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Handling of Microbiological OOS/OOL

Endotoxin and Pyrogen Testing

Düsseldorf/Neuss, Germany
19-20 November 2014

SPEAKERS

PETER BRÜGGER
Novartis Pharma

EMMANUELLE CHARTON, PH.D.
EDQM

DR ORLA CLOAK
Lonza

PETER CORNELIS
Toxikon

MICHAEL E. DAWSON, PH.D.
Associates of Cape Cod, Inc., USA

DR SVEN M. DEUTSCHMANN
Roche Diagnostics

DR WOLFGANG EDER
Roche Diagnostics

DR ANJA FRITSCH
Confarma

DR KATHARINA HALBIG
Labor L+S

FOSTER JORDAN
Charles River Laboratories

DR BETTINA LAUER
Vetter Pharma-Fertigung

DR ROBERT MELLO
FDA

DR DANIEL MÜLLER
Regierungspräsidium Tübingen

JOHANNES REICH
University Regensburg

DR MICHAEL RIETH
Merck Millipore

DR MAXIMILIAN SCHLICHT
Labor L+S

DR INGO SPREITZER
German Federal Institute for Vaccines and Biomedicines, PEI

DR FRIEDRICH VON WINTZINGERODE
Roche Diagnostics

HIGHLIGHTS:

- Handling of Microbiological OOS/OOL
  - Microbiological 'deviations' – regulatory expectations & experience
  - OOS on Sterility Testing
  - Water testing
  - Monitoring Deviations
  - Identification – First Step on Root Cause Analysis
- Endotoxin and Pyrogen Testing
  - Pharmacopoeial Developments
  - Development of Methods
  - Masking
  - Testing of Critical Substances
  - Low Endotoxin Recovery
  - MAT
  - OOS Handling

Handling of Microbiological OOS/OOL

Objectives

This conference will show the regulatory background as well as practical guidance for a scientific and systematic way to go for microbiological deviations. Experienced experts will give you guidance on how to handle deviations in the different fields of microbiological QC.

Background

Until today the non-compliant handling of OOS is one of the most common deviations in FDA's "483er" and Warning Letters independent of the different guidelines and recommendations for the handling of OOS results.

The FDA-"Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories" pointed out, that during FDA Inspections Re-Test Results should be assessed and verified with a special particularity. Especially the rationale for the re-testing should be challenged. Unfortunately, the FDA Guidance for Industry "Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production" addressed more the handling of classical analytical OOS and provides not really help for the handling of microbial deviations.

On the contrary to the chemical/physical tests in the within the quality control, microbial OOS result in special questions and challenges like the constrained recovery, effects of stressed microorganisms, influence of the used nutrient media inhomogeneous distribution of the microorganisms and so on. Following, a comprehensive and root cause analysis and risk assessment is extremely important, including the necessary documentation.

Furthermore basic definitions are important. What are "Out-of-Specification", what are "Out-of-Limit" and what are "Out-of-Expectation" results and what are the necessary approaches and strategies to handle such results according to regulatory requirements.

Target Audience

This conference is of interest to professionals in microbiology who are involved in

- Root cause analysis of microbial OOS and OOL
- Risk assessment of microbial deviations
- Determination of CAPA
- Communication and tracing of microbiological contract laboratories

Moderator

Dr Wolfgang Eder, *Roche Diagnostics*
Dr Bettina Lauer, *Vetter Pharma-Fertigung*

Social Event

On the evening of the first congress day, on 19 November 2014, all congress delegates and speakers are invited to a „Get together" in the Congress Center. Take advantage of this opportunity for an information exchange and enjoy the laid-back atmosphere and the entertainment programme.

Speakers

DR WOLFGANG EDER, *Roche Diagnostics GmbH , Penzberg, Germany*
Manager Quality Control.

DR KATHARINA HALBIG, *Labor L+S AG, Bad Bocklett, Germnany*
Divison Head, Microbiological Testing of Sterile Products.

DR BETTINA LAUER, *Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany*
Manager Quality Control Microbiology.

