



Technical Report No. 82

Low Endotoxin Recovery



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.

Richard M. Johnson
President & CEO, PDA

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Table of Contents

1.0 Introduction.....	1
1.1 Purpose.....	1
1.2 Scope	1
2.0 Glossary of Terms.....	2
2.1 Abbreviations.....	3
3.0 LER Hold-Time Studies	3
3.1 Test Method	4
3.1.1 Reagents and Materials	4
3.1.2 Spiking of Undiluted Sample	4
3.1.3 Storage Containers.....	5
3.1.4 Batch Requirements.....	5
3.1.5 Storage Time and Temperature	5
3.1.6 Controls	6
3.1.7 Equipment.....	6
3.1.8 Personnel.....	6
3.1.9 Data Analysis and Interpretation.....	6
4.0 Proposed Mechanisms of LER	7
4.1 Differentiation of LER and Test Interference.....	8
4.2 Investigation of LER Causes	8
4.3 Proposed Two-Step Reaction Model of LER.....	9
4.4 Factors Influencing Reaction Kinetics	10
4.4.1 Energy Input (Extrinsic)	10
4.4.2 Masking Capability of a Sample	11
4.4.3 Masking Susceptibility of Endotoxins.....	12
4.5 Potential Aggregation States of Detectable and Non-detectable Endotoxin	13
4.5.1 LER and Limited LPS Interaction with Factor C.....	14
4.5.2 Activity of Monomeric and Aggregated LPS ..	14
4.6 Summary	15
5.0 Mitigation of LER.....	15
5.1 Mitigation through Sample Treatment	15
5.1.1 Evaluation of the Product.....	16
5.1.2 Addition of Dispersants to Samples	16
5.1.3 Addition of Excess Divalent Cations.....	16
5.1.4 Other Sample Treatments	16
5.1.5 Evaluation of LAL Assay Reagents	16
5.1.6 Non-LAL Endotoxin Testing	17
5.2 Evaluation through a Biological System	17
5.2.1 Endotoxin Dosage	17
5.2.2 Product Dosage.....	18
5.2.3 Monocyte Activation Test	19
5.3 Interpretation of Results	20
5.4 Summary	20
6.0 History and Rationale for LER Studies	20
6.1 Regulatory Framework.....	20
6.2 Microbial Control During Manufacturing and Product Quality	21
6.3 Endotoxin Structure	21
6.4 <i>Limulus Amebocyte Lysate (LAL)</i> Assay	22
6.5 Endotoxin Reference Standards.....	24
6.5.1 U.S. FDA Development of Reference Standard Endotoxins.....	24
6.5.2 Harmonization of International Reference Standard Endotoxins	26
6.6 Natural Occurring Endotoxins (NOEs)	27
6.7 Immune Response	27
7.0 References	30
8.0 Appendix: Case Studies of LER Occurrences	37
8.1 Case Study 1: Low Concentration PS20 Caused LER Reaction in the Presence of Monoclonal Antibody Product	37
8.1.1 Introduction.....	37
8.1.2 Materials and Methods	37
8.1.3 Results and Discussion	38
8.1.4 Conclusion	39
8.1.5 References	40
8.2 Case Study 2: Mapping LER Effect in In-Process Stages of Purification	41
8.2.1 Introduction.....	41
8.2.2 Materials and Methods	42
8.2.3 Results and Discussion	42
8.2.4 Discussion	44
8.2.5 Key Lessons Learned	44
8.2.6 Conclusion	44
8.2.7 Recommendations	45
8.3 Case Study 3: Use of Purified and Nonpurified Endotoxins in Hold-time Studies	46
8.3.1 Introduction.....	46
8.3.2 Materials and Methods	47
8.3.3 Results and Discussion	47
8.3.4 Molecular Basis of LER Susceptibility	52
8.3.5 Conclusion	54
8.3.6 References	54
8.4 Case Study 4: Factors Affecting Low Endotoxin Recovery.....	55
8.4.1 Introduction.....	55
8.4.2 Materials and Methods	55
8.4.3 Results and Discussion	57
8.4.4 Effects of Temperature, pH, and Salt Concentration on LER.....	58
8.4.5 Effects of Matrix Components on LER at Relevant Concentrations	60
8.4.6 Effects of Dilution Methods on Recovery of RSE in LER Solutions.....	61
8.4.7 Conditions for Magnesium Dilution Method ..	62
8.4.8 Conclusion	63

