufacturing Recombinant Reagents



Target gene is added to expression vector.

Vector is transfected into host cell. Host cells are from working cell bank.

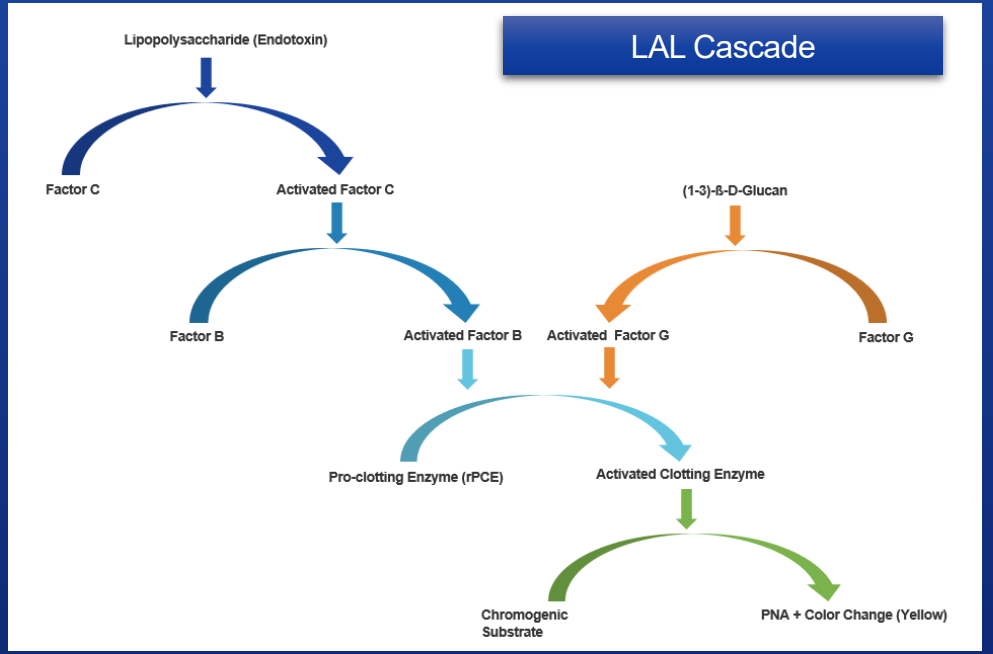
Protein expressed in bioreactor and purified.

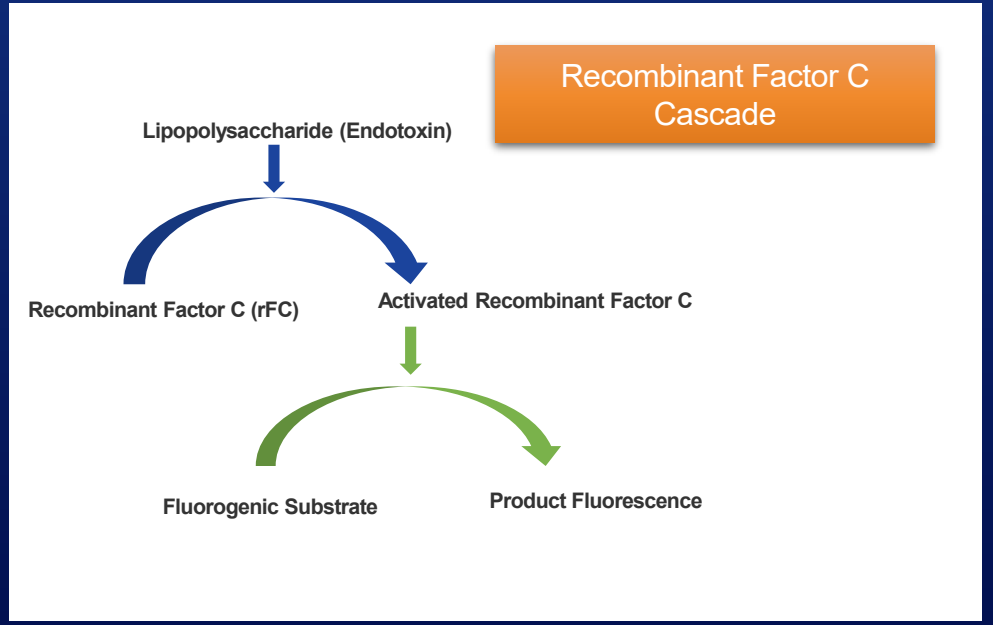
Recombinant BET reagent formulated.

charles river

Recombinant Factor C Reagent

- 100% Horseshoe crab blood free
- **Reduced lot to lot variation**
- **No glucan interference**
- **Sustainable supply chain**
- **Multiple suppliers**
- Recombinant fluorescence reagent
- Formulation includes one critical biological recombinant enzyme
- **Not globally harmonized**

