Defining the Microbial Control Strategy for LER Impacted Products

Strategies Today for Overcoming LER

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Microbial Control Strategy for Commercial LER Products

Risk Assessment Overview

Background: discovered Low Endotoxin Recovery (LER) phenomenon in registered commercial biologic products [1]

Strategy: ensure **Product Quality** and **Patient Safety** with comprehensive risk assessment

[1] Chen J., Vinther A. Low endotoxin recovery in common biologics products; Proceedings of the PDA Annual Meeting (2013)

Removal of Interim Rabbit Pyrogen Test (RPT)

Case Study: Commercial LER Impacted Product

Background:

- LER is due to polysorbate 20 and strong chelators enhanced by the intrinsic protease activity of the product
- Unable to determine risk since the product is a protease and includes polysorbate 20 from the beginning of the manufacturing process → **Implement RPT as an interim DP release test**

LER Mitigation: efforts were **not successful**

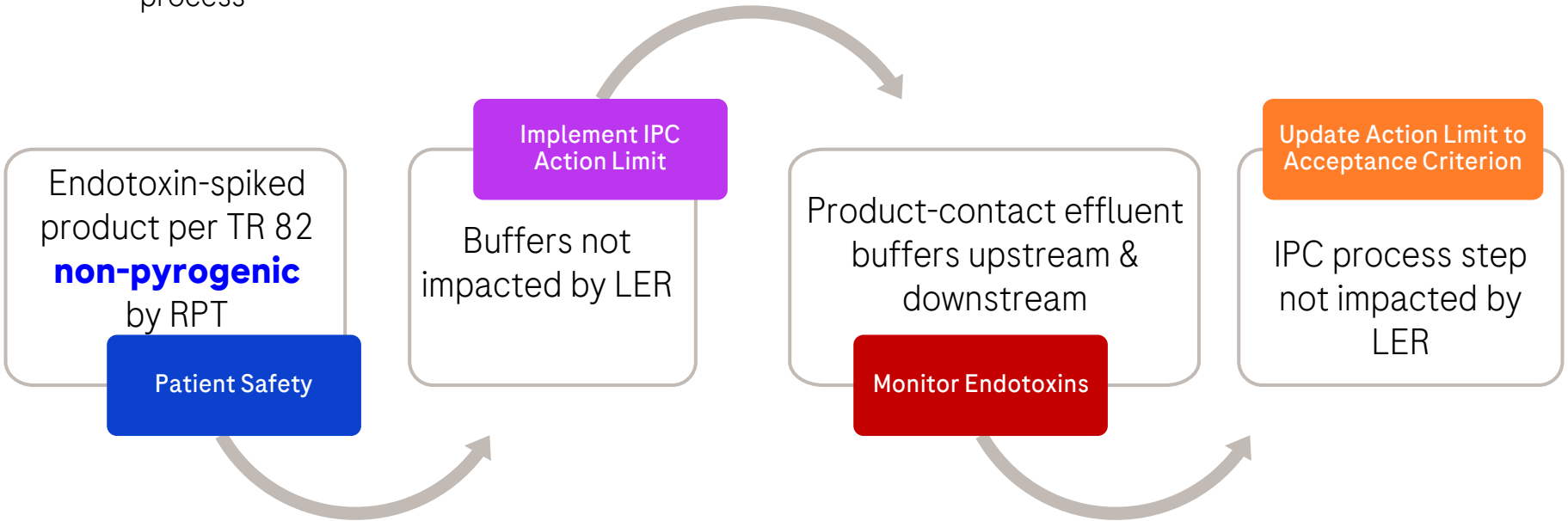
- EndoLISA® (false-positives due to cleavage of substrate)
- Recombinant Factor C (sample interference beyond MVD)
- Monocyte Activation Test[1] (sample interference)
- Several LAL methods + addition of dispersants, divalent cation agents
- Protease inhibitor treatment (limited effectiveness in eliminating protease activity)

[1] Ph. Eur. Chapter 2.6.30 "Monocyte Activation Test", EDQM, Strasbourg, France

Microbial Control Strategy | PAS Submission

Outcome: approval to stop the interim RPT and continue to test with LAL-based Bacterial Endotoxins Test

