Highlights: USP Expert Microbiology Committee's Activities Related to Endotoxin

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Disclaimer

The content on the slides is consistent with current USP activities on endotoxin.

Comments outside of the slides are solely those of the presenter, and do not reflect either the individual or collective opinions of the Committee members.

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Today's discussion on Expert Committee Activities

- Endotoxin Limits
- Informational Chapters on Depyrogenation
- Other thoughts

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Endotoxin Limits

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- USP instructions for the calculation of endotoxin limits have served us well over the years
- However, as therapies become more sophisticated, it may be time to re-think endotoxin limits for certain classes of products to assure continued patient safety.
- Discussions with and requests by FDA colleagues on the Committee have resulted in three proposals for new ways to think about endotoxin limits.
  - Endotoxin Limits in USP Product Monographs
  - Endotoxin Limits for LVPs used as diluents (infusions) or irrigation
  - Endotoxin Limits for Ophthalmic Injections

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Endotoxin Limits in USP Product Monographs

- In July, 2011, FDA withdrew the 1987 "Guidance on Validation of the Limulus Amebocyte Lysate Test as an End-product Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices" and the 1991 Interim Guidance, "Interim Guidance for Human and Veterinary Drug Products and Biologicals: Kinetic LAL Techniques"
  - Appendix E (April 1992), a listing of drug products and endotoxin limits was withdrawn as well because it was out of date
- The New Guidance (2012), "Pyrogen and Endotoxins Testing: Questions and Answers" contains no limits, and refers the reader to USP <85> for instruction on calculating a drug product endotoxin limit

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Endotoxin Limits in USP Product Monographs

- USP <85> instructs users to calculate the endotoxin limit for each product based on
  - the maximum dose/kg/hr,
  - the length of administration and
  - the route of administration
- USP monographs currently contain endotoxin limits for many products based on the dosage and administration when the drug was first approved
- Over time, dosages and administrations may change in the labeling, and the USP limits may be out of date with the most current labeling.

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Endotoxin Limits in USP Product Monographs

- Proposal: Eliminate endotoxin limits in USP Product Monographs and require that limits be calculated from the most current Product Insert (PI)
- Proposed new, more generic language: *Bacterial Endotoxins <85>, Meets the requirements set forth in <85>, "Bacterial Endotoxins Test"*
- Implications:
  - Firms will have to calculate endotoxin limits for all dosing regimens and administrations in their PI and choose the most stringent as their endotoxin limit
  - Firms will have to be attentive to changes in dosing that could affect the endotoxin limit

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Endotoxin Limits for Large Volume Parenterals

- Diluents and irrigation solutions (e.g. Sodium Chloride Injection, Dextrose Injection, Water for Injection, Ringers Injection, Lactated Ringers Injection, Potassium Chloride Injection and combinations of these) don't have specific doses, so they must default to a published limit, currently 0.5 EU/mL
- However, as these LVP solutions are required for drug infusion, whatever endotoxin they may contain (currently up to 0.5 EU/mL) is added to whatever endotoxin the drug may contain. For large infusions, this could, in theory, be a patient safety issue.

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Endotoxin Limits for Large Volume Parenterals

Infusion Volume	Maximum Infusion Contribution[1]	Maximum Drug Contribution[2]	Potential Patient Exposure
0	0	350 EU	350 EU
100	50 EU	350 EU	400 EU
500	250 EU	350 EU	600 EU
1000	500 EU	350 EU	850 EU

[1]Assumes the LVP at the current limit of 0.5 EU/mL

[2]"Average" 70 kg patient

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Product Endotoxin Limit vs Therapeutic Endotoxin Limit

- This problem can be further exacerbated by the dosing. For most drugs, the dose/kg and the volume of infusion are constants across the target patient population. For an adult population with a weight range of 45kg – 90 kg (approx 100-200 pounds):

Patient weight (kg)	Max Etox exposure (EU)	Drug dose mg/kg	Total drug dose (mg)	Infusion volume (mL)	Max etox from infusion (EU)	Drug product etox contribution (EU)	Adjusted drug etox limit (EU/mg)
70	350	20	1400	0	0	350	0.25
70	350	20	1400	200	100	250	0.17
45	225	20	900	200	100	125	0.13
90	450	20	1800	200	100	350	0.19

