PYROSMART NEXTGEN® RECOMBINANT LAL REAGENT

Associates of Cape Cod, Inc.
Your Endotoxin & Glucan Experts

Technical Brochure

PYROSMART® NEXTGEN

Recombinant *Limulus* Amebocyte Lysate

Recombinant Cascade Reagent for Bacterial Endotoxin Testing

The Bacterial Endotoxins Test (BET) is a release test for detection and quantitation of bacterial endotoxins in parenteral drug products and medical devices. *Limulus* Amebocyte Lysate (LAL) reagents have been used since the 1970s to perform the BET assay; Associates of Cape Cod, Inc.'s (ACC) Pyrotell® gel-clot reagent being the first LAL reagent to receive an FDA license for its manufacture. Subsequent developments led to modifications of the gel clot method to photometric methods (turbidimetric and later on chromogenic) used for the quantitative measure of endotoxins. All of these methods rely on the same mechanism of action – the LAL cascade (see Fig. 1).

Throughout the past decade, in an effort to continually improve BET incorporating current technological advances, the PyroSmart® reagent (based on genetic sequence of the Japanese horseshoe crab *Tachypleus tridentatus (TAL)*) was developed and characterized as the first recombinant Cascade Reagent (rCR)[1]. Later on, PyroSmart NextGen® was introduced which builds on the success and analytical performance of its predecessor but whose recombinant proteins are expressed based on the genetic sequence of *Limulus polyphemus*. This is due to the fact that LAL reagents, not TAL, are the primary reagents utilized by the vast majority of global end users and there are no FDA licensed TAL reagents for BET.

The Importance Of The Cascade

Naturally-Sourced LAL Reagent

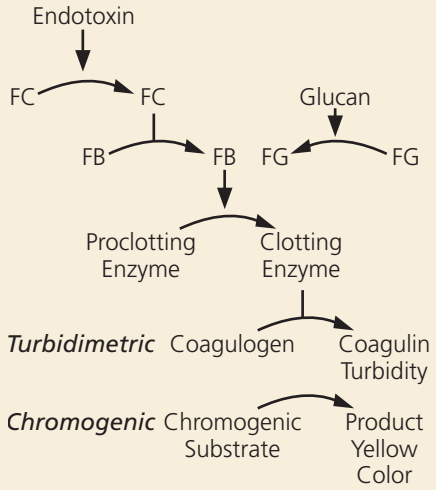

Figure 1: The LAL Cascade Mechanism (as triggered by endotoxin and/or 1,3-β-D-glucans)

In the presence of endotoxin, Factor C becomes an activated moiety which in turn activates Factor B and Proclotting Enzyme; ultimately resulting in the proteolytic cleavage of a substrate (either coagulogen in gel clot (not shown) and turbidimetric assays or a colorless chromogenic substrate in chromogenic assays). The cascade mechanism thus amplifies the response of Factor C and leads to an exceptional sensitivity for this biological assay, with kinetic output being preferable. In the presence of 1,3-β-D-glucans, Factor G becomes an activated moiety which also activates Proclotting Enzyme and thus resulting in the same signal as that triggered by endotoxins through Factor C. This has been often observed as glucan-derived enhancement or false positive results.

PyroSmart NextGen®

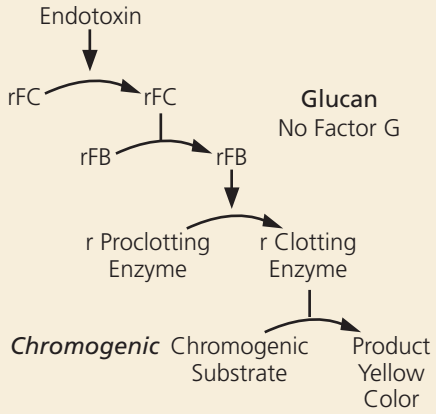

Figure 2: The Recombinant Cascade Mechanism (as triggered by endotoxin only)

As with naturally sourced LAL reagents, in the presence of endotoxin, recombinant Factor C becomes an activated moiety which in turn activates recombinant Factor B and recombinant Proclotting Enzyme; ultimately resulting in the proteolytic cleavage of a colorless chromogenic substrate formulated with PyroSmart NextGen®. By relying on the same cascade mechanism, the response of recombinant Factor C is amplified the same way as in LAL reagents and thus the same sensitivity is achieved using this kinetic assay. Due to absence of Factor G, PyroSmart NextGen® will not react with any 1,3-β-D-glucans and therefore will prevent glucan-derived enhancement and false positive results.

