Navigating FDA and USP Regulatory Guidance with LAL Reagents for Bacterial Endotoxin Testing

Navigating the regulatory landscape of the Bacterial Endotoxin Test (BET) involves a thorough review of guidelines from regulatory agencies such as the FDA, USP, and AAMI. While there is considerable overlap in the guidance from these agencies, there are also some points of obscurity that may be difficult to work through. A common reservation for those who perform compendial BET is whether the reagent they are using is FDA-licensed or not, and what that means in terms of FDA acceptance and USP chapter <85> compliance. An example of this will be looked at closely using FUJIFILM Wako's kinetic chromogenic LAL reagent, Limulus Colour KY.

In 1987, the FDA published guidance for LAL testing titled Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices. In 2011, the FDA determined that this document was obsolete and withdrew the guidance in lieu of USP and AAMI guidelines. There was dissonance in the requirements that the FDA stated in the document and those of the USP and AAMI. This included discrepancies regarding endotoxin limits, qualification and validation procedures, and medical device testing.

One source of uncertainty was the requirement for use of FDA-licensed LAL reagents. The 1987 guidance stated that LAL reagents used for endotoxin testing should be licensed by the FDA Center for Biologics Evaluation and Research (CBER); however, the USP does not include that same explicit requirement in chapter <85> on Bacterial Endotoxin Testing. The 1987 guidance stated that manufacturers "shall use an LAL reagent licensed by CBER in all validation, in-process, and end-product LAL tests." Instead, USP <85> states that LAL reagent "refers only to a product manufactured in accordance with the regulations of the competent authority." At the time, this was interpreted that LAL reagents should be FDA-licensed. However, this guidance has since been replaced by the FDA's 2012 Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers, and the interpretation of that statement in USP <85> has been further clarified.

In the 2012 FDA Guidance, the agency instead took to the USP and AAMI guidelines on the Bacterial Endotoxin Test, stating that the "FDA has found that the published USP and AAMI documents describing methods and calculation of pyrogen and endotoxins testing limits provide industry with appropriate information. We also note the continued development of USP Chapters <85> and <161> and FDA guidance documents. The Agency has withdrawn the 1987 Guidance because it "no longer reflects the Agency's current thinking on the topic." Additionally, the 2012 guidance did not put forth the same requirement that manufacturers must use FDA-licensed reagent for endotoxin testing, regardless of whether it is used for in-process or end-product testing.

With the 1987 Guidance withdrawn and the 2012 Guidance taking its place, there were no longer explicit requirements from the FDA that LAL reagents for endotoxin testing must be licensed. In the same year, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use provided harmonisation between major international pharmacopeial texts on BET.

ICH Q4B Annex 14 imparts harmonisation between USP <85>, Japanese Pharmacopeia (JP) 4.01, and European Pharmacopeia (Ph. Eur.) 2.6.14 texts on Bacterial Endotoxin Testing. ICH Q4B Annex 14 section 2.1 states that "...the analytical procedures described in the official pharmacopoeial texts, Ph.Eur. 2.6.14. Bacterial Endotoxins, JP 4.01 Bacterial Endotoxins Test, and USP General Chapter <85> Bacterial Endotoxins Test, can be used as interchangeable..."

Additionally, the guideline deems that there is interchangeability between the three reference standards (RSE) of the pharmacopeial bodies:

"The USP, JP, and Ph.Eur. reference standards are considered interchangeable as they have been suitably calibrated against the WHO (World Health Organisation) International Standard for Endotoxin."

The FDA's 2013 Guidance for Industry discusses the ICH Q4B Annex 14 harmonisation (Guidance for Industry: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions). This guidance provides the agency's current thoughts and practices for Bacterial Endotoxin Testing and ICH Q4B Annex 14 harmonisation. In reference to section 2.1 of the guidance, the document states that "the pharmacopeial texts referenced in section II.A (2.1) of this annex can be considered interchangeable." The guidance also states the FDA may still require method suitability testing for the specific product or material being examined, irrespective of the origin of the method. This means that even though it can be asked for those reagents that aren't FDA-licensed, it can also be asked for those reagents that are FDA-licensed. However, it is important to note that method suitability, or interference testing, is already a required preliminary step for verification of BET under the USP. This does not add an additional requirement, rather, it elaborates on and emphasises the thinking of the USP. In summary, regardless of the origin or licensure of a reagent, preliminary method suitability testing should be performed for all LAL reagents prior to compliant routine testing, following the Test for Interfering Factors in USP <85>.

With the licensing requirement of the 1987 guidance withdrawn and subsequent pharmacopeial harmonisation for BET, what does this mean for pharmaceutical manufacturers?

In order to examine the relationship between the FDA, USP, and ICH guidelines for Bacterial Endotoxin Testing, FUJIFILM

Wako's Limulus Colour KY reagent will be assessed as a case study. The kinetic chromogenic LAL reagent is manufactured by FUJIFILM Wako in Japan. Since the reagent is manufactured outside the US, it does not fall under FDA CBER's licensing jurisdiction as a manufactured biological product. However, as a test reagent for Bacterial Endotoxin Testing, it is accepted by FDA's Center for Drug Evaluation and Research (CDER) for all testing requiring USP <85>.

Limulus Colour KY is manufactured in Japan under requirements following Japanese Pharmacopeia 4.01 on BET, which includes the standardisation of matched control standard endotoxin (CSE) to JP-RSE. Under the ICH Q4B Annex 14 guidance, JP 4.01 and JP-RSE are both considered interchangeable with USP <85> and USP-RSE, respectively. This means that Limulus Colour KY reagent, although manufactured in Japan, is fully USP <85> compliant and can be used for compliant endotoxin testing. Because the reagent follows the guidelines set forth by the USP and ICH, the FDA accepts Limulus Colour KY for use as a kinetic chromogenic LAL reagent in the United States. This includes usage of the reagent for validation, in-process, and end-product testing.

When navigating the world of Bacterial Endotoxin and Pyrogen testing, there are various guidelines from different regulatory agencies to consider. In order to get an accurate understanding of the requirements for BET, it is important to examine the relationship between these guidelines and agencies. USP Chapter <85> and harmonised texts JP 4.01 and Ph. Eur. 2.6.14 provide the overarching requirements for BET. Guidance texts, such as the FDA Guidance for Industry documents, are able to fill in any gaps that may be left unanswered by the regulatory chapters and pharmacopeia. While the technologies and methodologies for BET continue to change and adapt, so does the regulatory landscape.

REFERENCES

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