8.4.9 References	63
8.5 Case Study 5: Comparison of Different Methods Used for Calculation of Percentile Endotoxin Recovery from LPS-Spiked Biological Therapeutic Products	65
8.5.1 Introduction.....	65
8.5.2 Materials and Methods.....	65
8.5.3 Results.....	66
8.5.4 Discussion.....	68
8.5.5 Conclusion	70
8.5.6 References	71
8.6 Case Study 6: Lipopolysaccharide Masking and Resolution of Low Endotoxin/Lipopolysaccharide Recovery (LER/LLR) in a Citrate Buffer Monoclonal Antibody containing Polysorbate and Chelating Agent	72
8.6.1 Introduction.....	72
8.6.2 Materials and Methods	72
8.6.3 Results and Discussion	74
8.6.4 Conclusion	78
8.6.5 References	78
8.7 Case Study 7: Evaluation of an Endotoxin Demasking Protocol	79
8.7.1 Introduction.....	79
8.7.2 Materials	79
8.7.3 Methods	80
8.7.4 Results and Discussion	80
8.7.5 Conclusion	84
8.7.6 References	84
8.8 Case Study 8: Strategy to Investigate and Overcome LER Driven by Protein	86
8.8.1 Introduction.....	86
8.8.2 Materials and Methods	87
8.8.3 Results	88
8.8.4 Discussion.....	92
8.8.5 Conclusion	93
8.8.6 References	93
8.9 Case Study 9: LER Case Study for a Monoclonal Antibody.....	94
8.9.1 Introduction.....	94
8.9.2 Materials and Methods	94
8.9.3 Results and Discussion	97
8.9.4 Conclusion	100
8.9.5 References	102
8.10 Case Study 10: Endotoxin Recovery Studies with a Biologic Formulated with Citrate and Polysorbate 20	103
8.10.1 Introduction.....	103
8.10.2 Materials.....	103
8.10.3 Methods	104
8.10.4 Results and Discussion	105
8.10.5 Conclusion	108
8.10.6 References	109
8.11 Case Study 11: No LER Effect in a Sodium Phosphate, Polysorbate 80 Formulation Matrix .	110
8.11.1 Introduction.....	110
8.11.2 Materials and Methods	110
8.11.3 Results and Discussion	111
8.11.4 Conclusion	112
8.11.5 References	112
8.12 Case Study 12: Lack of LER Phenomenon in A Therapeutic Protein Biologic with Known LER-Causing Ingredients	113
8.12.1 Introduction.....	113
8.12.2 Materials.....	113
8.12.3 Methods	114
8.12.4 Results and Discussion	114
8.12.5 Conclusion	117
8.12.6 References	117

Figures and Tables Index

Table 3.1.5.1-1	Example for Identification of LER Process-Relevant Steps.....	6
Table 4.2-1	Investigation of LER Driving Forces in Biopharmaceutical Drug Products	9
Figure 4.3-1	Schematic of Masking/Demasking Phenomenon.....	10
Figure 4.4.3-1	Covalent Modifications of Kdo2-lipid A in <i>E. coli</i> K-12 and <i>Salmonella</i>	13
Figure 6.3-1	<i>E. coli</i> K-12 Kdo-Lipid A Structure	22
Figure 6.3-2	Degree of Lipid A Acylation Impacts IL-1 Response	23
Table 6.5.1-1	U.S. Reference Standard Endotoxins development history	25

Table 6.5.2-1	Endotoxin standards and their assigned potency	26
Figure 6.7-1	Structural Basis of Lipopolysaccharide Recognition by TLR4-MD-2 Complex...	28
Figure 6.7-2	TLR Recognition of Microbial Components	29
Table 8.1.3-1	Recovery of CSE from Spiked DS and DP Samples	38
Table 8.1.3-2	Recovery of NOE from Spiked DS and DP Samples	39
Table 8.1.3-3	Recovery of CSE from Spiked DP Samples Stored at Below-freezing Temperatures (-30 °C)	39