RECOMBINANT LAL REAGENT

PyroSmart NextGen®

What Is It?

It is a recombinant cascade reagent for the detection and quantification of Gram-negative bacterial endotoxins (lipopolysaccharides). PyroSmart NextGen® is a **recombinant Cascade Reagent (rCR)** for a kinetic chromogenic assay.

PyroSmart NextGen®

What Can It Be Used For?

1. A test for the quantification of endotoxin in non-compendial articles (e.g. raw materials, process water, and for in-process samples, etc.).

2. An alternate test to compendial testing[2,3,4] for the end-product testing of human injectable drugs (including biological products), animal injectable drugs, and medical devices[5,6,7].

Keep Your Method

- Same Cascade
- Same Method
- Same Instrument
- Same Preparation Steps
- Same Data Analysis

Make An Impact

- Sustainable reagent
- Lot to lot consistency
- No cross-reactivity with 1,3-β-D-glucans

Maintain The Same Quality Standards

- cGMP
- ISO 13485

Keep Your Method

PyroSmart NextGen® reagent mimics the response of naturally sourced LAL reagent to the presence of endotoxin:

- **SAME CASCADE:** PyroSmart NextGen® reagent consists of three recombinant proteins: Factor C, Factor B and Proclotting Enzyme (see Fig. 2), which react the same way as the same factors in the LAL cascade.

- **SAME METHOD:** As in kinetic chromogenic assays, the cleavage of the substrate liberates para-nitroaniline (pNA), which is yellow and absorbs at 405 nm. The change in absorbance is measured over the course of the test by an absorbance reader equilibrated at 37 ± 1°C (see Fig. 3). The higher the endotoxin concentration, the faster the pNA release which leads to a faster change in absorbance – refer to the differences between 50 and 0.005 EU/mL in Fig. 3.

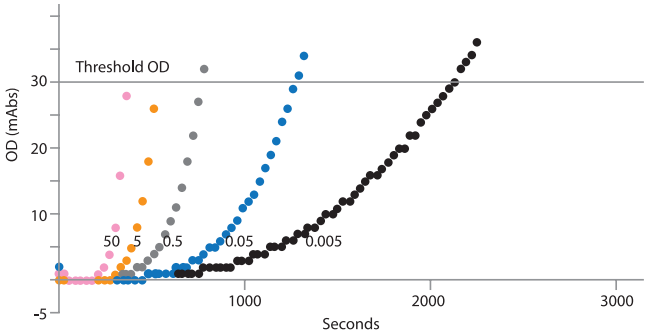

Figure 3: Kinetic plots for standard curve series (50 to 0.005 EU/mL) with PyroSmart NextGen®

- **SAME INSTRUMENT:** since the cascade and the method are the same, PyroSmart NextGen® assay is performed using the same validated incubating absorbance readers and software system as used for kinetic photometric assays.

  An example of a microplate absorbance reader and software system for PyroSmart NextGen® assay is illustrated in Fig. 4.

Figure 4: BioTek® ELx808™ and Pyros® eXpress software platform is one of the options used for the PyroSmart NextGen® assay. Pyros® eXpress includes a built-in default method for the PyroSmart NextGen® assay

- **SAME PREPARATION STEPS:** the following schematic illustrates the PyroSmart NextGen® assay preparation process which is the same flow as for kinetic chromogenic assay:

