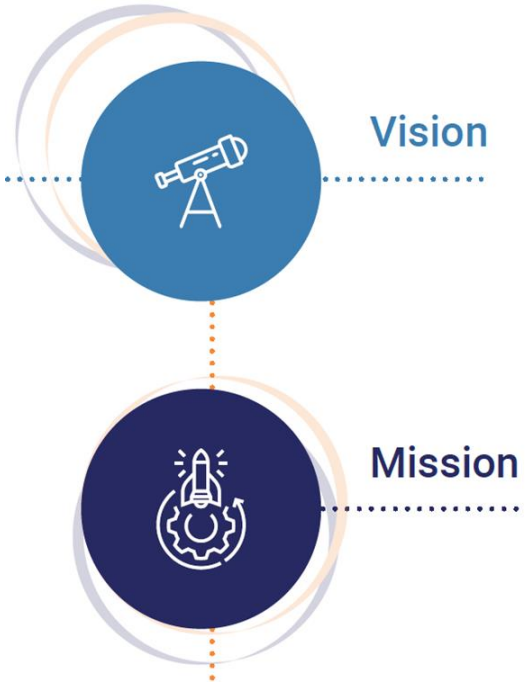
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

IQ Biologics Specifications Setting Challenges and Opportunities Working Group Endotoxin Subgroup Readout

CMC Strategy Forum North America 2025

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) was established in 2010 as a technically-focused, not-for-profit organization comprised of nearly 40 pharmaceutical and biotechnology companies.



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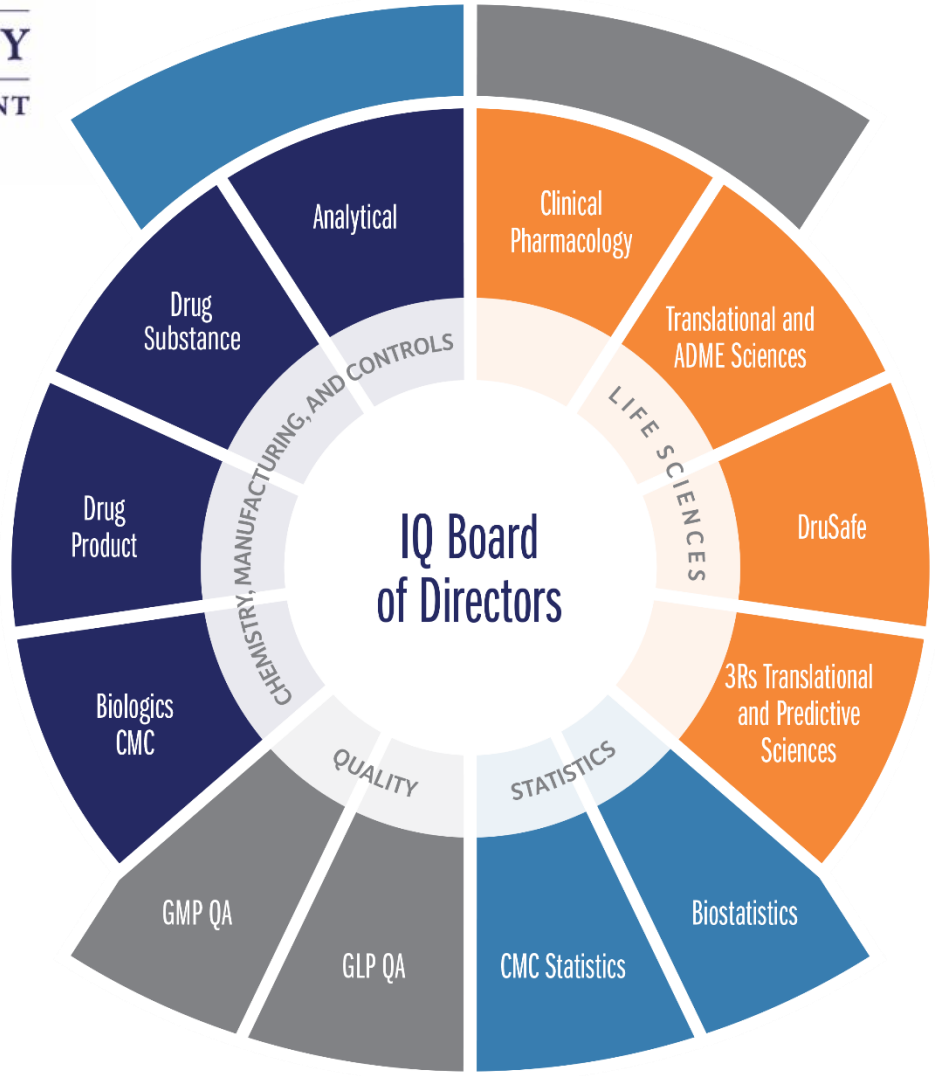
As a technically-focused organization of pharmaceutical and biotechnology companies**, IQ advances science and technology** to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.