Figure 8.2.1-1	Testing Setup Overview	41
Figure 8.3.3.1-1	Masking of Four Model Bacterial NOEs in LER solutions at Room Temperature	48
Figure 8.3.3.1-2	Masking of Different Bacterial NOE in LER Solutions at Room Temperature..	48
Figure 8.3.3.2-1	Masking of Bacterial NOE and Purified Endotoxin in LER Solutions at Room Temperature.....	49
Figure 8.3.3.3-1	Recovery of <i>P. aeruginosa</i> NOE as a Function of Nutrient Supply and Temperature.....	50
Figure 8.3.3.4-1	Recovery of <i>E. coli</i> 0113:H10 NOE as a Function of Bivalent Cation Supply a pH	51
Table 8.3.3.4-1	Varied Growth Conditions for <i>E. coli</i> .	51
Table 8.3.3.4-2	Varied Growth Conditions for <i>P. aeruginosa</i>	51
Figure 8.3.3.4-2	Recovery of <i>P. aeruginosa</i> NOE as a Function of Bivalent Cation Supply and pH.....	52
Figure 8.3.4-1	Lipid A Modifications in <i>E. coli</i>	53
Figure 8.3.4-2	Comparison of MALDI-TOF MS Spectra from NOE and Purified Endotoxin.....	53
Table 8.4.3.1-1	Kinetic Parameters for RSE Activity Change in LER Solutions Containing Citrate	57
Table 8.4.3.1-2	Kinetic parameters for RSE activity change in LER solutions containing phosphate	58
Figure 8.4.4-1	Effect of Temperature on Half-Life of RSE Activity in LER Solutions	59
Figure 8.4.4-2	Effect of pH on Half-Life of RSE Activity in LER Solutions.....	59
Figure 8.4.4-3	Effect of Salt Concentrations on Half-Life of RSE Activity in LER Solutions.	59
Figure 8.4.5-1	Effect of Citrate Concentrations on Half-Life of RSE Activity in LER Solutions....	60
Figure 8.4.5-2	Effect of Phosphate Concentrations on Half-Life of RSE Activity in LER Solutions	60
Figure 8.4.5-3	Effect of Polysorbate 20 Concentrations on Half-Life of RSE Activity in LER Solutions	60
Figure 8.4.6-1	RSE Activity Change in LER Solution at 25 °C with 3 Different Dilution Methods	61
Figure 8.4.6-2	RSE Activity Change in LER Solution at 2 °C–5 °C with 3 Different Dilution Methods.....	61
Figure 8.4.6-3	Effects of Sorts of Chelating Agents and Detergents on LER	62
Table 8.5.3-1	Endotoxin Activity Detected from LPS-spiked BTP-1 Over Time	66
Table 8.5.3-2	Comparison of Recovery % Calculated by Different Methods for BTP-1	66
Table 8.5.3-3	Endotoxin Activity Detected from LPS-Spiked BTP-2 Over Time.....	67
Table 8.5.3-4	Comparison of Recovery % Calculated by Different Methods for BTP-2	67
Table 8.5.3-5	Endotoxin Activity Detected from LPS-Spiked BTP-3 Over Time.....	67
Table 8.5.3-6	Comparison of Recovery% Calculated by Different Methods for BTP-3	68
Table 8.5.3-7	Endotoxin Activity Detected from LPS-Spiked BTP-4 Over Time.....	68
Table 8.5.3-8	Comparison of Recovery% Calculated by Different Methods for BTP-4	68
Table 8.5.4-1	Effect of Pyrosperse™ on LPS Activities by USP <85> BET Method	69
Table 8.5.5-1	Endotoxin Activities Recovered from LPS Spiked LRW Controls Over Time.	71
Figure 8.6.2.1-1	Schematic of test vial preparations for conducting the hold study	73
Figure 8.6.3.1-1	Pyrogen-Free Water (PFW) with Control Standard Endotoxin (CSE) Charles River Endosafe® Kinetic Turbidimetric Control after 3 days at 2-8 °C diluted with PFW and 100 mM Tris, 50 mM MgSO ₄ (1/10 Strength Cation Buffer)	75
Figure 8.6.3.1-2	Drug product with Control Standard Endotoxin (CSE) Charles River Endosafe® Kinetic Turbidimetric Control after 3 days at 2-8 °C diluted with PFW and 100mM TRIS, 50mM MgSO ₄ (1/10 strength Cation buffer)	75
Figure 8.6.3.1-3	Pyrogen-Free Water (PFW) with Control Standard Endotoxin (CSE) Lonza KQCL Kinetic Chromogenic Control after 3 days at 2-8 °C diluted with PFW and 25 mM Tris, 12.5 mM MgSO ₄ (1/40 Strength Cation Buffer).....	75
Figure 8.6.3.1-4	Drug Product with CSE Lonza KQCL Kinetic Chromogenic Control after 3 days at 2-8 °C diluted with PFW and 25 mM Tris, 12.5 mM MgSO ₄ (1/40 Strength Cation Buffer)	75
Figure 8.6.3.1-5	Reactivation of CSE (LPS) Contaminated into mAb/Citrate/PS Product 10 EU/ mL After 3 Days at 2-8°C Charles River Endosafe® Kinetic Turbidimetric.....	76