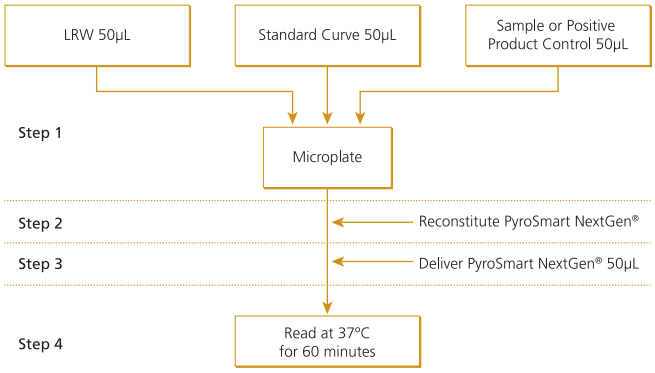

Figure 5: A diagram of PyroSmart NextGen® assay preparation steps

- **SAME DATA ANALYSIS:** the data generated by PyroSmart NextGen® assay is analyzed in the same way as the data from a typical kinetic chromogenic assay. For each well, the measured absorbance is transformed by using Onset OD – the time taken to reach the set threshold OD (referred to as Onset Time) is determined. Higher endotoxin concentrations give shorter Onset times (and vice versa) – see Table 1.

Table 1: Typical Onset Times observed for a series of RSE when using PyroSmart NextGen® for a kinetic chromogenic assay in a microplate reader

RSE Concentration (EU/mL)	Onset Times (seconds) for a typical LAL kinetic chromogenic assay at Onset OD 0.03	Onset Times (seconds) for a typical PyroSmart NextGen® assay at Onset OD 0.03
0.005	3900	2510
0.05	2240	1320
0.5	1350	765
5	820	461
50	500	283

PyroSmart NextGen® offers the added benefit of rapid test-to-result (decreased to approximately half the time of a typical kinetic chromogenic assay).

As shown in Fig. 6, the standard curve is constructed by plotting the Log Onset time (Y-axis) against the Log standard concentration (X-axis) and is used to back-calculate endotoxin concentrations in unknown samples. Following qualification, linear or polynomial regression may be used. High correlation coefficient values (R) are routinely achieved.

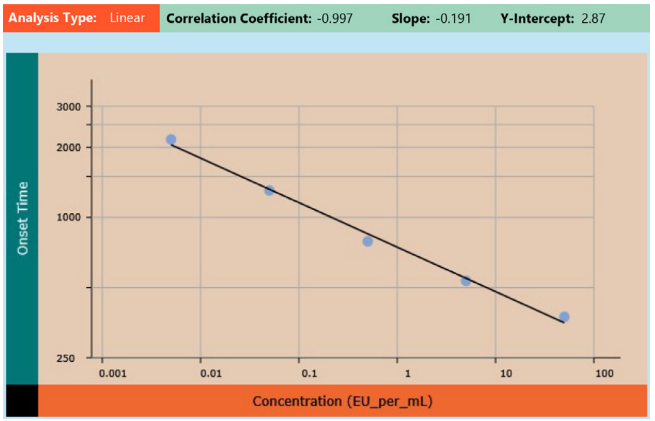

Figure 6: Standard curve for PyroSmart NextGen® assay using a linear fit for Log Onset Time vs. Log Concentration

For detailed instructions, refer to PyroSmart NextGen® Instructions for Use[9].

Make An Impact

- Sustainable reagent
- Lot to lot consistency
- No cross-reactivity with 1,3-β-D-glucans

Sustainable Reagent

Since PyroSmart NextGen® does not rely on a natural resource as the raw material, it is another contributor towards the long-term sustainability of horseshoe crabs.

Lot-To-Lot Consistency

The naturally sourced LAL reagents have an inherent lot-to-lot variability as a complex mixture of biological material obtained from individual horseshoe crabs.

Thanks to the genetic engineering and downstream purification processes, PyroSmart NextGen® reagent exhibits lot-to-lot consistency as illustrated in Fig. 7. Six individual reagent lots of PyroSmart NextGen® are plotted to demonstrate the repeatable and predictable performance of PyroSmart NextGen®.