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Endotoxin Specification Setting Strategies Discussion

Discussion included various questions related to :

- Are acceptance criteria (AC) calculated based on maximum dose or platform approach?
  - What body weight is used in calculations for flat-dose products?
- Safety factors and allowances for diluent contribution
- Reporting units
- Are AC tightened during late phase development?
- Are commercial AC based on product-specific batch history?

Endotoxin Specification Setting Strategy Trends

- Most companies calculate endotoxin AC based on maximum dose
- The majority of responding companies use average body weight in AC calculations
- Mixed responses for application of safety factors and/or allowances for diluent contribution
- Mixed responses for reporting units
  - Some use different units for DS vs DP
  - Some use different units for clinical vs commercial
- The majority of responding companies do not tighten AC during late phase development
- Mixed responses for commercial AC being based on product-specific batch data

Endotoxin Subgroup Discussion
History of 5 EU/kg/hr Compendial Limit

- Purified gram-negative lipopolysaccharide (LPS) derived from E. Coli was used for development of the 5 EU/kg/hr limit
- Purified LPS is considerably more potent than environmental endotoxins found in pharmaceutical products
- Multiple studies demonstrate that potency and sensitivity differences result in a safety margin of at least 8-fold built into the 5 EU/kg/hr limit
- Review of commercial product history indicated no systematic concerns from current industry AC for endotoxin

1. Weary, Marlys and Fred C. Pearson III. 1982. The Activity of Various Endotoxins in the USP Rabbit Test and in Three Different LAL tests. In: Endotoxins and Their Detection with the Limulus Amebocyte Lysate Test. S.W. Watson, J. Levin and T.J. Novitsky, eds. Pages 365-379. Alan R. Liss, New York.
2. J. Akers, J. Duguid, D. Guilfoyle, D. Hussong, K. McCullough and R. Tirumalai, "Will a proposed reduction in endotoxin limits for drugs and biologics improve patient safety?," *Am. Pharm. Rev.,* 2022.
3. F. C. Pearson, A comparison of the pyrogenicity of environmental endotoxins and lipopolysaccharides. Editors: J. W. Cate, H. R. Buller, A. Sturk, J. Levin. Bacterial endotoxins: structure, biomedical significance and detection with the limulus amebocyte lysate test. New York (NY): Alan R. Liss Inc; 1985. p. 251–63
4. E.C. Tidswell, A Nontrivial Analysis of Patient Safety Risk from Parenteral Drug- and Medical Device-Borne Endotoxin, *Drugs in R&D,* 2023, 23:65-76

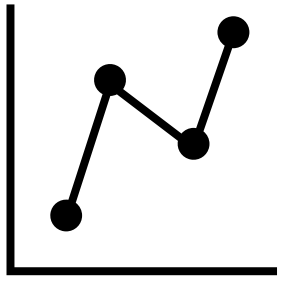
Endotoxin Subgroup Discussion
Patient Weight

- Considering the safety factor that is already built into the 5 EU/kg/hr compendial limit, use of average patient weight in the endotoxin calculation is justified
- USP <1085> refers to use of average body weight except for pediatric and other special category patients

Endotoxin Subgroup Discussion

Batch History and Manufacturing Experience vs Patient Centricity

- 5 EU/kg/hr is not only a demonstrated safe, patient-centric limit for endotoxin, but it is also a conservative limit that incorporates a built-in safety factor
- Endotoxin levels in excipients and water can fluctuate due to factors like sourcing, manufacturing methods, and environmental conditions.
- Tightening of endotoxin AC for commercial specifications based on batch history alone places future supply at risk



IQ Working Group Conclusion

The 5 EU/kg/hr limit for endotoxin is patient-centric, clinically relevant, and based on a science and risk-based enhanced approach across all stages of development and therefore should not require tightening based on batch history alone.

Acknowledgement

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

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