



**Future of Endotoxins and
Pyrogen Testing: Reference
Standards and Procedures**

June 10-11 • Rockville, MD

**Speaker Biographies & Abstracts
(listed alphabetically)**

Future of Endotoxins and Pyrogen Testing: Reference Standards and Procedures

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Jay Bolden

Senior Consultant Biologist
Eli Lilly and Co.
Indianapolis, IN

Mr. Jay Bolden is a Senior Consultant Biologist in the Eli Lilly and Company Global Quality Laboratories. He is an internal endotoxin subject matter expert and leads a team with global QC oversight for developing, validating, transferring and troubleshooting endotoxin, microbiology, QPCR and ELISA methodologies. Jay holds a B.S. in Biology and an Environmental Studies certificate from Indiana University, and has over 18 years of industry experience in development, process and laboratory microbiology, and microbiology laboratory leadership.

Presentation

Recombinant Factor C: Progressive Endotoxin Detection One Year In

Monday, June 10, 2019, 2:45 – 3:05 p.m.

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Gwenaël Ciréface, PharmD

Scientific Officer

European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
Strasbourg, Alsace, France

Gwenaël Ciréface is a Scientific Programme Manager at the European Directorate for the Quality of Medicines and HealthCare (EDQM).

Dr. Ciréface is responsible for the Ph. Eur. group of experts 15 elaborating monographs on vaccines for human use and supports expert group 6 on biological substances and the working party on host-cell protein assays, recently taking over the working party on bacterial endotoxin and pyrogen testing.

He holds a Doctorate in Pharmacy from the University of Strasbourg, France.

Dr. Ciréface joined the vaccine industry in 2007 as a regulatory affairs manager before joining the Quality of Medicines department of the European Medicines Agency in 2010, with responsibilities in the field of human vaccines and recombinant proteins.

He joined the European Pharmacopoeia department of the EDQM in May 2014.

Presentation

European Pharmacopoeia (Ph. Eur.) Perspectives

Monday, June 10, 2019, 9:00 – 9:15 a.m.

The European Pharmacopoeia (Ph. Eur.) sets up quality standards for medicinal products and their constituents that are legally binding in Europe and accepted in countries from all over the world. It has always been committed to adapting to a fast-developing environment, keeping pace with the advancement of scientific technologies and taking care of regulatory needs. The presentation will discuss the latest developments in the field of pyrogen and endotoxin testing at the Ph. Eur., including improvements to the general chapter on *Monocyte-Activation Test* (2.6.30) and the replacement of the Rabbit Pyrogen Test, and the draft general chapter on *Test for bacterial endotoxins using recombinant Factor C* (2.6.32) which recently underwent public consultation.

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John Dubczak

General Manager, Microbial Solutions
Charles River Laboratories
Charleston, SC

John Dubczak is the General Manager for the Microbial Solutions division of Charles River Laboratories. For the last 20 years, he has been responsible for the production and technical operations for the Endosafe® brand of Microbial Solutions in Charleston, SC. Prior to joining Charles River, John was a long-term employee of Baxter Healthcare Corp., where he developed Baxter's proprietary LAL formulation and manufacturing process. As a member of the R&D team, he also developed methods for product testing and explored the clinical applications of LAL. With seven years of Large Volume Parenteral manufacturing experience, he brings an in-depth understanding of issues surrounding all aspects of microbiological testing.

Presentation

Well Characterized Naturally Occurring Endotoxin Standards

Monday, June 10, 2019, 10:50 – 11:10 a.m.