DR DANIEL MÜLLER, *Regional Authority in Tübingen, Baden-Württemberg, Germany*
GMP-Inspector.

DR MICHAEL RIETH, *Merck Millipore, Darmstadt, Germany*
Global Regulatory Management Biological Materials.

Programme

Microbiological 'deviations' - regulatory expectations & experience

- Regulatory framework for pharmaceutical industry
  - Europe and Germany
  - Regulations, pharmacopeias, guidelines
  - State of the art documents
- GMP-expectations regarding
  - Proper workflow in case of OOS/deviation
  - Immediate action, root cause analysis, CAPA
  - Documentation work
  - Environmental monitoring, media fills
  - Drup substance- and drug product testing
- Tasks of QA, production and quality control department
- Experience from GMP-inspections

DR DANIEL MÜLLER, *Regional Authority, Tübingen, Germany*

OOS in microbial count determination

- Fishbone diagram
- Contamination of the sample during sample drawing / transport
- Laboratory contamination
- Preventive actions in the lab, monitoring
- Examples

DR MICHAEL RIETH, *Merck Millipore*

Pharmaceutical Water Qualities – Handling of OOS/OOL Results

- Definition of OOS and OOL
- Regulatory requirements
- Assessment and root cause analysis
- Alert levels and trending

DR WOLFGANG EDER, *Roche Diagnostics*

How to handle Monitoring Deviations

DR BETTINA LAUER, *Vetter Pharma-Fertigung*

OOS on Sterility testing

- Regulatory Requirements
- Immediate Measures and Root Cause Analysis
- Deviation Report
- CAPA
- Case studies

DR BETTINA LAUER, *Vetter Pharma-Fertigung*

Positive Sterility Testing – OOS or secondary Contamination

DR KATHARINA HALBIG, *Labor L+S*

Microbial Identification – An important part of an OOS Root Cause Analysis

- Identification as piece of an OOS root cause analysis
- Bacterial species concept
- Microbial diversity
- Identification strategy for pharmaceutical manufacturing
- Identification concepts

DR WOLFGANG EDER, *Roche Diagnostics*

Endotoxin and Pyrogen Testing

Objectives

This Conference will inform you about current developments in Endotoxin and Pyrogen testing as well as the practical use of established test methods like LAL for Endotoxin testing.

You will become familiar with
- International regulatory requirements
- Feasibility of new and innovative products and methods.
- Special issues like masking or testing of critical substances
- Testing of packaging materials
- Application of alternative pyrogen testing methods esp. MAT

Background

Testing for Endotoxins and Pyrogens is a critical in-process and final release test for parenteral products. Today, different methods like RPT, LAL, MAT are available on the market and the choice of solutions offered by suppliers for endotoxin testing becomes wider (e.g. recombinant factor C, ELISA-based test kits, automated LAL cartridge technology). To get the right choice of methodology, depending on the medicinal product, requires in-depth knowledge and expertise in the field of Endotoxins and Pyrogens.

Currently the discussions on low endotoxin recovery and endotoxin masking are especially in the focus of authorities and industry and will be one of the main topics of the conference.

Target Audience

This Conference addresses all persons from
- pharmaceutical manufacturers
- biopharmaceutical companies
- contract laboratories
- tissue establishments

who are involved in Endotoxin- and Pyrogen Testing.

Moderator

Dr Friedrich von Wintzingerode, *Roche Diagnostics*

Speakers

PETER BRÜGGER, *Novartis Pharma AG, Basel*
QC Expert Biological Analytics.

EMMANUELLE CHARTON, PH. D. , *European Directorate for the Quality of Medicines and HealthCare (EDQM)*
Deputy Head, European Pharmacopoeia Department.

DR ORLA CLOAK, *Lonza, USA*
Microbiologist and Commercial Development Manager.

PETER CORNELIS, *Toxikon Europe NV, Leuven, Belgium*
Department Supervisor Microbiology & In Vitro Toxicology.