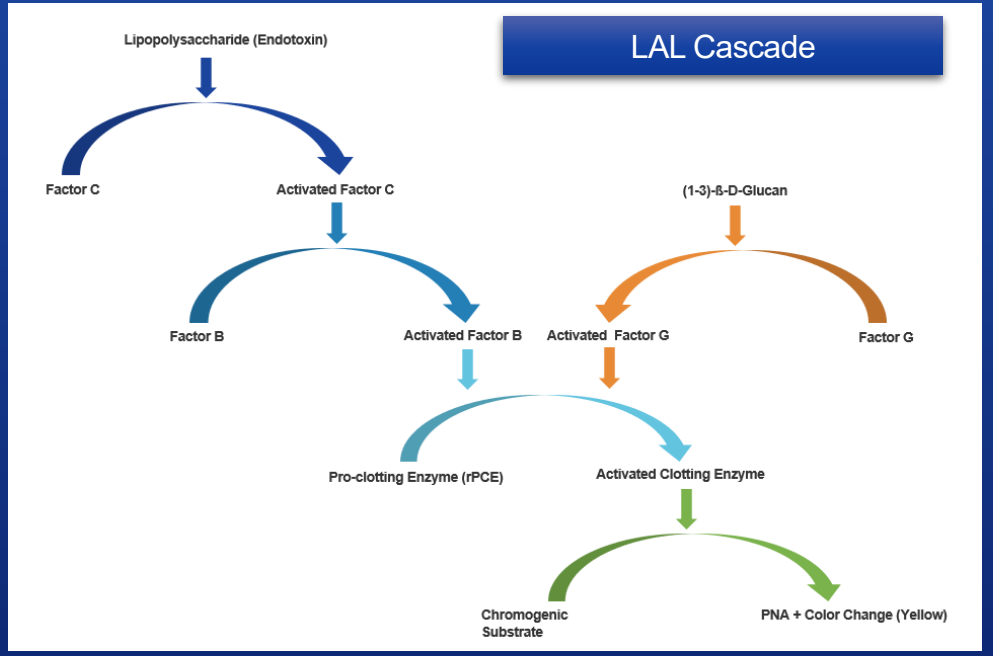


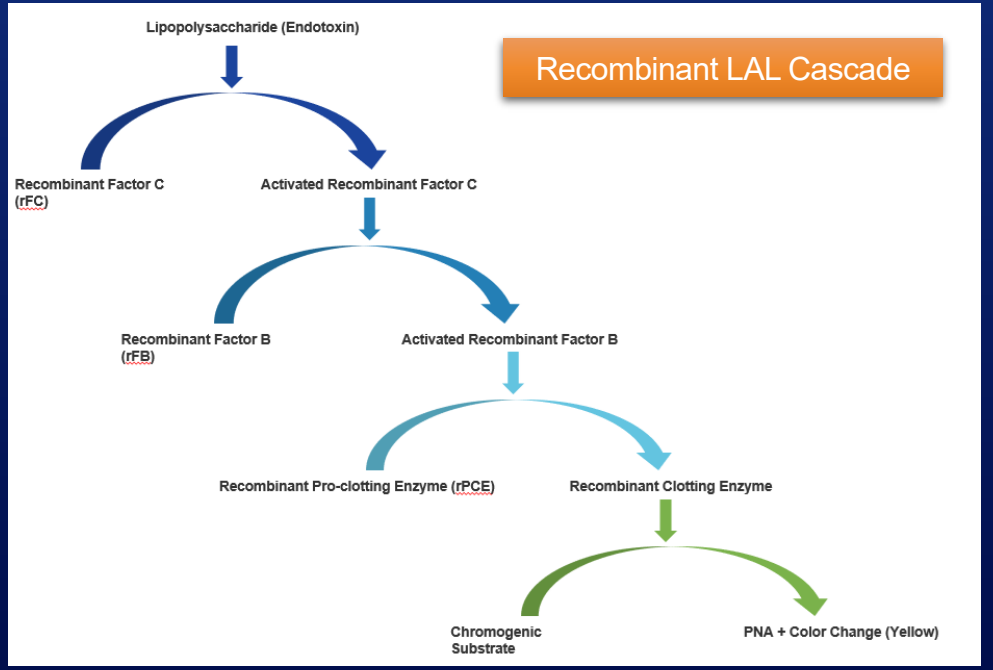


charles river

Endosafe® Trillium Recombinant Cascade Reagent

- 100% Animal free
- Recombinant kinetic chromogenic reagent
- Formulation includes the three critical biological recombinant enzymes.
- **No glucan interference**
- **Reduced lot to lot variation**
- **Sustainable supply chain**
- Formulated to accurately recover natural environmental endotoxins as well as RSE and CSE.
- **Not globally harmonized**
- **Multiple suppliers**





Recombinant Technologies

Comparison table LAL< rFC < rCR

	LAL	rCR – Recombinant Cascade Reagent	rFC – Recombinant Factor C
Enzymes / cascade	3 - yes	✓ Same as LAL	☒ 1 - no
Pre-test adjustment	No	✓ Same as LAL	☒ Yes (Gain adjustment)
Reagent format	all in 1 vial	✓ Same as LAL	☒ 3 vials (reagent, substrate, buffers)
Readout	Kinetic	✓ Same as LAL	☒ Endpoint
Detection method	Absorbance	✓ Same as LAL	☒ Fluorescence
Equipment/software	Absorbance reader	✓ Same as LAL	☒ Fluorescence reader
Training / technician qualification	-	✓ Same as LAL	☒ added training program to LAL
Specificity	Glucan Interference	• No glucan interference • Articles rCR equivalent to LAL (Kikuchi 2023)	• No glucan interference • Articles rFC NOT EQUIVALENT to LAL (Kikuchi 2023)
Sustainability	Variable	100% animal free	100% free HSC blood
Licensed	FDA Licensed	Not Licensed	Not Licensed
Compliance	Discussed in further slides		

charles river

Recombinant Technologies

Lab Operational Impact

	LAL	rCR – Recombinant Cascade Reagent	rFC – Recombinant Factor C
Sustainability	Variable	100% animal free	100% free HSC blood
	There are also sustainable LAL solutions: 1. Moving from GC or Kinetic Turbidimetric to Kinetic Chromogenic => save 54% of HSC blood 2. Moving from GC or Kinetic Turbidimetric to Cart tech (Kinetic Chromogenic microfluidic) => save 95% of HSC blood	No HSC blood and no animal derived components in the formulation.	Some suppliers use animal derived components in their formulation
Equipment/software	Absorbance reader	Absorbance reader (Same as LAL)	Fluorescence reader
	NA	Same equipment/software as LAL. During transition from LAL to rCR no need for equipment, software and maintenance program duplication	For same method, during transition, 2 different equipment or investment for a dual reader, software and maintenance program required.