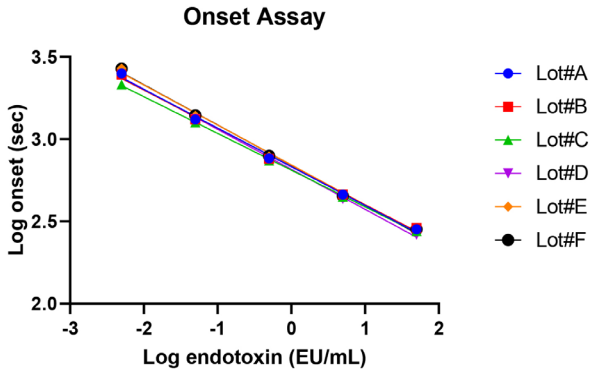

Figure 7: Standard curves using six (6) different lots of PyroSmart NextGen® as obtained during method validation (linear regression for Log/Log values) demonstrating strong lot to lot reproducibility

No Cross-reactivity With 1,3-β-D-Glucans

As shown in Fig. 2, PyroSmart NextGen® reagent does not contain Factor G and therefore does not allow reactivity with 1,3-β-D-glucans, if present in the sample. PyroSmart NextGen® is endotoxin specific.

The absence of reactivity with 1,3-β-D-glucans is illustrated in the Fig. 8 which shows standard series of 50 to 0.005 EU/mL, each per one PyroSmart NextGen® lot. X-axis represents the series where each concentration was spiked with 200 pg/mL of 1,3-β-D-glucan. Y-axis represents the same series without the addition of the 1,3-β-D-glucan spike. The excellent correlation between the curves demonstrates there was no interference caused by the added 1,3-β-D-glucan spike at either concentration.

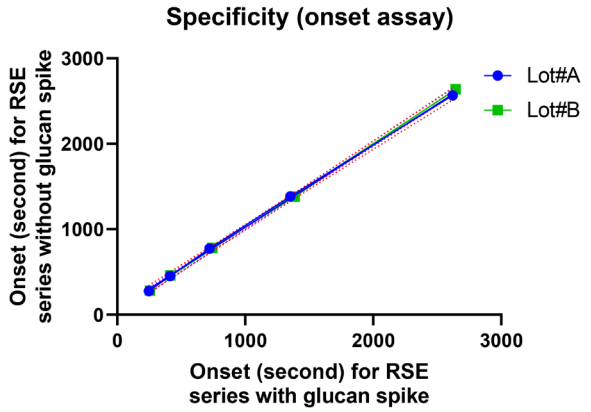

Figure 8: Linear regression of Onset Times (in seconds) for two RSE series with and without 1,3-β-D-glucan spike

Maintain The Same Quality Standards

- cGMP
- ISO 13485

While recombinant reagents for BET are not subject to FDA licensing, Associates of Cape Cod, Inc. proactively manufactures PyroSmart NextGen® under the same strict cGMP and ISO 13485 requirements as the FDA-licensed LAL reagents. This assures that the PyroSmart NextGen® reagent is manufactured under the same stringent Quality Management System as ACC's FDA-licensed LAL reagents.

PyroSmart NextGen®

Assessment of Analytical Characteristics

PyroSmart NextGen® as an rCR for BET is considered an alternative to LAL reagents. According to regulatory and guidance documents[5,6,7,8,10], alternative methods can be used if they provide advantages to the compendial methods. Alternative methods should be validated as described in the regulatory documents[5,6,7,8] demonstrating equivalent or better results. The specific validation requirements depend upon the requirements of the local competent authority, company requirements, material to be tested and its purpose (e.g. requirements for product release testing are different from those required for water or in-process component testing).

The capabilities of PyroSmart NextGen® are analyzed and summarized below.

1. Analytical Performance

Following ICH Q2 guideline[11], the analytical performance of PyroSmart NextGen® was determined for a plate reader kinetic chromogenic assay utilizing a standard curve ranging from 50 to 0.005 EU/mL as shown in Table 2 and Table 3. Results are compiled for a total 24 assays performed at two locations (two lots, four analysts, three days).

Table 2: Analytical performance of PyroSmart NextGen®

	Criteria	Results	Criteria Met?
Accuracy	50-200%	Min: 71% Max: 140%	✓
Intra Assay Precision	%CV ≤ 30 for 50-0.05EU/mL %CV ≤ 35 for 0.005EU/mL	Min: 4% Max: 30%	✓
Intermediate Assay Precision	%CV ≤ 30 for 50-0.05EU/mL %CV ≤ 35 for 0.005EU/mL	Min: 7% Max: 24%	✓
Linearity	r ≥ 0.980	Min: 0.996 Max: 1.000	✓
Specificity	No significant interference	No significant interference	✓

Table 3: Analytical performance of PyroSmart NextGen®

	Criteria	Final Determinations
Limit of Quantitation	The lowest concentration of endotoxin that can be quantitatively determined with suitable precision and accuracy	At 0.005EU/mL Accuracy: 71-88% Precision: 6-30%
Range	Precision, accuracy and linearity at suitable level	0.005-50EU/mL

In summary, PyroSmart NextGen® met all the required specifications.

