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European Directorate for the Quality
of Medicines & HealthCare (EDQM)
European Pharmacopoeia Department
Council of Europe
7 allée Kastner
CS 30026
F-67081 STRASBOURG
FRANCE

Reference: Proposed European Pharmacopeia Chapter 2.6.32. Test for Bacterial Endotoxins Using Recombinant Factor C

Dear European Pharmacopeia Members:

PDA believes that it is vital to address the continuing impact that endotoxins can have in the manufacturing and quality control of parenterals. We are encouraged to see the development of additional guidance for industry on this topic and appreciate the opportunity to provide comments to the newly proposed 2.6.32. Test for Bacterial Endotoxins Using Recombinant Factor C published in Pharmeuropa Issue 31.1.

Overall concerns and observations:

1. **Equivalency:** The draft document should address equivalency between chapters 2.6.14 and 2.6.32. Without further clarification, it could be stated that chapter 2.6.32 may be used as an equivalent method to the 2.6.14 without any equivalence to demonstrate as it is a new independent chapter.
2. **Harmonization:** The document is a starting point for change, but if the long-term goal is to add BET rFC as a common methodology, then the Pharmeuropa publication should be used to advance the current harmonized chapters through the PDG process. Essentially, 2.6.32 could be used as a model with a long-term goal of revising the harmonized USP <85>, JP 4.01, PhEur 2.6.14.
3. **Method development:** The document is not clear as to how this chapter applies related to the current chapter on Bacterial Endotoxins, 2.6.14. In the event that the chapter is applied independently, we offer considerations of peripheral changes needed to utilize the method without conflict to established chapter 2.6.14 methodologies (detailed in the attached comment table).
4. **Method support:** EDQM usage of focus pages on their website is a good way to consolidate information to advocate for positive change. We would request your consideration of creating a page for BET rFC.

A table with additional comments referenced to specific page and line numbers is also attached for your consideration.

Sincerely,

Richard Johnson
President, PDA
Cc: Tina Morris, Falk Klar, Josh Eaton

Submission of comments on PhEur proposed Chapter 2.6.32. Test for Bacterial Endotoxins Using Recombinant Factor C

Comments from:

Parenteral Drug Association (PDA)

1. General comments

Topic 1: Equivalency between chapters 2.6.14 and 2.6.32. It has to be stated somewhere that this last chapter 2.6.32 could be used as an exact equivalent method to the 2.6.14 without any equivalence to demonstrate as it is a new independent chapter.

Topic 2: Maximizing Value:
An independent chapter is a starting point for change, but if the long-term goal is to add BET rFC as a common methodology, then the Pharmeuropa publication should be used to advance the current harmonized chapters for BET (e.g., 2.6.14 method G).

- This will extend the EDQM initiative from regional to international benefit.
- It will avoid confusion in the future when established uses of the independent chapter may be added to the existing BET chapters.
- To extend this goal of a focused launch of the method, even if the PDG does not immediately accept this BET rFC procedure, we would encourage EDQM to consider this method as national text within chapter 2.6.14.

Topic 3: Ensure Compatibility:
It is not clear how to understand where this chapter applies in relation to the current chapter on Bacterial Endotoxins, 2.6.14. In the event that the chapter is applied independently, consider peripheral changes needed to utilize the method without conflict to established chapter 2.6.14 methodologies.

- 5.1.10 Guidelines for Using the Test for Bacterial Endotoxin: Currently, the guidance document only recognizes BET rFC as a possible alternative. As an alternative method, the question of equivalency may arise with traditional methodology. We would recommend updating the guidance to recognize the chapter 2.6.32 as a suitable method for BET analysis and eliminate the need for equivalency to other methodology. For example, Ph. Eur. allows for application of harmonized 2.9.40 Uniformity of Dosage Units and also the national text for 2.9.5 Uniformity of Mass… and 2.9.6 Uniformity of Content…without conflict.
- General monographs (ex. Substances for Pharmaceutical use): Add an acknowledgement of chapter 2.6.32 for application as a direct substitute for the harmonized method.
- In addition to the fluorometric technique, there is a commercial product that uses a kinetic chromogenic detection method. We recommend that this chapter cover both current rFC methodologies.

Topic 4: Utilize Supporting Resources:
EDQM usage of focus pages on the website is a good way to consolidate information to advocate for positive change. We would request your consideration of creating a page for BET rFC.

- With the publication of the chapter proposal, EDQM provided some high-level background information. We would encourage EDQM to consider writing a more in-depth article on the chapter development and any conformational/equivalency data generated during development of 2.6.32 with the other established methods.
- The focus page can consolidate other technical articles and international regulatory guidance that support the application of BET rFC.

Include this topic in future EDQM meetings (e.g., State-of-the-art Science for Tomorrow's Medicines) to promote recognition and application.

2. Specific comments on text

Line number(s) of the relevant text	*(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 1, Lines 8 – 9	Include a statement of equivalency, such that a product registered with 2.6.14 can be equivalently tested using 2.6.32.
Page 1, Lines 8 – 9	Recommend revising lines 8-9: "It is performed using a reagent containing recombinant.factor C based on the gene sequence of the horseshoe crab ***(Limulus polyphemus, Tachypleus tridentatus, Tachypleus gigas,* or *Carcinoscorpius rotundicauda*)** using a fluorimetric or colorimetric method"
Page 2, Line 38	After section 7, add a section to account for the use of rFC on a kinetic chromogenic assay, similar to current 2.6.14 text.
Page 1, Lines 28 – 29	Consider revising to: The standard endotoxin stock solution is prepared from an endotoxin that has been calibrated against an International Standard.
Page 1, Lines 37	We have found vortexing to be critical to achieving valid results. Can this step be better defined versus 'vigorously mixing'?
Page 1, Lines 43 – 44	Recommend modifying text to read: "Some substances or preparations may be more appropriately dissolved or diluted in other aqueous solutions unless the solution components are known to interfere with assay performance."
Page 2, Line 28	Replace 'peptide' with 'substrate'
Page 2, Lines 29	Consider adding kinetic fluorescent test as an option.
Page 3, Line 4	Replace '3 replicates' with '2 replicates' as this is the common and accepted industry practice and lines 13-14 in Section 8-2 and Table 2.6.32.-1 both reference 2 replicates.
Page 3, Line 28	Solution D (water) is mentioned as negative control. What if another buffer is used for recon/dilution as mentioned on Page 1, Lines 43 – 44? Consider revising text to reflect the option of using another solution as the negative control.