All laboratories conducting the Bacterial Endotoxin Test (BET) use a highly purified lipopolysaccharide (LPS) as a standard. The LPS standards most commonly used are the primary Reference Standard Endotoxin (RSE), supplied by USP, or a secondary Control Standard Endotoxin (CSE) that is calibrated to specific lot of LAL and provided by LAL manufacturers. These LPS standards are used to prepare endotoxin dilution series in both the gel clot and quantitative LAL methods. They are also a source for the Positive Product Control (PPC) that assures the validity of each LAL test. While they serve as a vital laboratory standard, they do not reflect the endotoxin that is measured in contaminated pharmaceutical test samples (WFI, process streams, or finished product). Contaminating LPS is shed from propagating bacteria in the form of outer membrane vesicles. Given the operational complexity of modern biopharmaceutical manufacturing and given the regulatory expectations to fully understand the endotoxin risks associated with those operations, the question arises as to what type of bacterial endotoxin to use; a highly purified LPS or a well characterized natural occurring endotoxin (NOE)? This presentation describes the chemistry and biological activity of a well characterized NOE. It highlights the benefits of an NOE when used to validate BET methods. This presentation also demonstrates the use of NOEs in the study of devices in contact with plasma containing endotoxin. A well characterized NOE represents a vital tool for pharmaceutical scientists investigating bacterial endotoxins that will most likely be encountered in a variety of manufacturing and clinical settings.

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Thomas Hartung, MD, Ph.D.

Professor, Evidence Based Toxicology
The Johns Hopkins University
Baltimore, MD

Thomas Hartung, MD PhD, is the Doerenkamp-Zbinden-Chair for Evidence-based Toxicology with a joint appointment for Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore. He holds a joint appointment as Professor for Pharmacology and Toxicology at University of Konstanz, Germany; he also is Director of Centers for Alternatives to Animal Testing (CAAT, <http://caat.jhsph.edu>) of both universities with the portal AltWeb (<http://altweb.jhsph.edu>). CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration (<http://www.ebtox.com>), the Good Read-Across Practice Collaboration, the Good Cell Culture Practice Collaboration, the Green Toxicology Collaboration, and the Industry Refinement Working Group. As PI, he heads the Human Toxome project (<http://humantoxome.com>), funded as an NIH Transformative Research Grant. He is the former Head of the European Commission's Center for the Validation of Alternative Methods (ECVAM), Ispra, Italy, and has authored more than 490 scientific publications.

Presentation

Non-Endotoxin Reference Materials for The Monocyte Activation Test (MAT)

Tuesday, June 11, 2019, 9:05 – 9:45 a.m.

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David Hussong, Ph.D.

Chair, USP General Chapters- Microbiology Expert Committee

Chief Technical Officer
Eagle Analytical Services
Kensington, MD

David Hussong is the Chief Technical Officer at Eagle Analytical Services (Houston, TX), and is the current the chair of the USP Microbiology Expert Committee for the 2015– 2020 cycle and has been active with USP for 20-years. David was a regulatory microbiology consultant (2015 – 2017) with ValSource LLC. David is a retired officer of the Commissioned Corps of the US Public Health Service and a 30-year veteran of the Food and Drug Administration (FDA), where he had served in many microbiology positions, culminating as the Associate Director for New Drug Microbiology in the Office of Pharmaceutical Science. David also previously was a research microbiologist at the US Department of Agriculture and the US Naval Medical Research Institute.

David earned a Ph.D. in microbiology from the University of Maryland, where he studied environmental microbiology and *Legionella* spp.

Presentations

USP Perspectives

Monday, June 10, 2019, 8:45 – 9:00 a.m.

Febrile responses by patients have been observed since medical observations of the infection process as far back as the 6th century BC. The general fever response was considered the result of pyrogens, and a subset of these pyrogens were from gram-negative bacteria. A great deal of interest evolved as studies of gram-negative bacteria were found to induce a variety of responses in patients exposed to portions of their cell walls. In 1923, studies by Siebert established the rabbit as the preferred model for pyrogens detection. Further studies showed this response was the same as those reactions following injections of drugs into patients. Concern about fever induction from injectable drugs was sufficiently established that the USP included a test for pyrogens in its 12 revision in 1942. This was the rabbit pyrogenicity test (RPT). The RPT test method was a resource challenge. It required an animal facility and special environmental controls. The animal test had complications related to biological influences that interfered with robustness, sensitivity and reproducibility.