MICHAEL E. DAWSON, PH.D., *RAC, Associates of Cape Cod, Inc.*
Director of Regulatory Affairs at Associates of Cape Cod, Inc. (ACC).

DR SVEN M. DEUTSCHMANN, *Roche Diagnostics GmbH, Germany*
Director of the Micro- and Cellbiology QC Department in the Pharma Division.

DR ANJA FRITSCH, *Confarma France SARL*
Head of Pharmacology / Toxicology / Cell Biology.

FOSTER JORDAN, *Charles River Laboratories, USA*
Corp. Senior Vice President, Charles River Endotoxin and Microbial Detection.

ROBERT J. MELLO, PH.D., *Office of Pharmaceutical Science/CDER, US Food and Drug Administration*
Senior Microbiology Reviewer , New Drug Microbiology Staff.

JOHANNES REICH, *University Regensburg, Germany*
PhD Student with focus on the aggregartion and interaction of Lipopolysaccharides as well as the related activities in limulus based detection systems.

DR MAXIMILLIAN SCHLICHT, *Labor L+S AG, Germany*
Head of Divison Sterile Products Testing.

DR INGO SPREITZER, *Paul-Ehrlich-Institut,German Agency for Vaccines and Biomedicines, Langen, Germany*
Deputy Section of Microbial Safety.

DR FRIEDRICH VON WINTZINGERODE, *Roche Diagnostics Gmbh Penzberg, Germany*
Group Leader Microbiological IPC and Analytics for Release.

DR MICHAEL RIETH, *Merck Millipore, Darmstadt, Germany*
Global Regulatory Management Biological Materials.

Programme

An update on current European Pharmacopoeia activities in the field of bacterial endotoxin, pyrogen and monocyte activation tests

- Update on the European Pharmacopoeia regulatory framework
- Ph. Eur. general chapters associated with bacterial endotoxin, pyrogen and monocyte activation tests and general overview of ongoing revisions
- Reference to bacterial endotoxins, pyrogens and monocyte activation tests in individual monograph

DR EMMANUELLE CHARTON, *EDQM*

Revision of Ph. Eur.-Chapter 5.1.10 'Guideline for Using the Test for Bacterial Endotoxins'

DR SVEN M. DEUTSCHMANN, *Roche Diagnostics*

Current Pharmacopoieal Developments on MAT

DR INGO SPREITZER, *Paul-Ehrlich-Institut*

Cryopreservation of human PBMC for pharmacopeial MAT

PETER BRÜGGER, *Novartis Pharma*

Detection and quantification of pyrogens by monocyte activation test

- Description of the test based on the cell line Mono Mac 6
- Practical experiences with the monocyte activation test in difficult matrices
- Interference between pyrogens

DR ANJA FRITSCH, *Confarma*

Alternative recombinant Factor C Method for Endotoxin Detection

- Outline of the Method Basis
- Validation of an Alternative rFC Method
- Supportive Data
- Regulatory Requirements & considerations
- Applications and Comparison with LAL

DR ORLA CLOAK, *Lonza*

Low Endotoxin Recovery (LER) – an FDA Reviewer's Perspective

- Background --Relevant Items from the 2012 LAL Q&A
- Agency concerns -- Safety
- Review Issues related to
  - Process Purity
  - Assay
  - Impact on Product Approvals

DR ROBERT MELLO, *FDA*

The Journey of Endotoxin Testing – Past, Present, Future

- LAL History and Efficacy as a Bacterial Endotoxin Test
- Current Topics within the BET Industry
- What Does BET Look Like in the Lab of Tomorrow?

