Short Course: A Harmonized Strategy for the Regulatory Submission of Immunogenicity Validation Data

The ADA Validation Testing and Reporting Global Harmonization (ADAH) AAPS sub-group was formed in 2017 following the intense debate at the National Biotechnology Conference that confirmed the need for standardized expectations and templates for data summary in immunogenicity validation reports. The ADAH sub-team has 32 members, representing 30 organizations (including 5 from Europe and 6 from FDA), selected to identify the best immunogenicity reporting practices from across the industry.

By harmonizing immunogenicity reporting for regulatory submission, the ADAH sub-group hopes to:

- streamline regulatory review,
- drive industry objectives,
- provide guidance for immunogenicity method assessment, and
- publish finalized recommendations that will be accessible to the community and adopted by the industry.

This short course will provide a detailed update of current expectations for immunogenicity validations and a preview of the ADAH recommendations. Presentations and discussions will prepare workshop attendees for future regulatory submissions.

Learning Objectives:

- Gain insight on the perspectives of leaders/scientists from the FDA, Pharma, and CROs.
- Have early exposure to imminent FDA expectations for the presentation of ADA assay validation data.
- Discuss implementation strategies for the FDA Immunogenicity draft guidance (2016).
- Explore approaches to defend sponsor position during regulatory filings.
- Participate in two panel discussions, scheduled to allow for community feedback and questions and interaction with key opinion leaders.

Presentations

All presentations will be available on the workshop webpage no later than 24 hours following the workshop. Presentations will remain online for registered attendees until August 7, 2019.

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Workshop Planning Committee

Heather Myler, Ph.D., PPD
An Song, Ph.D., Genentech
Joao Pedras-Vasconcelos, Ph.D., U.S. Food and Drug Administration

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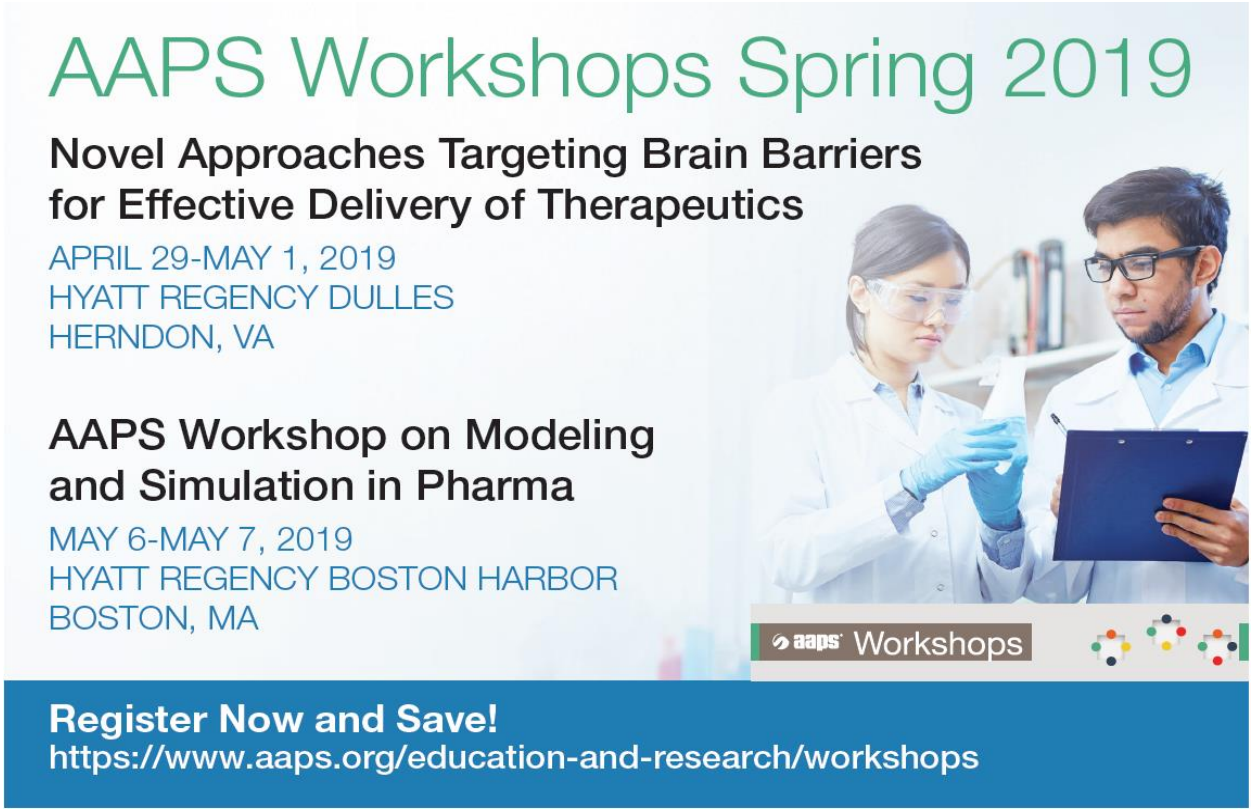