- Product quality is assured with a **holistic microbial control strategy** with demonstrated low endotoxin ingress risk and strong patient safety record
- Enhance endotoxin control strategy by Including additional endotoxin checks in the manufacturing process

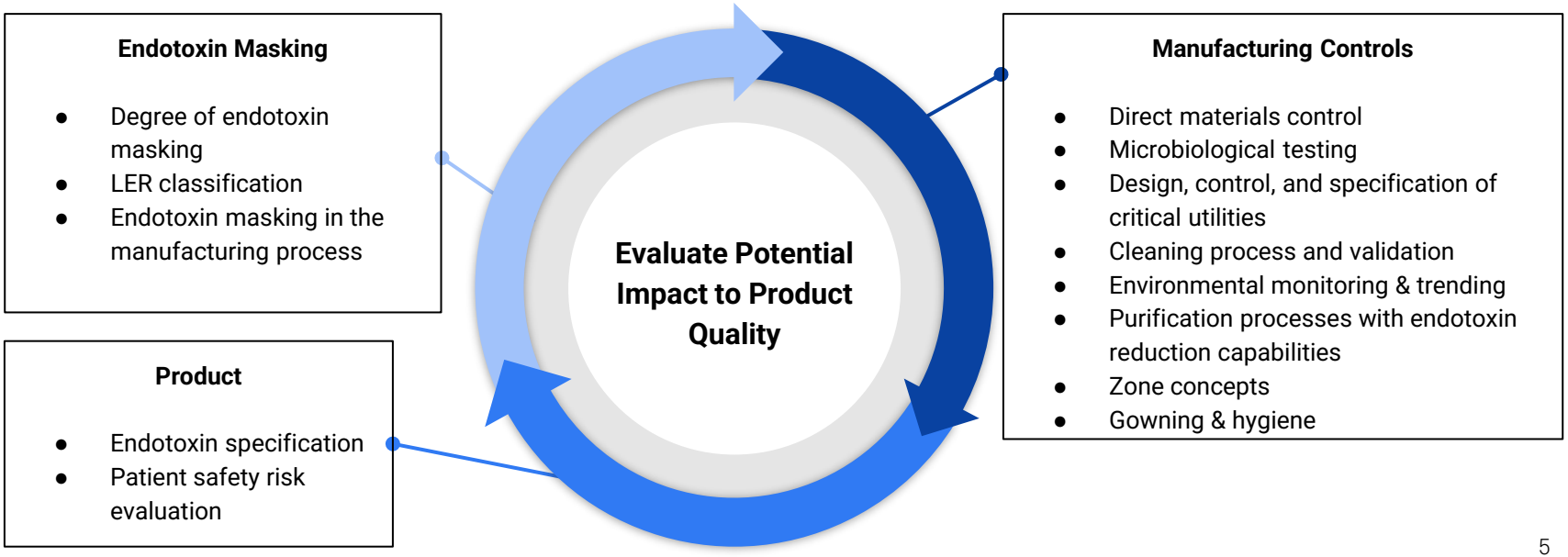


Microbial Control Strategy for Initial Marketing Authorization

Risk Assessment Overview per PDA TR 82 Guidance

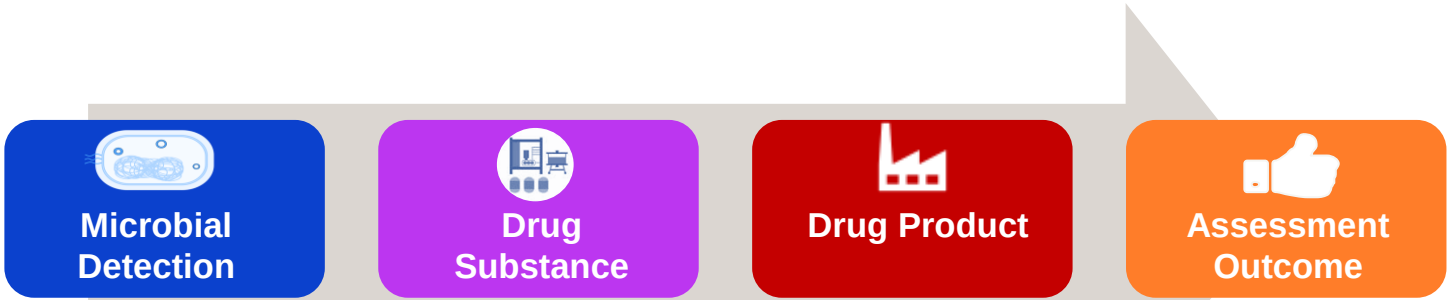
Background: studies to evaluate LER are performed per PDA TR 82 and are submitted in the IMA dossier. For products exhibiting LER, an adequate mitigation strategy is needed to assure patient safety.

Strategy: LER demasking method development with a **comprehensive risk assessment**



Overall Microbial Control of the Manufacturing Process

LER Risk Assessment



- Microbial testing (IPC, release) with stringent limits throughout the mfg process
- Microbial testing of direct materials using a risk-based approach
- Each batch of excipients tested for bioburden

- Review facility manufacturing controls for prevention against introduction of bioburden, endotoxin
- Assess product specific microbial control strategy, including product specific process hold time validation
- Review detection controls for microbial contamination

- DS and DP processes demonstrate suitable microbial control, including risk mitigation of microbial ingress and proliferation
- Risk of introducing endotoxins into the product is deemed to be low based on the process design

LER Risk Assessment | Endotoxin Masking

1

Degree of Endotoxin Masking

If the endotoxin recovery is stable around 40 – 49%, specification adjustment or correction factor may be considered.

2

LER Classification

Identify LER root cause

- Formulation masking
- API masking

Perform demasking method development per guidance in PDA TR 82

3

Endotoxin Masking in the Mfg Process

Assess DS and IPC steps (prior to final formulation) in order to ensure a complete understanding of endotoxin masking