2. Suitability Testing

Suitability testing (aka Test for Interfering Factors as described in the harmonized BET chapters[2,3,4]) is a product specific testing which is done at a dilution of the product that does not interfere with the test method. The suitability of PyroSmart NextGen® for testing a range of products was compared to two LAL methods (chromogenic and turbidimetric) and two recombinant Factor C (rFC) methods. A number of finished drug products, water and buffer were tested by each method in a series of dilutions. For each method, the Non Interfering Dilution (NID) was determined which is defined as the first dilution with a valid PPC recovery %.

Per FDA 2012 Guidance[5], testing a product at the lowest possible dilution is preferable. Therefore the lower the NID, the better. Within Table 4, NIDs of recombinant methods in green are within the 2-fold of the LAL methods and thus indicate the same interference with the recombinant method as with the LAL method. NIDs of a recombinant method in red are greater than the LAL method and thus indicate that the method suffers from greater interference from the product and the product has to be diluted to higher dilutions to overcome the interference. NID must not exceed the Maximum Valid Dilution (MVD).

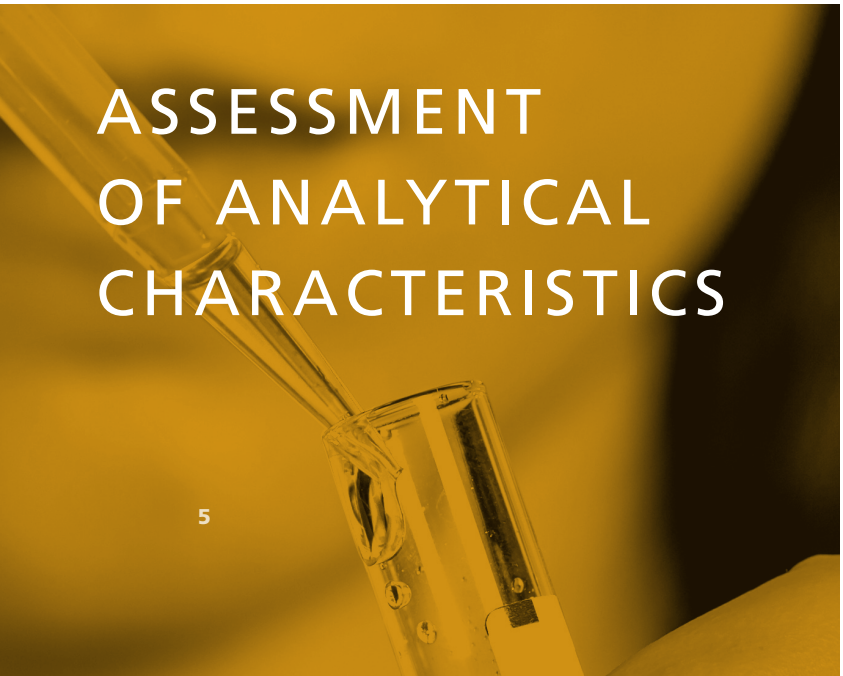

Table 4: Suitability study of a number of finished injectable drugs and process samples. The table summarizes NIDs determined with PyroSmart NextGen® reagent, recombinant Factor C (rFC) reagents vs. LAL reagents (chromogenic and turbidimetric). NIDs of a recombinant methods in red are greater than that of the LAL methods.

