General Chapter Prospectus: Use of Recombinant Reagents in Bacterial Endotoxins Test

Posting Date: 29–May–2020
Input Deadline: 28–Jun–2020
Expert Committee: General Chapters?Microbiology
Proposed New Title: <1085.1> *Use of Recombinant Reagents in the Bacterial Endotoxins Test - Photometric and Fluorometric Methods Using Recombinantly Derived Reagents*

Suggested audience: Suppliers and manufacturers of drug substances, biologics, drug products, excipients, parenteral products, medical devices, suppliers and users of water for injection, regulatory agencies, and QA/QC specialists.

Estimated proposal *PF*: *PF* 46(6) [Nov.-Dec. 2020]

Background and objective: USP intends to develop a new informational chapter that contains recommendations for the use and qualification of recombinant reagents as alternatives to naturally sourced reagents from horseshoe crabs Limulus polyphemus or Tachypleus tridentatus hemolymph (LAL or TAL) for the purposes of measuring endotoxins activity in injectable drugs, biologics and medical devices where applicable. The validation of these recombinant reagents as an alternative to LAL or TAL as described in <85> requires demonstration of comparability, based on criteria recommended in this new chapter proposal and other principles on validation and qualification of alternative methods, described in USP chapters such as <1223>, <1225>, and <1085> as noted.

Proposal and stakeholder engagement: For some time, USP has recognized a need for guidance on the use of alternative methods/reagents for endotoxins testing. Providing guidance could support early adoption of an in vitro method using recombinant factor C by manufacturers who wish to use the data generated to further engage with regulatory agencies to advance the implementation of alternative methods/reagents into their filings.

We refer stakeholders to USP General Notices and the existing general chapter that define criteria for the use of alternative methods, providing flexibility in using alternative reagents such as recombinant factor C, in conjunction with the endotoxin test. USP General Notices 6.30, *Alternative and Harmonized Methods and Procedures*, allows for the use of alternative procedures to those described in the compendia. The alternative

procedures must be validated and demonstrated to produce comparable results. Chapter <1225> *Validation of Compendial Procedures* describes applicable performance characteristics that must be addressed for the validation of the alternative procedure. In addition to validation, users are expected to demonstrate that comparable results are obtained with the alternative method. For endotoxins testing, the purpose of the test for comparability is to demonstrate that detection and quantitation of endotoxins using LAL and the proposed recombinant reagent produce results that are within a certain predefined range. For this purpose, users are required to compare test results using product that contains known levels of endotoxins.

This type of approach advances USP's commitment to transition to non-animal based assays and reagents where supported by the science. Our goal with this notice is to indicate our active development of additional guidance to allow flexibility in our compendial approaches to support developers of new products in bringing these to patients in a timely manner.

Preliminary outline of the proposed chapter: The following represents the sections for the proposed General Chapter

- Background
- Validation
- Preparatory testing
- Test for interfering factors
- Comparability
- Test Procedure
- Interpretation
- Additional quality concerns

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