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Hydration Therapy: LVP

- Hydration volumes (large volumes up to or exceeding 1000mL/hr) of LVPs frequently exceed the endotoxin limit for the patient
  - Example:
    - An average adult patient (70kg) can have up to 350 EU
    - If a hydrating dose of 1000mL of an LVP is required, and if the LVP is at the current endotoxin limit of 0.5 EU/mL, then the person could receive 500 EU total, which exceeds the total body limit of 350 EU

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Endotoxin Limits for Large Volume Parenterals

- Proposal: To minimize patient risk from the potential endotoxin contribution by infusion and irrigation volumes, it is proposed that these diluents, when packaged as LVPs, be assigned an endotoxin limit of not more than 0.05 EU/mL.
- Implications:
  - Those firms using gel clot for test/release will default to a limit test where $\lambda = 0.03$ EU/mL
  - WFI used in the manufacture of these products will need to be controlled to a level that will assure a finished product of not more than 0.05 EU/mL
  - Bacteriostatic Sodium Chloride and Bacteriostatic Water for Injection would be included in this change, but SVP presentations of these products would not.

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Ophthalmic Injections

- The standard endotoxin limit calculation in USP <85> is based on IV, IM, IT dose/kg/hour
- However, the eye is a much smaller and more confined space that requires a much smaller injection volume
  - A limit based on dose/kg of body weight may be inappropriate
- A current reference for intraocular administration can be found in ISO 11979-8:2011, “Ophthalmic implants – intraocular lenses”
- This ISO standard sets an endotoxin limit of not more than 0.5 EU/lens

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Ophthalmic Injections

- Proposal: To minimize patient risk from the potential endotoxin contribution for intraocular administration, a limit of not more than 0.5 EU/dose/eye is proposed.
- Implications:
  - Drug products that provide for multiple routes of administration, including intraocular administration, would need to comply with the new limit.

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Proposed Language, USP <85> Footnote #2

K is 5 USP-EU/kg of body weight for any route of administration other than intrathecal (for which K is 0.2 USP-EU/kg of body weight), or intraocular. For ophthalmic injection products, the endotoxin limit should not exceed 0.5 EU per dose per eye. For large volume parenteral products used as irrigation or diluting solutions, the endotoxins limit is 0.05 EU/mL. For radiopharmaceutical products…

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Publication

Note: These are only proposals.

Proposals will be published in *Pharmacopeial Forum* for public comment.

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USP 1228.x Series

Informational Chapters on Depyrogenation

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Why Create These Chapters?

- Previously, depyrogenation and sterilization were treated as connected processes
- 1229.x series of informational chapters are being written to address different methods of sterilization (many chapters have been published in Pharmacopeial Forum)
- 1228.x series of informational chapters are being written to address different methods of depyrogenation.

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1228.x Series of Chapters on Depyrogenation

- Chapters:
  - 1228. Introductory chapter (almost done)
  - 1228.x Individual chapters on methods of depyrogenation
    - Methods that destroy endotoxin
      - Dry Heat
      - Chemical inactivation
    - Methods that remove endotoxin
      - Filtration
      - Adsorption
      - Rinsing
      - Distillation
    - Methods that may reduce endotoxin (e.g. autoclaving)
    - Endotoxin Indicators
    - Monitoring processes for endotoxin

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1228.x Chapters

- Chapter Content will be consistent:
  - Discussion of the technology
  - Mode of action of the technology
  - Discussion of appropriate uses/applications of the technology
  - Discussion of appropriate validation approaches
- This series will challenge some current “rules” via assessment of risk
  - Appropriate use of the current requirement for 3-log reduction vs reduction to safe levels
  - Is CSE always the best endotoxin to use for depyrogenation studies?

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Other Activities

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Other Activities

- USP <161> Revision
  - Committee is working with FDA to revise content to align with AAMI ST72:2011, “Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing”
- Consideration is being given to an Informational Chapter on BET
  - Information in 1987 Guideline is “lost”
    - RSE:CSE
    - Training
    - Guidance on archived and product standard curves
  - Guidance on Sampling
  - Guidance on OOS/Retesting
  - Guidance on validation of alternate methods

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