Endotoxin Specification Limit

Set as low as reasonably achievable, whichever is lower:

- Manufacturer's process capability [1] or
- Compendial pharmacopoeia calculation

[1] Setting Endotoxin Acceptance Criteria for Biologics Intravenous (IV) and Subcutaneous (SC) Mono- and Combination Therapies. American Pharmaceutical Review. (2018)

Spiked Endotoxin Detection Through a Biological System

Compendial Rabbit Pyrogen Test

PDA TR 82: *if the mitigation efforts have failed, the next phase of study may be to determine if the spiked endotoxin is detected in a biological system. When endotoxin-spiked or -held samples are found to be pyrogenic, manufacturers should implement the RPT as an interim QC release test until a suitable in vitro test method can be developed.*

Discussion: Is there still a need to perform spiked endotoxin detection by RPT when the risk assessment outcome **concludes low risk to patient safety**?

- After 10 years, research and analysis of industry data indicate that LER is not a safety concern from parenteral drugs (23 million lines of FDA data published) [1]
- Health authorities are moving away from animal testing [2,3,4,5]

[1] Tidswell, EC. 2023. A Nontrivial Analysis of Patient Safety Risk from Parenteral Drug- and Medical Device-Borne Endotoxin. DOI: 10.1007/s40268-023-00412-y
[2] EDQM press release "European Pharmacopoeia to put an end to the rabbit pyrogen test" (2021). link
[3] EDQM "Strategy for removing or replacing the rabbit pyrogen test: New pyrogenicity strategy of the European Pharmacopoeia Commission". Pharmeuropa, September 2022. Link
[4] Gwenaël Cirefice et al. The future of pyrogenicity testing: Phasing out the rabbit pyrogen test. A meeting report. Biologicals, Volume 84, November 2023, 101702, link
[5] EDQM press release "Ph. Eur. bids adieu to rabbit pyrogen test in its monographs" (2024). link

Acknowledgements

Thank you for your attention

Thanks to the Roche cross functional teams that are actively working on Low Endotoxin Recovery

Doing now what patients need next