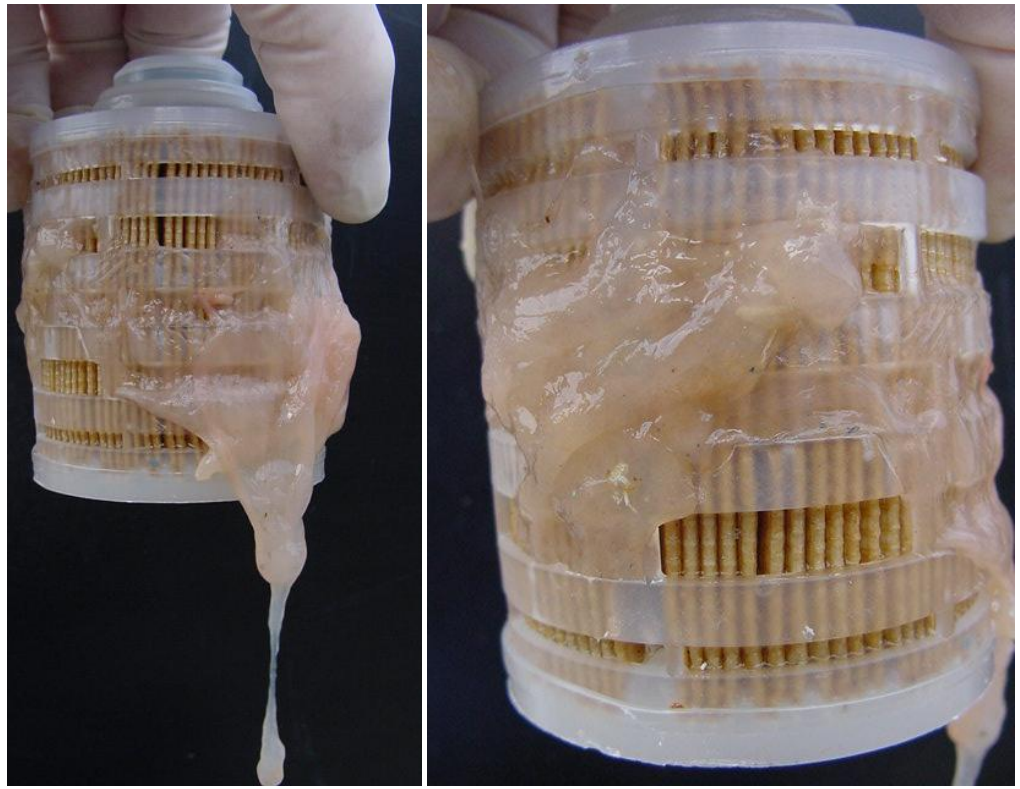
Endotoxin In Dialysis



BACTERIAL GROWTH AND ENDOTOXIN

Biofilm

- Most bacteria found in dialysis water and sterile supply fluids are endotoxin producing Gram Negative Bacteria
- Rapid bacterial growth in water, dialysate or liquid bicarbonate concentrate produces substantial endotoxin
- Biofilm is a major source of endotoxin



charles river

Bacteria and Endotoxin

Pyrogenic Reaction and Harmful Effects

BACTERIA AND PYROGENIC REACTION

Analysis of pyrogenic outbreaks found the following:

Rate of pyrogenic reaction directly related to bacterial concentration

Pyrogenic reactions ceased when cultures were <10 CFU/mL

HARMFUL EFFECTS OF ENDOTOXIN

Below 5 EU/kg	No pyrogenic reaction
Above 5 EU/kg	Fever, chills & hypertension or if high enough Life-threatening septic shock

AVOIDING and RECOGNISING reactions

What to Look For

PYROGENIC REACTIONS

Design surveillance policies for critical fluids

Outline procedures for sample collection and assay

Plan methods for recording and interpreting results

Record patients' adverse reactions

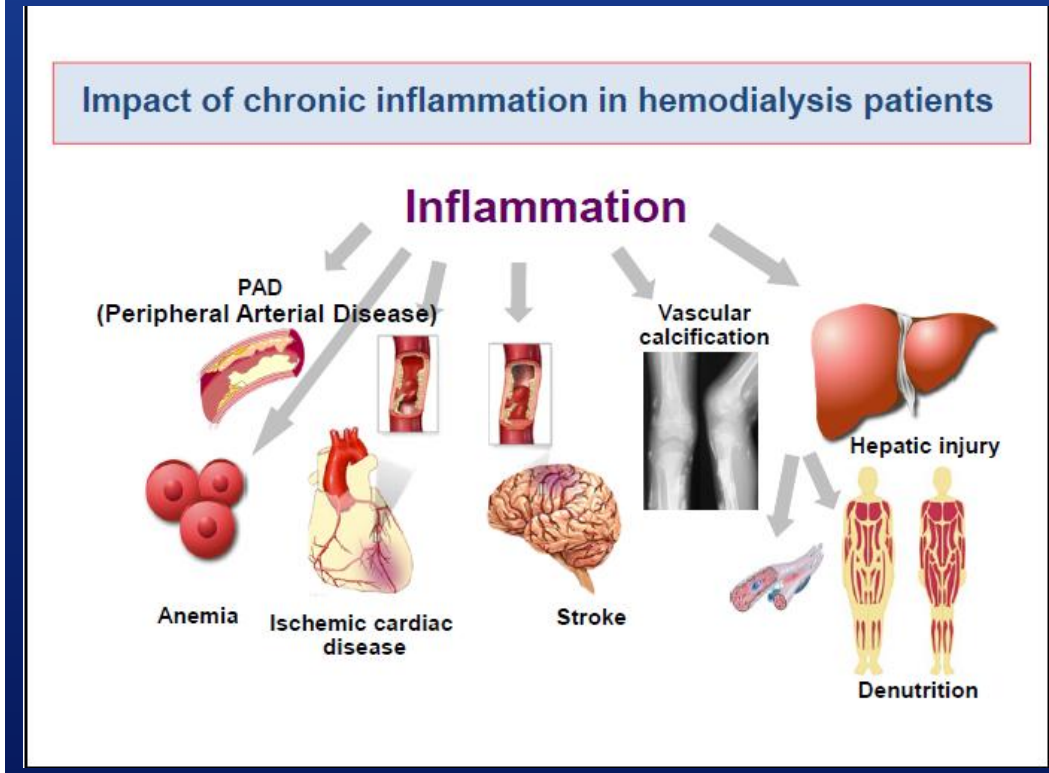
FEVER CURVE IN ENDOTOXEMIA

Rapid temperature rise @ 2-3 hrs

Peak endotoxic signs @ 3-6 hrs

Patient may become ill after leaving clinic

Endotoxins Drive Chronic Inflammation and Poor Prognosis in Dialysis Patients



charles river

Dialysis hospitalizations can result from endotoxin-driven pyrogenic and inflammatory events



Cause and effect

Dialysis

PRACTICES AND ENDOTOXIN

Potential danger from microbial and endotoxin contamination increasing because of the following:

- Reuse of hemodialyzers
- Bicarbonate dialysate
- High-flux dialysis units

POTENTIAL EFFECTS OF CHRONIC EXPOSURE

Cardiovascular disease

Malnourishment

Amyloidosis

- Reduced incidence of Carpal Tunnel Syndrome with ultrapure dialysate

Endotoxin and Mortality Risk

130,781 patients receiving thrice-weekly in-center hemodialysis for more than 6 months were enrolled at 2,746 facilities in Japan at the end of 2006.

Of 130,781 hemodialysis patients, 91.2% had facility endotoxin levels below the limit set for dialysis fluid in Japan (<0.05EU/mL).

During a 1-year follow-up, 8,978 (6.9%) patients died of all causes. The rate of all-cause mortality at 1 year was highest in the ≥0.1-EU/mL category (88.0 deaths/1,000 person-years).

Patients in the ≥0.1-EU/mL group exhibited an increased risk of all-cause mortality of 28% (95% CI, 10%-48%) compared to the <0.001-EU/mL group.

