Table 29: Strategies for Setting Phase Appropriate Endotoxin Specifications

Facilitator: Danielle Leiske, *Seagen Inc., Bothell, WA, USA*

Scope:

Control of endotoxin levels in drug product is important to ensure patient safety. The threshold pyrogenic dose defined by USP<85> of 5 EU/kg/hour is widely used to set safe endotoxin specifications for drug products. However, parenteral drug products are often administered in combination with other components which increases the theoretical endotoxin exposure to patients at the time of product administration. For example, some drug products are reconstituted using commercially available WFI and many products are diluted before administration using commercially available diluents (e.g., saline). Furthermore, drug products may be administered as part of a multidrug regimen (i.e., two or more products marketed separately but administered concomitantly). New regimens may be assessed for investigational and commercial products as part of the clinical development and product lifecycle management, which requires continuous assessment of existing endotoxin control strategies.

Endotoxin limits for commercially available diluents and marketed drugs may not have been established in consideration for use with other drug products. If theoretical endotoxin levels of all administration components are considered in totality (drug product, diluents, concomitantly administered drugs, etc.), there may be little space to set endotoxin limits for investigational medicines or to establish new multidrug regimens. Wholistic endotoxin control strategies such as tightening product endotoxin limits and/or adjusting the administration protocols can help ensure patient safety. However, these strategies present practical challenges for developing manufacturing processes and sourcing raw materials capable of meeting tight endotoxin specifications, as well as clinical operational challenges for drug administration. Such limitations are particularly challenging for high dose products or products in the dose escalation phase of clinical development.

This discussion will explore practical strategies for wholistic endotoxin control while maintaining patient safety.

Questions for Discussion:

1. Are potential endotoxin contributions from diluents (i.e., saline) considered when setting drug product endotoxin specifications? If yes, at what phase in development? If different strategies are used in different phases of development, what justification is used to support a phase-appropriate approach? Are endotoxin limits in devices considered?
2. What safety factor is included when setting endotoxin specifications? How is the safety factor selected?
3. Is clinical indication and/or administration setting considered when setting endotoxin limits?

4. What challenges are faced when setting endotoxin limits for products with high dose levels? What strategies are used for manufacturing and/or administration?
5. How are endotoxin levels and administration strategies established for products administered in a multidrug regimen to ensure patient safety? What strategies are used when adding a multidrug regimen to a product initially designed as a monotherapy?
6. Endotoxin limits for commonly used clinical diluents and water for reconstitution are set by pharmacopeia. What is known about actual endotoxin levels of these products? Is there appetite to tighten these limits?

Discussion Notes:

1. Are potential endotoxin contributions from diluents (i.e., saline) considered when setting drug product endotoxin specifications? If yes, at what phase in development? If different strategies are used in different phases of development, what justification is used to support a phase-appropriate approach? Are endotoxin limits in devices considered?

- Participants voiced differing experiences for setting endotoxin specifications and differing feedback from health authorities
    - One participant shared that clinical diluents had not been considered before and then received questions from FDA during review where it was required. Although they pushed back initially, endo spec for diluents were required and addressed by adjusting clinical time of administration infusion.
    - Another participant shared that they were able to successfully push back. Participant voiced that endo from diluents is a theoretical concern. Saline can be administered 6-10L at a time for sepsis without endotoxin-related issues. Asking sponsor to assume responsibility for diluents is not reasonable as there are many diluents and devices which are not manufactured under sponsor control.
    - Another participant received health authority feedback and initially pushed back, but then was required to adjust infusion volume to accommodate the diluent spec requirement.
- Ideas discussed for how to address outside of sponsor: a) Could the USP tighten diluent specs ? This option was brought up by an individual at USP several years ago, but it did not move forward. B) maybe suppliers could make available to market a low endo' diluent option to purchase to address this new request, however global availability of low endotoxin diluent might be challenging if required on the label

2. What safety factor is included when setting endotoxin specifications? How is the safety factor selected?

- Participants shared that a 2X safety factor is typically used. One shared that strategy is to not take 2X safety factor until reach commercial stage. This can be limiting, particularly when accounting for diluent.

3. Is clinical indication and/or administration setting considered when setting endotoxin limits?

- Indication is not considered when setting endo limits.

4. What challenges are faced when setting endotoxin limits for products with high dose levels? What strategies are used for manufacturing and/or administration?

- Analytical capability, Manufacturing capability and formulation interference challenges need to be taken into consideration. Patient experience is also a consideration, one option to meet endotoxin limits with both product and diluent is to lengthen infusion time, which puts additional burden on patients.

5. How are endotoxin levels and administration strategies established for products administered in a multidrug regimen to ensure patient safety? What strategies are used when adding a multidrug regimen to a product initially designed as a monotherapy?

- One participant indicated two combination products were recently filed. For one product they received an IR to consider the totality of endotoxin when setting limits. No questions related to endotoxin were received related to endotoxin on the second product. Other participants voiced that his has not been requested by Health authorities and would see this as difficult to manage specifications for other co-administered drugs. Approach to date is to clearly state what you have under control for your drug (control strategy).
- Participants discussed if health authorities would provide pre-filing feedback on strategy for setting endotoxin specifications (i.e., which components would be considered). Typically regulators will not provide feedback on proposed specifications before review.
- Lengthening time between drugs during administration is a strategy but risk identified by clinical and safety medical as being higher for extending administration time compared to theoretical risk of endo from diluents.
- Administering more saline at end of dosing is sometimes done in the clinic, which is outside administration instructions and therefore not accounted for in product specifications.

6. Endotoxin limits for commonly used clinical diluents and water for reconstitution are set by pharmacopeia. What is known about actual endotoxin levels of these products? Is there appetite to tighten these limits?

- Participants voiced that guidance is desired but caution on a having blanket requirement from Health Authorities without input from industry

- Recommend that industry continue to bring up topic at conferences (ex/ PDA) , and voice clear rationale to health authorities during regulatory review. More clarity is needed on regulator expectations on this topic: currently feedback on this topic seems reviewer-dependent.