Samples	MVD at Λ=0.005 EU/mL	NID				
		PSNG (rCR)	Reagent A (rFC)	Reagent B (rFC)	Chromo (LAL)	Turb (LAL)
Sodium Citrate Injection for Transfusion	1,120	1	256	512	4	4
Vancomycin Hydrochloride Injection	5,000	64	128	32	32	128
Glucose Injection	100	8	8	4	8	4
Heparin Calcium	15,000	512	> 60,000	> 60,000	128	8
D-Mannitol Injection	100	2	2	1	4	2
Aciclovir 75 mg/vial	N/A	4	128	256	8	8
Insulin 8 mg/mL	N/A	1	16	64	2	1
PBS (Dulbecco)	N/A	1	1	2	1	1
WFI	50	1	1	1	1	1

Key conclusions:

- Products tested by PyroSmart NextGen® have NIDs that are equivalent to LAL methods or lower.
- Four of the drug products can be tested at significantly lower dilutions by PyroSmart NextGen® than when tested with rFC reagents.

In addition, Muroi *et. al.*[1] reported on a battery of 128 products tested using PyroSmart® reagent, the predecessor of PyroSmart NextGen®, with similar results. Based on the data, it can be concluded that rCR methods are suitable for testing of a wide range of products.

3. Comparability Testing

As per FDA, 2012 guidance[5], the comparability testing may include spiked samples and a battery of field samples of product which contain detectable endotoxin in order to compare the sensitivity of the alternative method to LAL reagent. Table 5 below demonstrates the mean potency for a number of lipopolysaccharides (chemically purified endotoxins) as determined by PyroSmart NextGen®, two rFC reagents and compared to that determined by two LAL reagents (chromogenic and turbidimetric). The results of the recombinant reagents were normalized as relative recovery % (e.g. PSNG Relative recovery % = PyroSmart NextGen® result ÷ Mean LAL x 100%). The acceptable relative recovery range is 50 to 200%.

Table 5: Comparability study for purified lipopolysaccharides derived from various Gram negative bacteria with calculated Relative recovery %

Endotoxins	Potency (EU/ng)						Relative Recovery (%)		
	PSNG (rCR)	Reagent A (rFC)	Reagent B (rFC)	Chromogenic (LAL)	Turbidimetric (LAL)	Mean LAL	PSNG (rCR)	Reagent A (rFC)	Reagent B (rFC)
***Pseudomonas aeruginosa* 10**	**4.18**	4.91	2.17	4.55	8.56	**6.56**	**64**	74	33
Salmonella thyphimurium	**7.05**	2.85	1.26	4.56	5.27	**4.92**	**143**	58	26
***Salmonella minnesota* R595**	**107.75**	10.00	2.61	72.99	47.92	**60.46**	**178**	17	4
Serratia marcescens	**4.13**	5.66	3.04	2.62	5.41	**4.02**	**102**	140	76
***Escherichia coli* O55:B5**	**11.96**	5.94	4.45	6.95	7.59	**7.27**	**164**	81	61

The relative recovery % in green indicates valid recoveries while the recoveries in red are invalid (outside of the acceptable range).

Key Conclusions:

- The relative recovery of PyroSmart NextGen® is well within 50 – 200% of the mean LAL value for all tested lipopolysaccharides (with min of 64% and max of 178%).
- There is no indication of under-determination by PyroSmart NextGen®.

Comparability data was also generated for a battery of water samples containing detectable levels of endogenous endotoxin and for a culture supernatant of *E. coli* O113:H10 with the results summarized in Table 6.

Table 6: Comparability study for deionized water samples from various sites with calculated Relative recovery %

Sample	Endotoxin Concentration (EU/mL)						Relative Recovery (%)		
	PSNG (rCR)	Reagent A (rFC)	Reagent B (rFC)	Chromogenic (LAL)	Turbidimetric (LAL)	Mean LAL	PSNG (rCR)	Reagent A (rFC)	Reagent B (rFC)
DI water #1	**8.965**	3.490	2.108	7.059	6.067	**6.563**	**137**	53	32
DI water #2	**1.354**	0.504	1.034	1.182	1.813	**1.498**	**90**	34	69
DI water #3	**5.260**	1.530	1.317	4.610	6.603	**5.607**	**94**	27	23
DI water #4	**1.190**	0.407	0.722	0.991	1.119	**1.055**	**113**	39	68
DI water #5	**0.063**	0.044	0.055	0.065	0.041	**0.053**	**119**	83	104
DI water #6	**0.238**	0.040	0.083	0.278	0.125	**0.202**	**118**	20	41
DI water #7	**0.037**	0.013	0.012	0.038	0.047	**0.043**	**86**	30	28
DI water #8	**1.718**	0.400	0.547	1.570	1.399	**1.485**	**116**	27	37
DI water #9	**1.423**	0.364	0.383	1.122	1.691	**1.407**	**101**	26	27
Culture Supernatant *E. coli* O113:H10	**65,400**	72,600	120,000	52,700	67,700	**60,200**	**109**	121	199