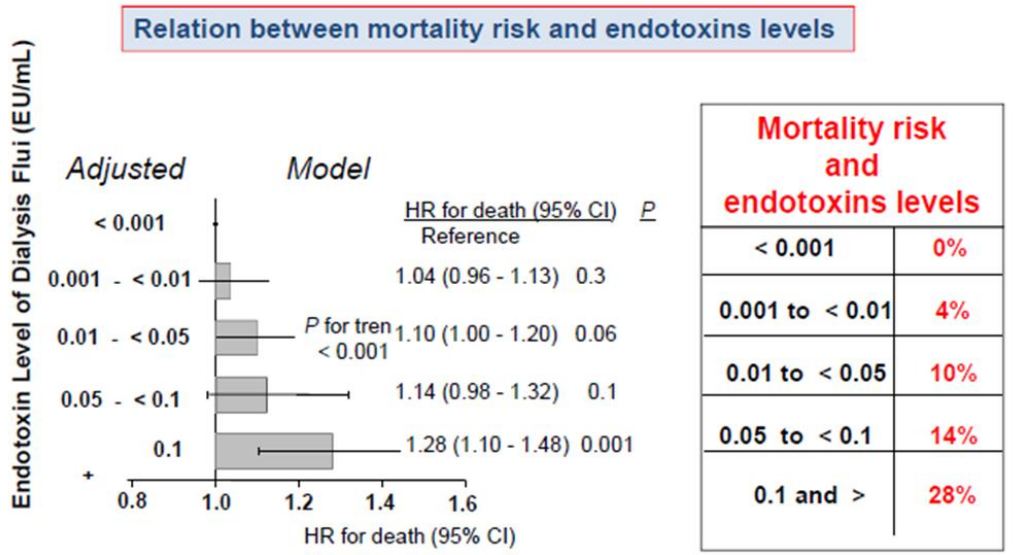
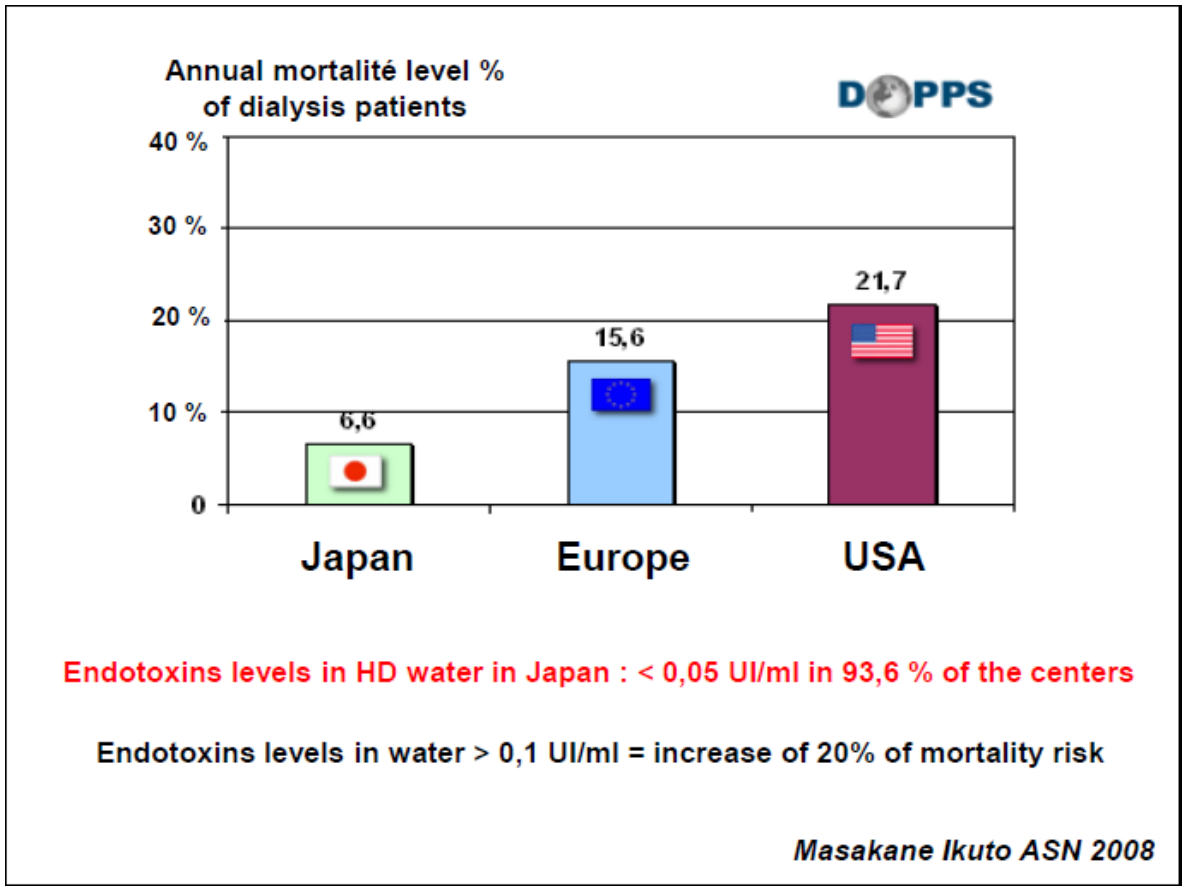


Figure 3. Hazard ratio (HR) of all-cause mortality for in-center hemodialysis patients stratified by facility dialysis fluid endotoxin level ( ) adjusted for age, sex, dialysis vintage diabetes mellitus, Kt/V, normalized protein catabolic rate, dialysis sessions duration, serum albumine level, hemoglobin level

T.Hasegawa, S.Nakai, I.Masakane et al. Am J Kidney Dis. 2015;65(6):899-904

charles river

Endotoxin Concentration in HD Globally



Endotoxins levels in HD water in Japan : < 0,05 UI/ml in 93,6 % of the centers

Endotoxins levels in water > 0,1 UI/ml = increase of 20% of mortality risk

Masakane Ikuto ASN 2008

charles river

charles river

Regulatory Requirements and Guidelines

Dialysis



European Pharmacopoeia (EP)

4 Monographs

Water for dilution of concentrates = 0.25 EU/mL

Solutions for Haemodialysis = 0.25 EU/mL, in the solution diluted for use

Solutions for Hemofiltration and Hemodiafiltration = 0.05 EU/mL

Solutions for peritoneal dialysis 0.05 EU/mL, unless otherwise justified and authorised.