FOSTER JORDAN,*Charles River Laboratories*

Low Endotoxin Recovery (LER): Assuring the Validity of Endotoxin Test Results

- Defining Low Endotoxin Recovery- What is it and What is it not
- Regulatory Aspects of LER
- LER and the Pharmacopoeial Endotoxin tests
- LER for stored samples
- Strategies for Addressing LER, incl. the Use of Native Endotoxin

DR MICHAEL DAWSON, *Associates of Cape Cod*

A comparative study of Pyrogen detection assays and the effect on Endotoxin Masking and Inhibition or Enhancement

- Inhibition or enhancement of the test enzyme
- False positive results
- Effect of using alternative methods to overcome these issues

PETER CORNELIS, *Toxikon Europe*

Endotoxin Masking

- Roche definition of Low Endotoxin Recovery (LER) and Endotoxin Masking (EM)
- LER-Task Force and Endotoxin Task Force at Roche
- Endotoxin hold time studies and LER and EM examples

DR FRIEDRICH VON WINTZINGERODE, *Roche Diagnostics*

De-Masking techniques for endotoxin detection in bio-pharmaceuticals

- Endotoxin testing
- Sample vs. Test Interference
- Masking Kinetics in Biopharmaceutical Formulations
- Mechanism of Masking
- Spike Comparison: Reference Standard Endotoxin vs. Naturally Occuring Endotoxin
- De-Masking

JOHANNES REICH, *University Regensburg*

OOS in endotoxin determination

- Fishbone diagram
- Contamination of the sample during sample drawing / transport
- controls during the test procedure
- Laboratory contamination
- false-negative results (masking and low endotoxin recovery)
- false-positive results (interference by glucans)
- inhomogenous distribution of endotoxins
- examples

DR MICHAEL RIETH, *Merck Millipore*

Image: Labor L+S

Sample Preparation for LAL Test on Oily Formulation

- Bacterial Endotoxin Testing with Turbidimetric-Kinetic Method
- Recovery of „spiked Endotoxins
- Extraction of Endotoxins from Oily Substances
- Testing of Water in Oil Emulsions

DR MAXIMILIAN SCHLICHT, *Labor L+S*

Agenda

Time	Handling of Microbiological OOS/OOL Wednesday, 19 November 2014	Endotoxin and Pyrogen Testing Wednesday, 19 November & Thursday, 20 November 2014		Time
9.00 h	Welcome and Introduction	Welcome and Introduction		9.00 h
9:15 h 9.30 h 9:45 h	Microbiological 'deviations' - regulatory expectations & experience *Dr Daniel Müller, Regional Authority, Tübingen, Germany*	An update on current European Pharmacopoeia activities in the field of bacterial endotoxin, pyrogen and monocyte activation tests *Dr Emmanuelle Charton, EDQM* Revision of Ph. Eur.-Chapter 5.1.10 'Guideline for Using the Test for Bacterial Endotoxins' *Dr Sven M. Deutschmann, Roche Diagnostics*	Low Endotoxin Recovery (LER): Assuring the Validity of Endotoxin Test Results *Dr Michael Dawson, Associates of Cape Cod, Inc.*	9:15 h 9.30 h 9:45 h
10.00 h 10:15 h 10.30 h	OOS in microbial count determination *Dr Michael Rieth, Merck Millipore*	Current Pharmacopoieal Developments on MAT *Dr Ingo Spreitzer, Paul-Ehrlich Institut*	A comparative study of Pyrogen detection assays and the effect on Endotoxin Masking and Inhibition or Enhancement *Peter Cornelis, Toxikon Europe*	10.00 h 10:15 h 10.30 h
10:45 h 11.00 h 11:15 h	Break *(Take advantage of the break to visit the exhibition)*	Break *(Take advantage of the break to visit the exhibition)*		10:45 h 11.00 h 11:15 h
11.30 h 11:45 h 12.00 h	Pharmaceutical Water Qualities – Handling of OOS/OOL Results *Dr Wolfgang Eder, Roche Diagnostics*	Cryopreservation of human PBMC for MAT *Peter Brügger, Novartis Pharma*	Endotoxin Masking *Dr Friedrich v. Wintzingerode, Roche Diagnostics*	11.30 h 11:45 h 12.00 h
12:15 h 12.30 h 12:45 h	How to handle Monitoring Deviations *Dr Bettina Lauer, Vetter Pharma-Fertigung*	Detection and quantification of pyrogens by monocyte ac-tivation test *Dr Anja Fritsch,Confarma*	De-Masking techniques for endotoxin detection in bio-pharmaceuticals *Johannes Reich, University Regensburg*	12:15 h 12.30 h 12:45 h
13.00 h 13:15 h 13.30 h 13:45 h 14.00 h 14:15 h	Lunch Break *(Take advantage of the break to visit the exhibition)*	Lunch Break *(Take advantage of the break to visit the exhibition)*		13.00 h 13:15 h 13.30 h 13:45 h 14.00 h 14:15 h
14.30 h 14:45 h 15.00 h	OOS on Sterility testing *Dr Bettina Lauer, Vetter Pharma-Fertigung*	Alternative recombinant Factor C Method for Endotoxin Detection *Dr Orla Cloak, Lonza*	OOS in endotoxin determination *Dr Michael Rieth, Merck Millipore*	14.30 h 14:45 h 15.00 h
15:15 h 15.30 h 15:45 h	Positive Sterility Testing – OOS or secondary Contamination *Dr Katharina Halbig,Labor L+S*	Low Endotoxin Recovery (LER) – an FDA Reviewer's Perspective *Dr Robert Mello, FDA*	Break *(Take advantage of the break to visit the exhibition)*	15:15 h 15.30 h 15:45 h
16.00 h 16:15 h 16.30 h	Break *(Take advantage of the break to visit the exhibition)*	Break *(Take advantage of the break to visit the exhibition)*	Sample Preparation for LAL Test on Oily Formulation *Dr Maximilian Schlicht, Labor L+S*	16.00 h 16:15 h 16.30 h
16:45 h 17.00 h 17:15 h	Microbial Identification – An important part of an OOS Root Cause Analysis *Dr Wolfgang Eder, Roche Diagnostics*	The Journey of Endotoxin Testing – Past, Present, Future *Foster Jordan, Charles River Laboratories*	Final Discussion	16:45 h 17.00 h 17:15 h
17.30 h 17:45 h 18:00 h	Discussion	Discussion		17.30 h 17:45 h 18:00 h
18.30 h	Social Event for Congress Delegates, Speakers and Exhibitors			18.30 h

