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Low Endotoxin Recovery

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PDA Low Endotoxin Recovery Technical Report Team

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Foreword

PDA is at its heart a science-based organization. Our activities and processes have been implemented to promote the free exchange of ideas and promote inclusion in participation, regardless of the organization to which a member may belong. We also strive to achieve consensus among the subject matter experts and to inform our members (and others) of the best practice (and in some cases, the regulatory requirements). Our aim is always to make recommendations that advance patient safety.

PDA has also implemented a multistage review process for technical reports and position papers, which includes not only the task force itself and the relevant advisory board, but also peer reviewers who offer independent input on the subject matter. Finally, of course, the Board of Directors reviews and approves all these documents. In every step, we document the resolution of all comments, and that resolution is communicated to the next level of review. This process, although cumbersome, is how we are working to ensure that we are exercising due diligence in positions adopted by the PDA.

Specifically, regarding this Technical Report, low endotoxin recovery (LER) has been discussed in open fora many times over the last several years. The task force includes subject matter experts from several organizations, as well as U.S. FDA. We increased the number of peer reviewers on this draft report to 30 individuals from 23 different industry, academic, and regulatory authority organizations.

The reliable and sensitive detection of bacterial endotoxin is a key test underpinning patient safety in the manufacturing of parenteral drugs. The globally harmonized compendial tests linked to well-characterized reference standards have provided this assurance to industry and regulators for decades despite the complex nature of both the assays and the reference materials being. This complexity has been demonstrated each time new assay approaches or reference materials have been proposed. Over the past decade, biologics manufacturing has exploded, and new products, formulations, and delivery systems continue to push the boundaries of modern manufacturing. In this context, it should not be surprising that a phenomenon like LER arises to once again challenge our current understanding of assay systems, reagents, and our own manufacturing process.

To that end, the PDA task force commissioned with this technical report went to the greatest lengths possible to present as complete a picture of the current LER situation. This includes the historical and mechanistic aspects of the endotoxin measurement challenges, as well as a standard protocol for developing product-specific hold studies, supported and informed by actual industry case studies. Both the technical report team and the approving Biopharmaceutical Advisory Board understand that this is a very complex and still evolving area of science that is not without controversy. Extensive peer review comments were addressed, and the findings were widely presented in public fora before the completion of this report. PDA believes it is vitally important to make this information available to further the scientific dialog and progress in this area and remains committed to revising and updating this material as new discoveries and conclusions are made.

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Table of Contents

Figures and Tables Index

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