EDTNA/ERCA

European Dialysis and Transplant Nurses Association and European Renal Care Association Guidelines

Water for Haemodialysis <0.25 EU/mL. Action limit <0.125 EU/mL

Solutions for Haemodialysis (concentrates + water) <0.25 EU/mL each. Action limits <0.125 EU/mL

Ultrapure dialysis fluid <0.03 EU/mL. Action limit <0.015 EU/mL

Substitution Fluids – No limit specified but should be lower than Ultrapure dialysis fluid

Should be tested routinely

Samples should be collected from the point(s) expected to have the highest load

United States Pharmacopoeia

USP

Chapter <1230> Water for Hemodialysis Applications = 1 EU/mL. Action level 0.25 EU/mL

Sampling should be done at all use points where the water enters the dialysis equipment

ANSI/AAMI

American National Standard/Association for the Advancement of Medical Instrumentation

AMMI 13959:2014

Microbiological Level	Standard Dialysis Fluid	
	Maximum Allowable Level	Action Level
Colony Forming Units	< 100 CFU/mL	≥ 50 CFU/mL
Endotoxin Units	< 0.50 EU/mL	≥0.25 EU/mL

Microbiological Level	Water Standard	Water Action Level
Colony Forming Units	< 100 CFU/mL	≥ 50 CFU/mL
Endotoxin Units	< 0.25 EU/mL	≥0.125 EU/mL

charles river

Japanese Society for Dialysis Therapy

MICROBIOLOGICAL QUALITY STANDARD FOR DIALYSIS FLUIDS

Attainment level

- Dialysis water (Reverse Osmosis [RO] Water)
  Bacteria: <100 CFU/mL
  Endotoxin: <0.050 EU/mL
- Standard dialysis fluid
  Bacteria: <100 CFU/mL
  Endotoxin: <0.050 EU/mL
- Ultrapure dialysis fluid
  Bacteria: <0.1 CFU/mL
  Endotoxin: <0.001 EU/mL (less than the detection limit)

Note: The action level shall be set depending on the quality condition of each facility, typically at 50% of the maximum allowable level, except for the endotoxin level of ultra-pure dialysis fluid.

- Online prepared substitution fluid
  Sterile and non-pyrogenic
  Bacteria: $<10^{-6}$ CFU/mL
  Endotoxin: <0.001 EU/mL (less than the detection limit)

charles river

Japanese Society for Dialysis Therapy

Sampling sites

- Dialysis water: Outlet of RO equipment
- Dialysis fluid: Inlet line of dialyzer
  Note: Push and pull hemodiafiltration (HDF) systems should be tested on the outlet line of dialyzer.
- Online prepared substitution fluid: extraction site of substitution fluid

Frequency of monitoring

- Dialysis water: Every 3 months
  If the quality of each facility is not maintained to allowable levels, the monitoring frequency should be increased to once a month.
- Standard dialysis fluid: Monthly
  At least two machines are tested each month so that each machine is tested at least once per year.
- Ultrapure dialysis fluid: Monthly when used for conventional hemodialysis (including internal filtration enhanced hemodialysis)
  At least two machines are tested each month so that each machine is tested at least once per year.
- Ultrapure dialysis fluid for the preparation of online substitution fluid and the dialysis system for active use of back filtrate: Every 2 weeks until the system is validated
  After the quality is validated by the dialysis equipment safety management committee, monitor the same frequency as standard dialysis fluid.
- Online prepared substitution fluid: Monthly
  Endotoxin: Every 2 weeks until the system is validated. After the quality is validated by the dialysis equipment safety management committee, monitor monthly on every machine of dialysis fluid and substitution fluid.

charles river

CSA/ISO Standards

Clinical Practice Standards and Procedures for Dialysis Water Quality

Standards for hemodialysis grade water/dialysate

	Hemodialysis Grade Water/Dialysate
Endotoxin Concentration	<0.25 EU/mL
Action Level	=>0.125 EU/mL
	Ultrapure Dialysate
Endotoxin Concentration	<0.03 EU/mL

	Dialysis Water
Assay Time	Within 4 hours of collection or 24 hours if immediately refrigerated
Assay Technique	Limulus amoebocyte lysate (LAL) test

NSW ACI Renal Network

These are the recommended levels for Australian dialysis units.

Table 3.5 Levels of contaminants in product water

MICROORGANISMS	ISO 13959:2014
CFU/mL maximum	100
CFU/mL action level	50
ENDOTOXINS	
EU/mL maximum	0.25
EU/mL action level	0.12

Table 3.6 Maximum contaminant concentration levels in the dialysis permeate/product water

Contaminant	Maximum concentration for dialysis product water (mg/L = ppm) ISO13959:2014
Bacteria	100 CFU/ml (Action level : 50 CFU/mL)
Endotoxin	0.25 EU/mL (Action level: 0.12 EU/mL)

Table 3.7 Maximum contaminant concentration levels in dialysate

Contaminant	Maximum concentration for dialysate (mg/L = ppm) ISO13959:2014
Bacteria	100 CFU/mL (Action level: 50 CFU/mL)
Endotoxin	0.25 EU/mL (Action level 0.12 EU/mL)

Table 3.8 Maximum contaminant concentration levels in ultra-pure fluid

Contaminant	Maximum concentration for ultra-pure fluid (mg/L = ppm) ISO13959:2014
Bacteria	0.1 CFU/mL (Action level: n/a)
Endotoxin	0.03 EU/mL (Action level: n/a)

3.2.3 Bacteria (CFU) and endotoxin (EU) testing

Bacterial levels should be tested during commissioning, then monthly for a period of validation progressing to a maximum interval of three months.

Sample at the points where all haemodialysis equipment connects to the distribution piping system (post-RO, post-water loop).

charles river

QLD Health Water for Haemodialysis Handbook v4

Maximum allowable levels

Maxiumum allowable levels for endotoxins in **dialysis water**[a] post RO.

Contaminant	Maximum allowable level	Typical action level[b]
Endotoxin	<0.25 EU/ml	0.125 EU/ml

[a]The reader is cautioned to refer to the latest version of ISO 23500-3 to ensure that there have been no changes to the values presented in this table.

[b]Typically set at 50% of the maximum allowable levels. Other values may be set.

Maxiumum allowable levels for endotoxins in **dialysis water**[a] post dialysis machine.

Contaminant	Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Action level[b]	Maximum allowable level
Endotoxin	<0.5 EU/ml	0.25 EU/ml	<0.03 EU/ml

[a]The reader is cautioned to refer to the latest version of ISO 23500-5 to ensure that there have been no changes to this table.

[b]Typically set at 50% of the maximum allowable level. Other values may be set.

