Early Input Sought on Proposed Naturally Occurring Endoxtoxin (NOE) Reference Standard

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USP is requesting early input from stakeholders on a new endotoxin reference standard which is being considered for development by USP. The proposed endotoxin reference standard would be prepared from cell wall extracts of a well characterized Gram negative bacterium

The purpose of this proposed reference standard will be for use in hold time studies, depyrogenation studies, and other pharmaceutical studies that require or would benefit from the use of a "naturally occurring" endotoxin (NOE)[1].

It is not USP's intent to replace the current USP Endotoxin RS used as a reference standard for *Bacterial Endotoxins Test <85>* with this new reference standard. This cell wall extract will serve to act as an alternative analyte to the USP Endotoxin RS (purified lipopolysaccharide),for consideration by pharmaceutical, biopharmaceutical, and medical device companies for studies such as hold time for certain product formulations and for depyrogenation of process streams.

Endotoxin Indicators for Depyrogenation <1228.5> includes guidelines for the identification of bacterial strains, along with methodology suggestions for the preparation, use, storage, and documentation of a NOE and this proposed standard is designed meet all of the guidelines outlined in that chapter. The proposed alternative endotoxin standard will have the following characteristics:

- It will be a liquid standard, universally available and distributed by USP.
- It will be available in large quantities to assure consistency.
- It will be accompanied by a Certificate stating its activity in EU/mL.
- To reduce lot-to-lot variability, it will be:
  - Prepared from a well characterized bacterial species that is considered in industry to be a representative contaminant of pharmaceutical products such as IV products[2]. A member of the larger family Enterobacteriaceae is consistent with this definition and is closely related to the current purified LPS calibration standards, which are prepared from various strains of *E. coli.*
  - Manufactured and vialed under GMP conditions, meaning that it will have a batch record, will be subject to change control, and will have appropriate specifications that will be recorded on the Certificate.

A Stimuli Article titled, "The Use of Endotoxin as an Analyte in Biopharmaceutical Product Hold-Time Studies" on the potential use of this proposed RS was recently published in *Pharmacopeial Forum* 41(5) [Sep.-Oct. 2015]. USP would like to further engage stakeholders to identify and discuss the potential impact of this proposed reference standard on the pharmaceutical, biopharmaceutical and medical device industry. In order to accomplish this objective, USP welcomes interested stakeholders to provide preliminary feedback on this proposed reference standard.

If you would like to submit input or feedback please contact Radhakrishna Tirumalai, Ph.D., Principal Scientific Liaison (301-816-8339, rst@usp.org) by June 30, 2016.

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[1] Bolden, Jay, Cheryl Platco, John Dubczak, James F. Cooper, and Karen Zink McCullough. 2015. The Use of Endotoxin as an Analyte in Biopharmaceutical Product Hold-Time Studies. United States Pharmacopeia, Stimuli to the Revision Process. 41(5).

[2] Mackel, Donald C.,Dennis G. Make, Roger L. Anderson, Frank S., Rhame, John V. Bennett. 1975. Nationwide Epidemic of Septicemia Caused by Contaminated Intravenous Products: Mechanisms of Intrinsic Contamination. J. Clin. Microbiol. 2(6): 486-497