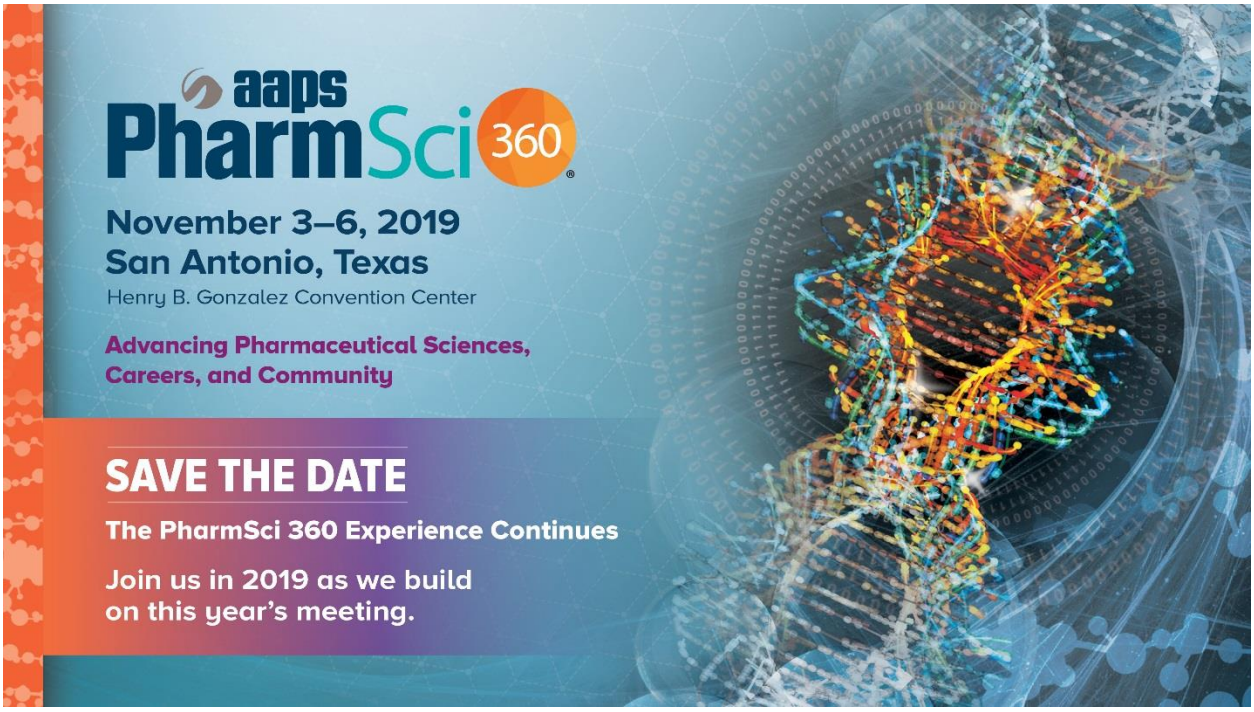

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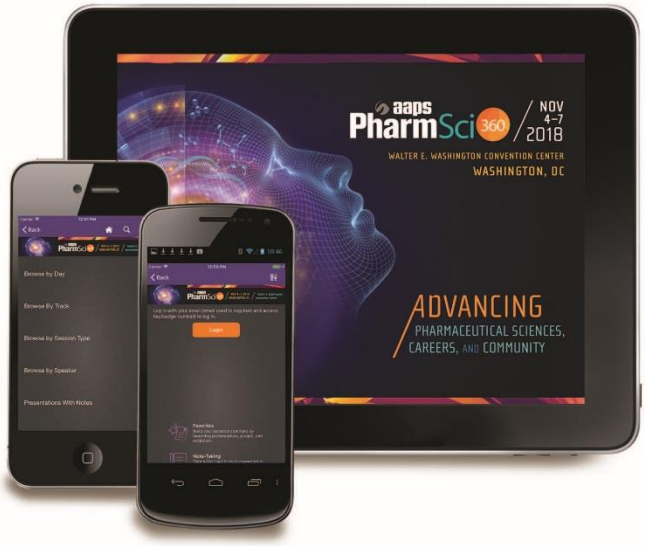