Frequency and collection points

- Post RO – Monthly in-centre / 3 monthly home
- Distribution loop – Monthly
- Dialysis fluid – Monthly (rotated among machines so that each machine is tested at least once a year, and different machines are sampled on each occasion). Home or in-community machines should be tested every 1-3 months, depending on resources

charles river

QLD Health Water for Haemodialysis Handbook v4

Escalation process (Endotoxins)

	No action	Action	Infingement
WRO	‹0.125 EU/ml	›0.125 EU/ml	›0.25 EU/ml
Machine	‹0.03 EU/ml	›0.03 EU/ml	›0.03 EU/ml

If the results are greater than the guidelines then disinfection and increased monitoring may be required using the following testing points:

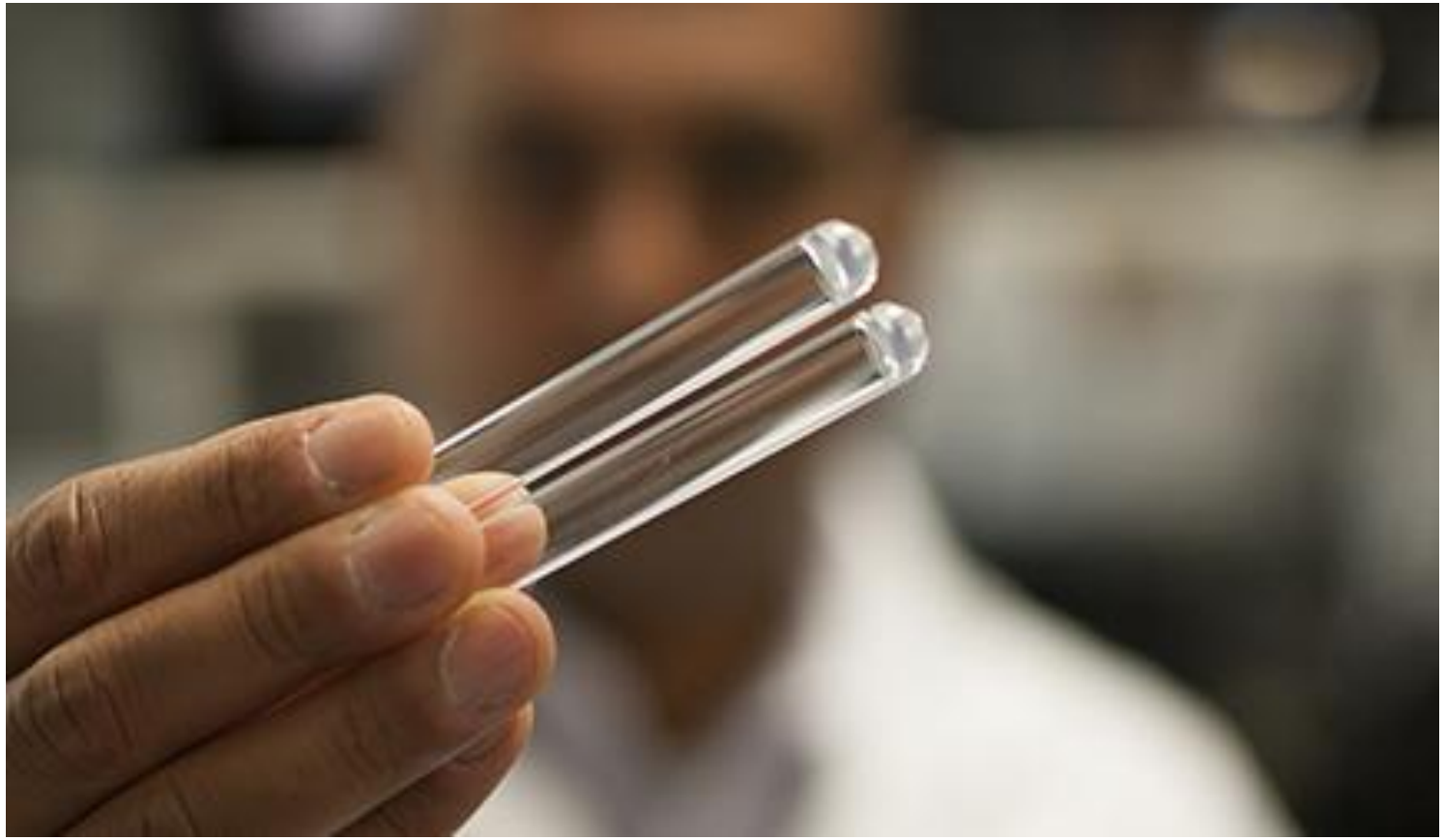
- Post UV irradiation (product water) – if applicable
- Post RO (permeate)
- Start, random outlets and end of distribution loop (permeate)
- Distribution loop (permeate) – in-centre only
- Dialysis machine (dialysis fluid)