Easy Registration

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Dates
Wednesday, 19 November, 09.00 – 18.00 h
Thursday, 20 November 2013, 09.00 – 17.30 h
(Registration Tuesday, 18 November, 19.00 – 20.30 h and
Wednesday, 19 November/Thursday, 20 November 08.00 – 09.00 h)

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Fees
EUR 690,- for one day plus VAT
EUR 1.380,- for two days plus VAT

The conference fee is payable in advance after receipt of invoice and includes lunch on that day as well as beverages during the event and during breaks. It also includes the Social Event on the evening of the first congress day (19 November 2014) VAT is reclaimable.

Your registration also entitles you to participate in all other PharmaLab Congress conferences during the day of your conference/during the two days. For further information please visit www.pharmalab-congress.com.

Registration
Via the attached reservation form, by e-mail or by fax message. Or you register online at www.pharmalab-congress.com

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Please note that there will **not be any print-outs** at the Congress. Instead you will receive all presentations prior to the Congress as Downloads. All Congress delegates (excluding exhibition visitors) will also receive the presentations on a USB stick at the registration center.

Please further note that there will be no room reservations via Concept Heidelberg. Please book your **hotel room directly with the reservation form** which you will receive together with your confirmation/invoice! Charges are payable after receipt of the invoice.

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I would like to attend the following conference:
☐ **Handling of Microbiological OOS/OOL** (19 November 2014)
☐ **Endotoxin and Pyrogen Testing** (19-20 November 2014)
Part of PharmaLab 2014, Düsseldorf/Neuss, Germany, 19-20 November 2014
☐ 2-Days Ticket for entire PharmaLab Congress (19-20 November 2014)

☐ Yes, I would like to participate in the Social Event on 19 November.
☐ Mr ☐ Ms

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