Key Conclusions:

- The relative recovery of PyroSmart NextGen® for all tested samples falls well within the acceptable range of 50 – 200% (with min of 86% and max of 137%).
- There is no indication of under-determination by PyroSmart NextGen®.

Recently, there were a number of peer-reviewed studies published examining the utility and comparability of rCR and rFC to naturally sourced LAL reagents. Two collaborative studies organized by the Japanese National Institute of Health[12,13] included only PyroSmart®, the predecessor of PyroSmart NextGen®, since the latter was not commercially available at the time of the studies. The most recent study[14] which focused on examining endotoxin activity in deionized water samples as measured by a recombinant LAL reagent and two rFC reagents did not include PyroSmart® or PyroSmart NextGen®. Thus its conclusions, that all recombinant reagents have a tendency to under-predict endotoxin activity when compared to LAL, must not be extrapolated to either PyroSmart® or PyroSmart NextGen®.

In summary, based on its documented analytical capability, PyroSmart NextGen® rCR is a great candidate to be evaluated as an alternative to any kinetic chromogenic LAL reagent. In addition, it may be also evaluated on samples being currently tested by a kinetic turbidimetric assay. PyroSmart NextGen® as a recombinant cascade reagent delivers results that are:

- Rapid (around 30 minutes to 0.005 EU/mL)
- Lot to lot consistent
- Endotoxin specific
- Achievable in a wide-range of products
- Equivalent to those obtained by LAL reagents

Evaluation Program

Join our evaluation program. Obtain PyroSmart NextGen® and follow our expertly built Evaluation Protocol when using PyroSmart NextGen® to determine in-house whether PyroSmart NextGen® is suitable for your products.

Validation Support

ACC understands the steps needed to transition to a new recombinant reagent, alternative to LAL. PyroSmart NextGen® reagent was developed to make the transition easy.

Whether you intend to use PyroSmart NextGen® reagent to test compendial or non-compendial articles, ACC can support the process of validation through all three stages:

1. Analytical Suitability
2. Product Validation
3. Comparability Testing

ACC has developed a comprehensive validation support program for its customers. With established validation templates, and access to ACC's team of dedicated technical experts, we will help to guide our customers through their validation process and the ultimate transition to a sustainable reagent.

Meeting your sustainability objectives has never been simpler than with PyroSmart NextGen®.

Ordering Information

PyroSmart NextGen® (PNG050-2) reagent is provided as a pack of 2 vials of reagent and 2 vials of reconstitution buffer. This is sufficient for a total of 110 wells (55 wells per vial).

A complete catalog listing of product, equipment and accessories needed for the kinetic chromogenic assay using recombinant PyroSmart NextGen® reagent is provided below in Table 7.

RECOMBINANT LAL REAGENT

Table 7: A complete list of equipment, consumables and accessories needed for PyroSmart NextGen® assay