charles river

charles river

Cartridge Technology



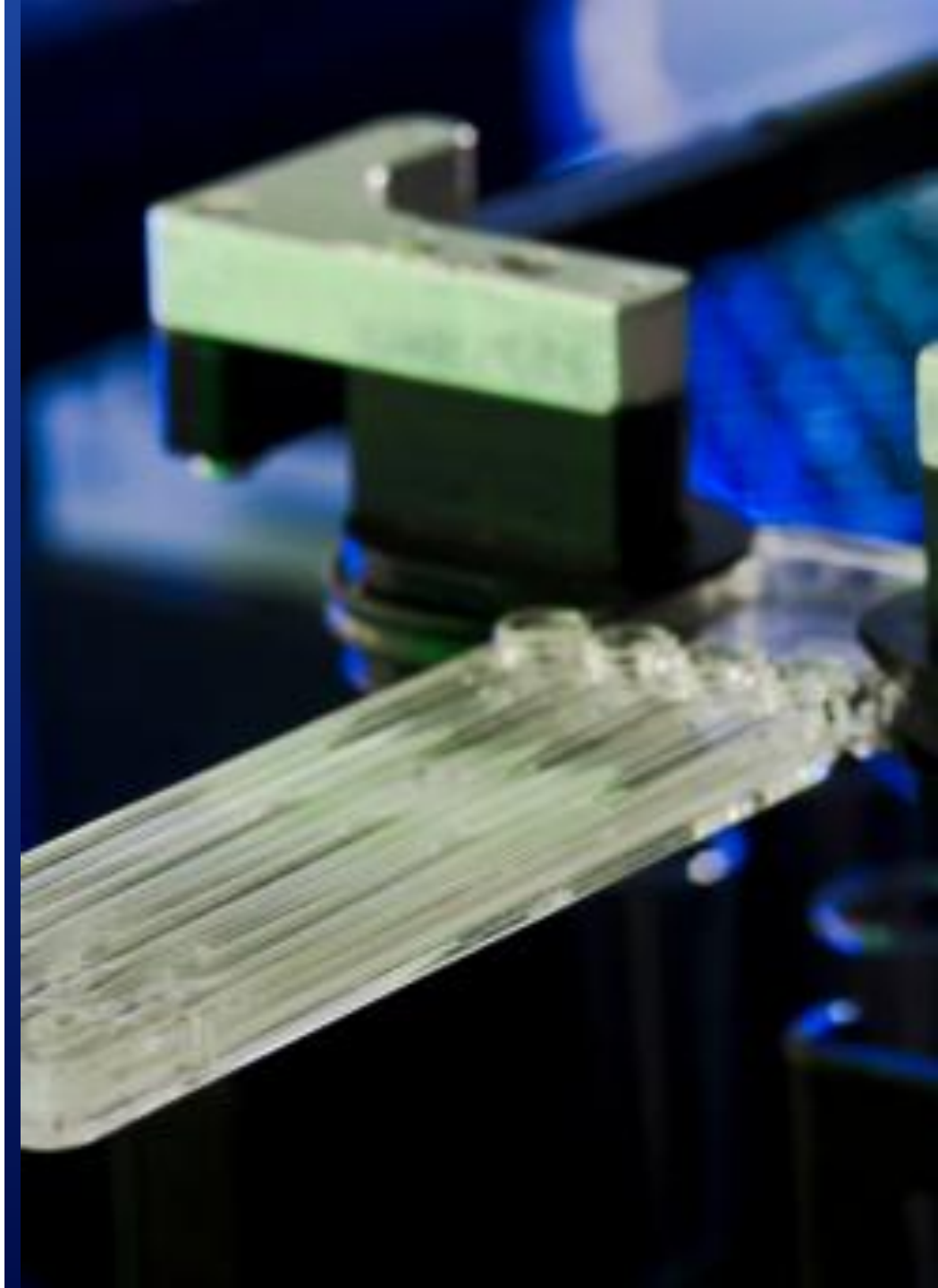


Traditional BET testing can be high maintenance, requiring comprehensive training and high skill levels for success

- Traditional techniques can be labour-intensive and susceptible to human error through:
  - Reconstitution of reagents
  - Preparation of the standard curve
  - Sample and reagent addition to the plate/tube
- Additionally, traditional BET testing is inherently susceptible to:
  - High retest rates due to process inconsistencies and analyst variability
  - Training for proficiency is extensive, adding to the overall cost and complexity of the test.

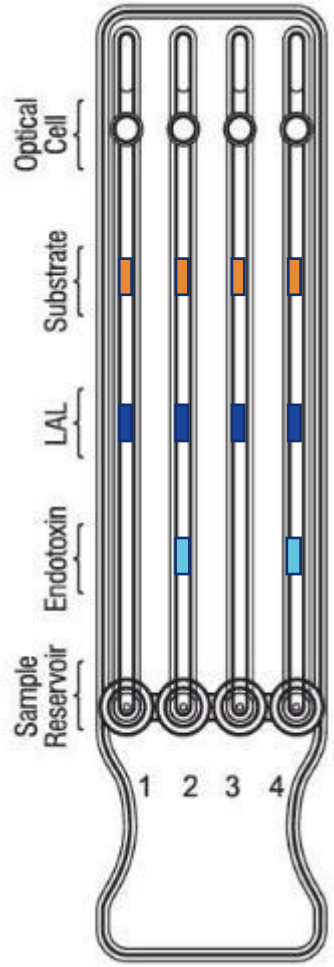
Uniqueness of Cartridge Technology

- The pre-calibrated reagents and archived standard curve replace the need for manipulating cumbersome liquid reagents and standards.
- Contains duplicate channels for samples and positive controls, called spikes.
- Systems are robust, efficient and rapid when samples are inoculated accurately without touch contamination.
- **Eliminates:**
  - User Prepared Endotoxin standards, the main source of test errors
  - Variability in Positive Product Control (PPC) preparations
  - The use and qualification of multiple accessories
  - The need for hours of special training
- Reduces the number of laboratory investigations



HOW DO THE CARTRIDGES WORK?

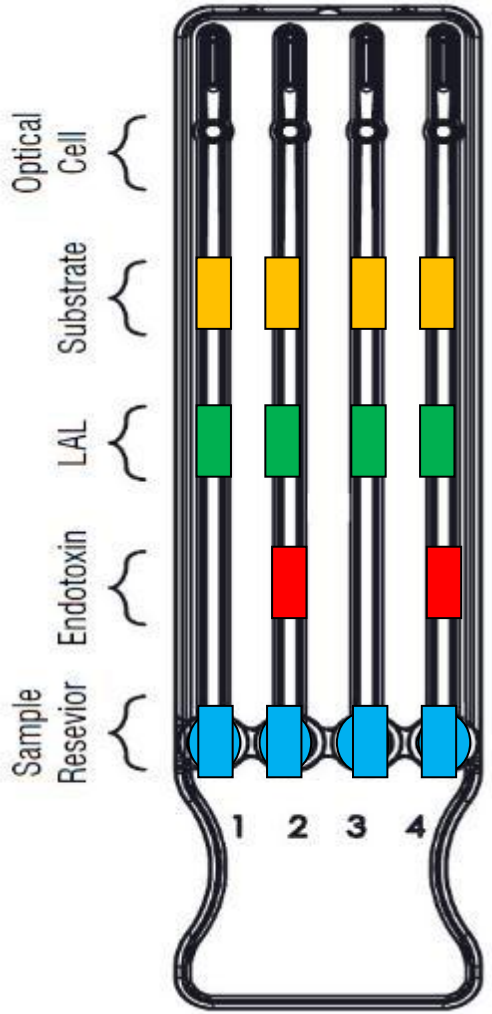
Endotoxin results in 15 minutes



Insert Cartridge

Pipette Sample





charles river



Endosafe® nexgen-PTS™

- Quantitative BET test results in 15 minutes.
- USP/EP BET-compliant.
- Embedded operating system for true portability.
- Designed for wireless capability for remote system access, data export and printing, and fleet management capabilities.
- Utilizes cartridge technology that detects between 0.005-10 EU/mL.
- Proprietary Endosafe® nexgen-PTS™ endotoxin detection software ensures users are in full compliance with the requirements of the FDA's 21 CFR Part 11 and data integrity requirements.

Test Report

```
********* ENDOSAFE Test Record *********
            V7.12B 9/15/2009
DateTime: ........ 04/15/10 @ 08:13:47AM
Device: ............................ 1601
OperatorID: ..................... AGC
Cartridge: ..................... Endotoxin
Temperature: .. Start: 36.9C  End: 37.0C
Method: ........................... KX-122
Cartridge Lot#: ................. 8134161
Cartridge Cal Code: ....... 511332973735
Range: ........................... 5-0.05
Range Time: ................ Sec: 113-729
Onset Times: ........  >729 296 >729 336
Slope: -0.405 ........ Intercept: +2.336
Dilution: ............................ 1
Sample Lot: ....................... HWFI
Sample ID: .....................PORT 12
Sample Rxn Time CV: .......... 0.0% Pass
Spike Value: ..............  0.344 EU/mL
Spike Rxn Time CV: ........... 9.0% Pass
Spike Recovery: .............   80% Pass
Test Suitability: ................. Pass
Sample Value: ............. <0.050 EU/mL
```

Reaction time of 4 channels. 1 & 3 are sample channels, 2 & 4 are spiked channels.