In 1969 Greisman and Hornick reported confirmatory studies on the effect of endotoxins from different species of bacteria on humans and rabbits, confirming quantitative correlation between reactivity in man and rabbits, as well as differing degrees of reactivity between endotoxins from Gram-negative bacterial species. However, they noted that febrile responses to endotoxins total doses in man exceeded the rise in fever response of rabbits. The U.S. Food and Drug Administration (FDA) has established regulations relating to testing for possible pyrogenicity of drug products, and had provided guidance relating to the use of the LAL assay as an indicator of pyrogenicity in lieu of the rabbit pyrogenicity test. The United States Pharmacopeia (USP) harmonized Chapter <85> Bacterial Endotoxins Test describes the procedures for performing Limulus Amebocyte Lysate (LAL) assays for the detection of endotoxins in pharmaceutical products.

Compendial harmonization of the Japanese Pharmacopeia, European Pharmacopeia, and USP allowed the FDA to update its 1985 guidance for the use of the LAL. These updates



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were reflected in the withdrawal of the 1987 FDA guidance and publication in 2012 of a question and answer (Q&A) document intended to explain how to use the LAL assay for product release, and process development and control.

While the LAL assay remains the most commonly used test for pyrogenic substances, it too has limitations. It also has great advantages in its abilities for application to process control testing. This workshop will review the development and evolution of the LAL assay, its uses, limitations and new technologies that have emerged as candidates for alternative test methods.

Summary and Conclusions

Tuesday, June 11, 2019, 12:15 – 12:30 p.m.

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Karen Zink McCullough

Member, USP General Chapters- Microbiology Expert Committee

MMI Associates
Principal Consultant
Whitehouse Station, NJ

Karen Zink McCullough is owner and principal consultant at MMI Associates. She has served in a number of positions in pharma, medical device and cell/gene industries including Director of Microbiology, Sr. Director of Quality Compliance, Quality Site Head and Vice President of Quality Operations. Karen has been involved with LAL testing for a “very long” time, and is a frequent author and presenter on the topic. She is the founder of the LAL Users Group. She has served on the USP Expert Committee Microbiology General Chapters since 2010 and is a representative to ISO 14648 standard on Biocontamination. She received her BA in Bacteriology from Rutgers University and MS in Molecular Biology from the University of Oregon.

Presentation

Current Bacterial Endotoxins Test (BET) and its Intended Use

Monday, June 10, 2019, 9:30 – 9:50 a.m.

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Ned Mozier, Ph.D.

Chair, USP JS3 – Biologics Expert Committee

Vice President, PPM, Biotherapeutics Pharmaceutical Sciences
Pfizer
Saint Charles, MO

Ned Mozier is Vice President of Portfolio and Project Management in Pfizer's Research and Development organization within the division of Biotherapeutics Pharmaceutical Sciences. He chairs Pfizer's Impurity Council. Pfizer has a diverse development portfolio including monoclonal antibodies, conjugates, therapeutic proteins, gene therapies and vaccines. Ned previously led the Bioassay and Impurity Testing group in Pfizer. He has also worked at Pharmacia, Baxter and The Upjohn Company. He received his Ph.D. in Biochemistry from the University of Louisville.

Presentation

User Experience with MAT

Tuesday, June 11, 2019, 9:45 – 10:15 a.m.

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Terry Munson

Technical Vice-President (Retired)
Parexel Consulting
Fairfax, VA

Mr. Munson retired from Parexel International in 2018 where he was a Technical Vice President. He focuses on sterile drug manufacturing, API manufacturing, facility design, utilities and assistance with responses to FDA inspection and regulatory actions. He joined Parexel in 1994 after 24 years with the FDA, where he held the positions of Chief of the Sterile Drug Branch, Office of Compliance/Center for Drug Evaluation and Research (CDER) from 1988 to 1994, Consumer Safety Officer in OC/CDER from 1977 to 1988 and Microbiologist in the New York Regional Laboratory from 1970 to 1977. Mr. Munson was Chairperson of the FDA LAL Task Force and responsible for maintenance of the 1987 FDA LAL Guideline.