Equipment Type	Specification	Description/Catalog No.
PyroSmart NextGen®	Recombinant Cascade Reagent	PNG050-2
Incubating absorbance platereader	Capable of maintaining a temperature of 37°C while reading at 405nm	BioTek® ELx808™* Molecular Devices readers
Platereader software	Allows for data reduction to Onset Time	Pyros® eXpress or Gen5™ - ELx808™ Softmax® Pro - MD
Control Standard Endotoxin (CSE)	10ng/vial calibrated against RSE with PyroSmart NextGen®	ACC EC010-5
Microplates 96-well	Covered, non-coated, untreated microplates, free of interfering endotoxin, should not interfere with the test	ACC CA961-10
Repeating pipette with compatible syringe barrels	Auto-delivery of reagent aliquots	Eppendorf® Xstrem repeater with BioPur® combi-tip 2.5mL
Multichannel pipette with BET compatible reservoirs	Eight channel	Integra reservoir No. 4331
LAL Reagent Water (LRW)	Free of interfering endotoxins	e.g. ACC WP050-C*
Depyrogenated Glass Dilution Tubes	Free of interfering endotoxin, should not interfere with the test	ACC TB240-5, TB013-5 or TB016-C*
A set of adjustable single-channel micropipettes	Capable of delivering volumes of 5-20 µL, 20 – 100 µL and 100-1000 µL	Gilson®, Rainin® traditional or Eppendorf® model fit the tips below*
Pipette tips	Capable of delivering volumes of 5-20 µL, 20 – 100 µL and 100-1000 µL Free of interfering endotoxin	ACC PPT25 ACC PPT10
Vortex mixer	Any	
Timer	Any	
Parafilm M®	The side in contact with the paper backing is typically free of detectable endotoxin.	American National Can™
Tube rack	Any	
Slanted plate stand	Any	

*Or equivalent

All trademarks are property of their respective owners.

ORDERING INFORMATION

REFERENCES

1. Application of a Recombinant Three-Factor Chromogenic Reagent for BET filed in the Pharmacopeias. Biol Pharm Bull (2019) 42(12) 2024-2037 Muroi, M., Ogura, N., *et. al.*
2. <85> (current revision) Bacterial Endotoxins Test, United States Pharmacopeia, United States Pharmacopeial Convention, Rockville, MD.
3. 2.4.16 (current revision) Bacterial Endotoxins, European Pharmacopoeia, European Pharmacopoeia Commission, Strasbourg, France.
4. 4.01 (current revision) Bacterial Endotoxins Test, Japanese Pharmacopoeia, Tokyo, Japan.
5. Guidance for Industry, Pyrogen and Endotoxins Testing: Questions and Answers. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, July 2012.
6. <1085> Guidelines on the Endotoxins Test, United States Pharmacopeia (current revision), United States Pharmacopeial Convention, Rockville, MD.
7. 5.1.10 (current revision) Guidelines for Bacterial Endotoxins Testing, European Pharmacopoeia, European Pharmacopoeia Commission, Strasbourg, France.
8. General Notices, European Pharmacopoeia, European Pharmacopoeia Commission, Strasbourg, France.
9. PyroSmart NextGen® Instructions for Use, www.pyrosmartnextgen.com.
10. <1225> Validation of Compendial Procedures, United States Pharmacopeia (current revision), United States Pharmacopeial Convention, Rockville, MD.
11. International Conference on Harmonisation (ICH) Q2 (R1) Validation of Analytical Procedures: Text and Methodology (1994).
12. Collaborative Study on the Bacterial Endotoxins Test Using Recombinant Factor C-based Procedure for Detection of Lipopolysaccharides, Pharm.Med. Dev. Reg. Sci. 48 (2017): 252-260 Kikuchi, Y., *et. al.*
13. Collaborative study on the bacterial endotoxins test using recombinant Factor C-based procedure for detection of lipopolysaccharides (Part 2). Pharm. Med. Dev. Reg. Sci. 49 (2018):708-718 Kikuchi, Y., *et. al.*
14. Evaluation of limulus amebocyte lysate and recombinant endotoxin alternative assays for an assessment of endotoxin detection specificity. Euro J Pharm Sci 159 (2021) Dubczek *et. al.*

Notes:

Associates of Cape Cod, Inc.
Your Endotoxin & Glucan Experts

Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive
East Falmouth, MA 02536 USA
Tel: (800) LAL–TEST (525–8378) or
(508) 540–3444
Fax: (508) 540–8680
www.acciusa.com
US Customer Service:
custservice@acciusa.com

United Kingdom/Europe
Associates of Cape Cod, Intl, Inc.
Unit 1 F/G/H Academy Business Park
Lees Road, Knowsley
Liverpool L33 7SA
United Kingdom
Tel: (44) 151–547–7444
Fax: (44) 151–547–7400
www.acciuk.co.uk
UK Customer Support:
customerservices@acciuk.co.uk
Company Registration Number:
BR002906

© Copyright 2024 Associates of Cape Cod, Inc. -
a Seikagaku Group Company All Rights Reserved.

G_2282 Rev2