CV % of channels 1 & 3. Must be less than 25% to pass

CV % of channels 2 & 4. Must be less than 25% to pass

Represents % of spike that was recovered; 50-200% is passing range

Indicates pass or fail; if any of the suitability criteria fail the test is invalid

charles river

charles river

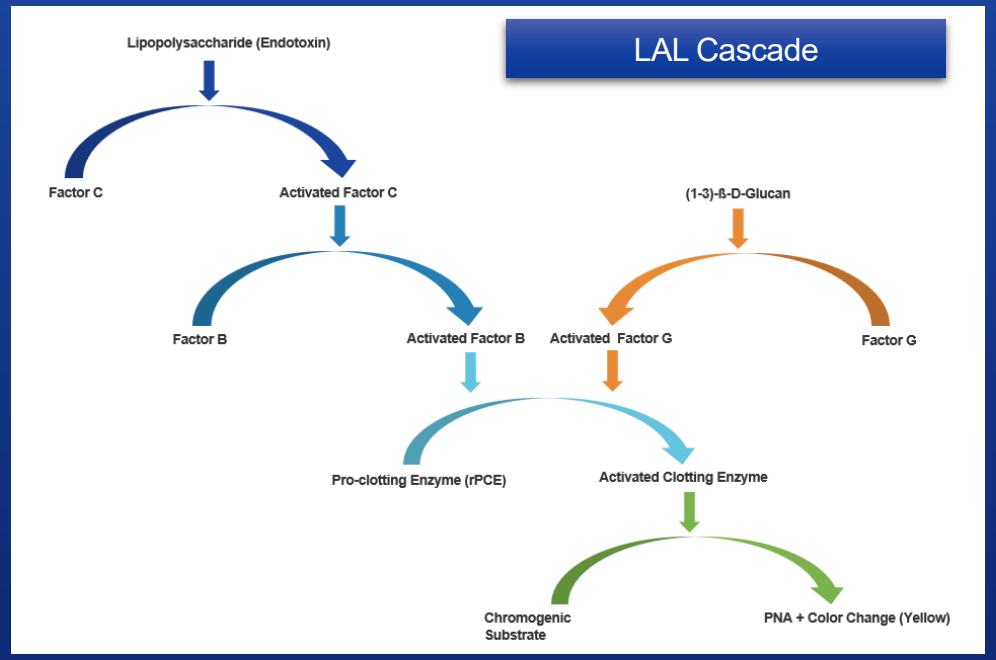
Endosafe® Trillium® Recombinant Cascade Reagent

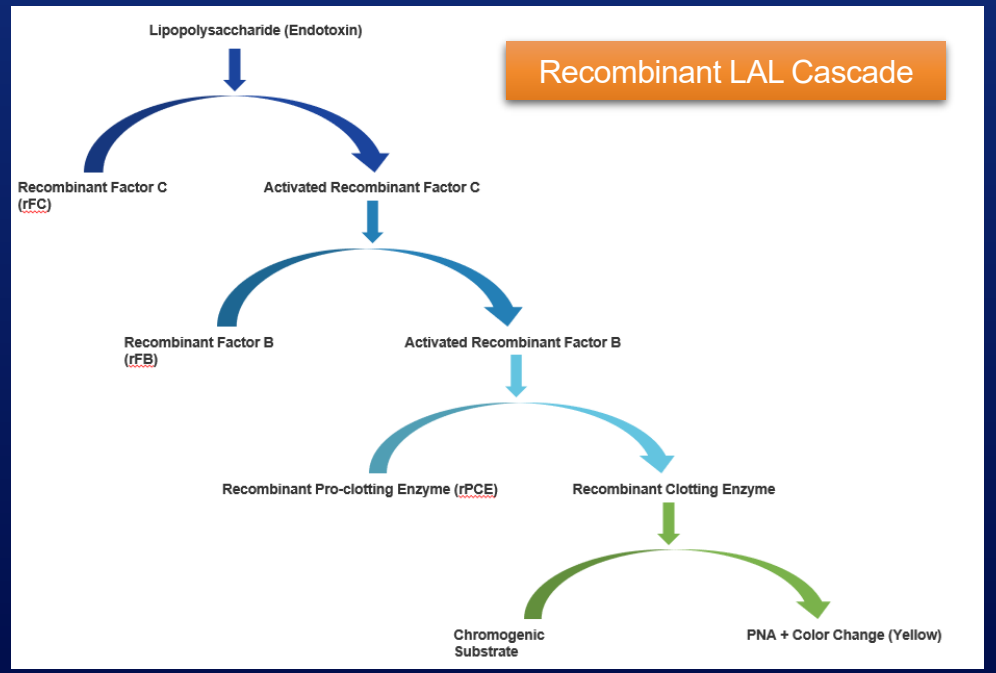


Endosafe Trillium Recombinant Cascade Reagent

100% Animal-Free Bacterial Endotoxin Testing

- Recombinant kinetic chromogenic reagent
- Formulation includes the three critical biological recombinant enzymes.
- Eliminates the risk of false positives from (1-->3) ß-D-Glucan.
- Formulated to accurately recover natural environmental endotoxins as well as RSE.
- Follows natures pattern more precisely than rFC*





Embracing Sustainable Endotoxin Testing…

Choose a method that decreases dependence on the horseshoe crab

Reducing Horseshoe Crab Raw Material Usage



Gel-Clot LAL

0%
Reduction

Kinetic Turbidimetric LAL

Zero reduction in horseshoe crab blood from Gel-Clot

54%
Reduction

Kinetic Chromogenic LAL

54% reduction in horseshoe crab blood from Gel-Clot



95%
Reduction

LAL Cartridge Technology

95% reduction in horseshoe crab blood from Gel-Clot



100%
Replacement

Recombinant Cascade Reagent Vials & Cartridges

100% animal and horseshoe crab blood free

charles river

Sustainable Endotoxin Testing Complete Solution

A complete, sustainable, and scalable BET Portfolio

Endosafe Endotoxin Testing Portfolio

Traditional kinetic chromogenic	**KCA in vials** **Reduction 54%[1] LAL**
	Trillium rCR vials **100% LAL Replacement**



Cartridge Technology (advanced Kinetic)	**LAL cartridges** **Reduction 95%[1] LAL**
	Trillium rCR cartridges **100% LAL Replacement**



charles river

charles river

Questions?

Alan.Hoffmeister@crl.com

Websites:
www.criver.com/microbialsolutions
https://hsc.criver.com/

Email:
askcharlesriver@crl.com