Mr. Munson received his B.S. in Microbiology from Colorado State University located in Fort Collins, Colorado.

Mr. Munson was a member of the United States Pharmacopeia (USP) Committee of Experts from 1990 to 2005, serving on the Microbiology subcommittee and Home and Hospital Parenterals Subcommittee and later on the Analytical Microbiology Committee.

He was also a U.S. Delegate to ISO Technical Committee 209, Cleanroom and Controlled Environments, Workgroup 2 Biocontamination in Cleanrooms and Workgroup 8 Condensable Chemical Contamination.

Mr. Munson has served as a member of the Board of Director of the Parenteral Drug Association from 1994 to 2000.

Presentation

Current USP Endotoxin Reference Standard: Evolution and Intended Use

Monday, June 10, 2019, 9:50 – 10:10 a.m.

FDA in the early 70's commissioned the production of a bulk endotoxin lot. They received 31 grams of purified E. coli O113:H10:K negative endotoxin. Three USP reference Standard Endotoxin lots have been produced from this bulk purified endotoxin bulk. The current lot is Lot H (CBER lot EC6). The intent of the reference was to provide a reference point for the determination of Lysate sensitivity and calibration of control endotoxin standard preparations. It should be used to determine the sensitivity of any test for endotoxins. It can be used for the endotoxin test using recombinant reagents and the MAT test. It can also be used to calibrate a naturally occurring endotoxin preparation for the LER studies.

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Yukari Nakagawa, Ph.D.

Director, Department of Reference Standards
Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ)
Osaka, Japan

Dr. Nakagawa has worked for Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ) over 10 years. The PMRJ is registered by the Ministry of Health, Labour and Welfare as the JP reference standards producer, then she is responsible for producing and distributing the Japanese Pharmacopoeia (JP) Reference Standards at the Osaka office. Regarding activities relevant to the JP, she is a member of the expert committee on biological methods and the expert committee on biologicals. Prior to her arrival at the PMRJ, she worked for the National Institute of Health Sciences (NIHS) for ten years. During at the NIHS, she was in charge of biological tests such as bacterial endotoxins test and pyrogen testing and was involved in developing an in vitro pyrogen test. She received a PhD in pharmaceutical sciences from Kyoto university in 2003 and majored in biochemistry at the university.

Presentation

JP Perspectives: Evaluation of endotoxin assay method using recombinant protein-reagents and future directions in the JP

Monday, June 10, 2019, 9:15 – 9:30 a.m.

The bacterial endotoxins test (BET) <4.01> in the Japanese Pharmacopoeia (JP), which is harmonized with the United States Pharmacopeia and the European Pharmacopoeia, is an in vitro test using lysate reagents to detect endotoxin contamination in pharmaceuticals with high sensitivity. Recently a recombinant factor C-based procedure for detection of endotoxin has been developed as an alternative method to the BET. This presentation will describe our collaborative study to evaluate recombinant protein-reagents for endotoxin assay (recombinant reagents) and future directions in the JP.

In Japan, three kinds of reagents constituted of recombinant protein(s) are available. Two reagents are recombinant factor C-based reagents which measure endotoxins by an endpoint-fluorometric method; PyroGene™ rFC (Lonza Japan) and EndoZyme® II (bioMérieux/Hyglos). The other is a reagent constituted of three recombinant proteins of factor C, factor B, and proclotting enzyme by a kinetic-chromogenic method; PyroSmart® RS-50M (Seikagaku corporation).

At this point, JP's policy is that since the recombinant reagents are not lysate reagents, methods using the recombinant reagents are not applicable to the BET in the JP. The JP states in the general chapter that if the test methods specified in the JP are replaced by alternative methods, those alternative methods are required to be validated. However, in fact, these recombinant reagents have hardly been used because it has been hard for users to validate these reagents and replace the BET.