Figure 8.6.3.1-6	Kinetic turbidimetric testing of <i>E. cloacae</i> NOE 76	Figure 8.9.3-1	Percent Recovery of Six Preparations of LPS in LRW or Protein Sample at Room Temperature 98
Figure 8.6.3.1-7	Kinetic chromogenic testing of <i>E. cloacae</i> NOE 76	Table 8.9.3-2	Recovery of CSE in Various Levels of PS80 in 20 mM Histidine buffer, pH 5.5 99
Figure 8.6.3.1-8	Monoclonal Antibody in PFW and 100 mM Tris, 50 mM MgSO ₄ (1/10 Strength Cation Buffer) Kinetic Turbidimetric (CRE) with CSE on Day 7 76	Figure 8.9.3-2	Recovery of CSE Spiked into Protein vs. LRW Held for 3 days at Ambient Temperature 99
Figure 8.6.3.1-9	Monoclonal Antibody in PFW and 100 mM Tris, 50 mM MgSO ₄ (1/10 Strength Cation Buffer) Kinetic Turbidimetric (CRE) with NOE on Day 7 77	Table 8.9.3-3	CSE Spiked at 1700 EU/mL in ~150 mg/mL Product 100
Figure 8.6.3.1-10	Monoclonal Antibody in PFW and 25 mM Tris, 12.5 mM MgSO ₄ (1/40 Strength Cation Buffer) Kinetic Chromogenic (Lonza) with CSE on Day 7 77	Figure 8.9.3-3	LER Hold Time Spiked Protein Sample Study Calculated vs LRW and vs Theoretical 101
Figure 8.6.3.1-11	Monoclonal Antibody in PFW and 25 mM Tris, 12.5 mM MgSO ₄ (1/40 Strength Cation Buffer) Kinetic Chromogenic (Lonza) with NOE on Day 7 77	Figure 8.9.3-4	Comparison of Endotoxin Assay Kits in a Hold Time LER Study at Ambient Temperature 101
Figure 8.7.4.2-1	Reverse Hold/Time Study and Demasking Study of Endotoxin 82	Figure 8.10.2.1-1	Manufacturing Steps for Biotech Product X Drug Substance 103
Figure 8.7.4.4-1	Reproducibility and Robustness of the Developed Demasking Protocol 83	Table 8.10.3.1-1	Endotoxin Spiking and Container Types 104
Figure 8.7.4.4-2	Robustness of Sample Preparation Protocol 84	Table 8.10.4.1-1	Product X DS Spiked with 5 EU/mL CSE, BET with Dilution 1:8 106
Figure 8.7.4.4-3	Comparison of Different lots of LAL Reagent, Endo-RS Components, and Sample Tested 85	Table 8.10.4.1-2	Product X DS Spiked with 5 EU/mL CSE, BET with Dilution 1:16 106
Figure 8.7.4.6-1	Detection of Endotoxins from Different Species and Sensitivity 85	Table 8.10.4.1-3	Product X DS Spiked with 5 EU/mL <i>R. pickettii</i> , BET with Dilution 1:8... 106
Figure 8.8.1-1	Reverse Hold Time Study Setup 87	Table 8.10.4.1-4	Product X DS spiked with 5 EU/mL <i>R. pickettii</i> , BET with Dilution 1:16. 107
Figure 8.8.3.1-1	14-Day Hold Time Study for Drug Product at 2-8 °C with RSE 89	Table 8.10.4.3-1	Formulation Buffer Spiked with 5 EU/mL CSE, BET with Dilution 1:8.. 107
Figure 8.8.3.1-2	7/3-Day Hold Time Study for Drug Product at 20-25 °C with RSE 90	Table 8.10.4.3-2	Formulation Buffer Spiked with 5 EU/mL CSE, BET with Dilution 1:16..... 108
Figure 8.8.3.2-1	8-Day Hold Time Study for a Drug Product at 2-8 °C with High-Potency Endotoxin, 055:B5 (Lonza) 91	Table 8.10.4.5-1	Unconditioned Bulk Spiked with 5 EU/mL CSE, BET with Dilution 1:8 108
Figure 8.8.3.2-2	14-Day Hold Time Study for Intermediate of a Drug Substance at 2-8 °C with High-Potency Endotoxin, 055:B5 (Lonza) 91	Figure 8.11.3-1	Endotoxin Recovery 112
Table 8.9.3-1	Recovery of CSE Spiked into 20 mM Histidine +/- 83 mg/mL Trehalose, pH 5.5 97	Figure 8.11.3-2	Average Relative Endotoxin Recovery Results 112
		Table 8.12.4.1-1	LAL Assay Validity Criteria Summary. 115
		Table 8.12.4.2-1	Endotoxin Recovery Results from the Drug Product and LRW Control 115
		Figure 8.12.4.2-1	Endotoxin Recovery Curves from the Test Article and LRW Control 116
		Table 8.12.4.2-2	Endotoxin Recovery Results from Two Additional Drug Product Lots 116
		Figure 8.12.4.2-2	Endotoxin Recovery Curves from Two Test Articles and LRW Control 116



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