First of all, the JP expert committee on biological methods determined that the committee needed objective third-party data to discuss the possibility of replacing the BET. Therefore, members relevant to the JP organized a workgroup to conduct a collaborative study on the recombinant reagents. This study conducted a comparative evaluation of those recombinant reagents and 3 kinds of lysate reagents. The results showed that the reactivities of those recombinant reagents to the endotoxin panel, and basic quality and performance of those reagents, were almost identical to those of the lysate reagents.

The JP expert committee is now discussing that a new chapter about the BET and endotoxin assay methods using the recombinant reagents will be adopted to the General Information in



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the JP 18th edition, which is scheduled to be released in April 2021. We hope that pharmaceutical companies will try to use these new methods and validation data will increase in the future. The JP expert committee intend to continue to discuss replacing the BET with endotoxin assay methods using the recombinant reagents, adopting to the General Method and harmonizing with the USP and the EP on the next stage.

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Edward Tidswell, Ph.D.

Member, USP General Chapters- Microbiology Expert Committee

Executive Director, Sterile QA
Merck and Co.
Chicago, IL

Edward C. Tidswell is Executive Director within the Sterile and Microbiology QA organization of Merck. In this role, he oversees microbiology issues across sterile and non-sterile sites within the Global Manufacturing Division. Previously, Dr. Tidswell held leadership roles supporting and innovating across large and small volume parenteral, medical device and bulk active pharmaceutical ingredient manufacturing and testing platforms for Baxter Healthcare, Eli Lilly and Evans Vaccines. He is an active author and served on PDA's Scientific Advisory Board and, since 2010, also serves on the USP expert committee on Microbiology and Sterility Assurance.

Presentation

Need for Alternate / Additional Endotoxin Reference Standard

Monday, June 10, 2019, 10:30 – 10:50 a.m.

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Radhakrishna Tirumalai, Ph.D.

Principal Scientific Liaison, Science-General Chapters
USP
Rockville, MD

Dr. Tirumalai has been at the USP since 2003 and is currently a Principal Scientific Liaison-General Chapters in the Science Division. He is the Liaison to the USP Expert Committee on Microbiology. He works with the industry, regulatory agencies and other external science based organizations in the development and revision of General Chapters. Dr. Tirumalai represents USP on PDA expert task forces and committees related to Microbiology and Sterility Assurance 2005-till date, the organizing committee of PDA Global Microbiology Conference 2006-till date, on AAMI expert Working groups related to Microbiology, Sterilization, Sterility Assurance and Biocompatibility 2004-till date, and on the editorial board of FDA's Pharmaceutical Microbiology Manual.

Dr. Tirumalai's prior industry experience encompasses process and product research and development, transfer, and product manufacturing. He has a Ph.D. degree in Biochemistry. He has authored numerous publications, review articles and several book chapters. He has organized numerous workshops and conferences on Pharmaceutical Microbiology topics and is a frequent speaker at conferences and has taught Pharmacopeial Microbiology courses at numerous locations globally.

Presentations

Wrap-Up, Day One

Monday, June 10, 2019, 5:15 – 5:30 p.m.

Follow up from Day One

Tuesday, June 11, 2019, 8:30 – 8:45 a.m.

Summary and Conclusions

Tuesday, June 11, 2019, 12:15 – 12:30 p.m.

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Jaap Venema, Ph.D.

Executive Vice President & Chief Science Officer
USP
Rockville, MD

Jaap Venema, Ph.D., is Executive Vice President and Chief Science Officer (CSO) for USP. He leads the organization's scientific strategy and is responsible for the development of quality standards for medicines, dietary supplements, food ingredients and healthcare, including collaborations with other pharmacopeia and scientific groups. Dr. Venema guides USP's exploration of emerging technologies that may inform future quality standards and oversees USP's Up-to-Date program, which continuously evaluates and revises standards to reflect current and best practice. Dr. Venema also serves as Chair of the Council of Experts, spearheading USP's work developing science-based standards. This body guides and approves the draft standards developed by USP's numerous expert committees, comprised of nearly a thousand scientific experts from academia, industry, healthcare, as well as government agencies.

Dr. Venema's more than 25 years' experience in global research and development, as well as academic research, informs his scientific leadership at USP. Dr. Venema previously served in a variety of scientific leadership positions at Solvay and AbbVie (formerly Abbott Laboratories), where he held various roles in drug discovery and development in vaccines, pain care and immunology, and developed and implemented a global scientific and medical strategy for biotherapeutics. Before his transition to industry, Dr. Venema was a post-doctoral fellow at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, and a Fellow of the Netherlands Academy of Sciences at the Free University of Amsterdam.

A native of the Netherlands, Dr. Venema earned his Master's degree in Chemistry from the Free University of Amsterdam, and his Ph.D. in Biochemistry and Molecular Biology from Leiden University in the Netherlands.

Presentation

Welcome

Monday, June 10, 2019, 8:30 – 8:45 a.m.

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Marlys Weary, BA, MS, MBA

Owner and Chief Technical Consultant
MERIT Consulting Services
Mount Prospect, IL

Marlys Weary, BA, MS, MBA is the happily retired owner and chief technical consultant of MERIT Consulting Services, Mount Prospect, Illinois. Before going into business for herself, she was both Manager of Microbiology Technical Support and Services and Senior Research Scientist for Baxter International, Inc. In that capacity, she initially both supervised and supported the company's rabbit pyrogen test program and then also assisted in developing and supporting Baxter's FDA licensed LAL test reagent and LAL test systems, which were used throughout the company's international manufacturing operations for more than 25 years. During her career, she was active in many pharmaceutical and medical device inter-industry organizations, lectured worldwide on pyrogen and endotoxin testing topics, and published numerous publications on those subjects.

Presentation

USP Rabbit Pyrogen Test –History and Current Status

Tuesday, June 11, 2019, 8:45 – 9:05 a.m.

The heavy demand for large volume parenteral (LVP) drug therapy prior to and during World War II, and the need to ensure that commercial parenteral solutions and administrative devices were free from pyrogen contamination, caused the United States Pharmacopeia (USP) to undertake the development of a compendial test for pyrogens. Following a collaborative study conducted by the FDA, the National Institutes of Health (NIH) and 14 pharmaceutical manufacturers, the first compendial Pyrogen Test <151>, commonly referred to as the USP rabbit pyrogen test, was included in the 1942 USP 12th Edition. Although the test has had refinements made to it over the years, the pyrogen test described in the current edition of USP and, in other international compendia, follows the same basic format as did the original rabbit pyrogen test.

In simple terms, the rabbit pyrogen test involves measuring the rectal temperature of rabbits both prior to and after the intravenous injection of a test solution. If the animals exhibit febrile responses that exceed established limits, the test solution is judged to be pyrogenic. Although the rabbit pyrogen test has proven to serve the industry well for many years, like most biological test systems, it has both advantages and disadvantages. The primary advantage of the test is that it best replicates and demonstrates the production of fever in humans. The test is not specific for one class of pyrogens, as is the Bacterial Endotoxins Test <85>. Instead it detects all kinds of injectable pyrogens.

On the other hand, the rabbit test has many disadvantages. It is a time-consuming, elaborate, expensive procedure that requires a large capital investment in animal housing, trained animals and skilled animal handlers and technicians. It cannot be used to test certain toxic drugs or drugs that depress fever. Tolerance to certain classes of pyrogens can develop in rabbits, and like all animal tests, the rabbit test suffers from the wide variety of responses imposed on it by biological variation.

Nevertheless, the continued use of the rabbit pyrogen test by the pharmaceutical industry is evidence of the fact that in certain cases, it is apparently the most useful pyrogen test available for specific pharmaceutical products. It therefore remains in place as one of several choices that a manufacturer can consider for determining the absence of pyrogens from their products.