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Workshop Agenda

Sessions will take place in the Washington Convention Center, room 146 A

Saturday, November 3, 2018	
1:00 pm – 1:10 pm	**Introduction of Team and Objectives** Heather Myler, Ph.D., PPD
1:10 pm – 1:30 pm	**OBP Immunogenicity Review Challenges and Solutions** Joao Pedras-Vasconcelos, U.S. Food and Drug Administration
1:30 pm – 2:00 pm	**Cut Point Considerations** Viswanath Devanarayan, Ph.D., Charles River Laboratories
2:00 pm – 2:20 pm	**FDA Cut Point Perspective** Steven Bowen, U.S. Food and Drug Administration
2:20 pm – 2:40 pm	**Immunogenicity Studies; Recently Issued 483s** Mohsen Rajabi Abhar, Ph.D., U.S. Food and Drug Administration
2:40 pm – 3:00 pm	**Panel Discussion**
3:00 pm – 3:15 pm	Coffee and Snack Break
3:15 pm – 3:35 pm	**Defining Assay Sensitivity** Kelli Phillips, Ph.D., PPD
3:35 pm – 3:55 pm	**Defining Assay Drug Tolerance** Marta Starcevic-Manning, Ph.D., Amgen
3:55 pm – 4:15 pm	**FDA Perspective on Assay Sensitivity and Drug Tolerance** Haoheng Yan, U.S. Food and Drug Administration
4:15 pm – 4:35 pm	**Defining Assay Domain Specificity/ Selectivity** Shobha Purushothama, Biogen
4:35 pm – 4:55 pm	**MRD, Titer Reporting and Stability** Jad Zoghbi, Sanofi

Speaker Abstracts and Biographies

Introduction of Team and Objectives

This introductory session will describe the purpose of the ADAH team, most significantly to provide recommendations for the harmonization of validation data reporting in alignment with FDA/EMA expectations. We hope that this will increase clarity of communications across functions and organizations and reduce data reporting-related HA queries received during filing. Six FDA representatives have been included throughout this process as core contributors.

Heather Myler, Ph.D., PPD

Heather received her PhD in Biochemistry and Cell Biology at Rice University and completed her post-doctoral training at Pfizer in Drug Safety Evaluation, later holding positions of increasing responsibility at Amgen, Ambrx, Merck and BMS where she has contributed to the growth of the bioanalytical discipline, supporting PK, immunogenicity and biomarker bioanalysis with an expertise in biologics. Heather currently serves as the Director of R&D, Immunochemistry at PPD leading a group scientist responsible for PK, ADA and neutralizing antibody bioanalytical method development, tech transfer, validation and automation supporting biosimilars and novel biologics. Heather has a strong external science presence, currently serving as co-Leader of the Bioanalytical Community within AAPS and actively participating on multiple bioanalytical and cross-functional initiatives. Specifically, Heather is currently leading a team focused on the Harmonization of ADA validation testing and reporting, comprised of over 30 KOL from across industry and from various health authority agencies with a strong FDA presence.

OBP Immunogenicity Review Challenges and Solutions

Provide an overview of current challenges faced by OBP immunogenicity reviewers working on IND, BLA and post approval regulatory submissions and how validation templates and integrated summaries of immunogenicity could facilitate review processes.

João Pedras-Vasconcelos, U.S. Food and Drug Administration

João Pedras-Vasconcelos, Ph.D., OBP-CDER-FDA Dr. Pedras-Vasconcelos has been a biologics quality and immunogenicity reviewer with the Office of Biotechnology Products, Center for Drugs- FDA for 16 years. He received his Ph. D. in Immunology in 1999 from Cornell University, Ithaca NY USA. He joined the FDA in 2002, first with CBER and then CDER and has extensive regulatory experience in reviewing cytokines, monoclonal antibodies, fusion proteins, therapeutic toxins, hormones, and enzyme replacement therapies. Joao is a co-chair of the OBP Immunogenicity Working Group and a member of the coordinating committee for CDER Office of Pharmaceutical Quality Infectious Disease and Inflammation Center of Excellence. He is also a member of the AAPS Immunogenicity Discussion Group, the NAb Assay Working Group and the ADA Validation Reporting Subteam.

Cut Point Considerations

A simplified overview of the process for evaluating various types of cut points will be provided. If time permits, some frequently asked questions such as Titer Cut Points, comparison of different cut point formula, outlier criteria and outlier-resistant methods, extension to other disease populations, when and how to evaluate in-study cut points, etc., may also be addressed. All concepts and proposals will be conveyed using data from several case study examples.

Viswanath Devanarayan, Ph.D., Charles River Laboratories

Devan has 22 years of pharmaceutical research experience from Eli Lilly, Merck, and AbbVie. In addition to leading global teams for over 15years, his scientific contributions cover a wide variety of statistical methods and applications across drug discovery and clinical research. He has filed 10 patent applications, given over 100 invited talks, and coauthored over 60 manuscripts. This includes several white-papers with regulatory, academic and industry scientists on compound screening, genomics, predictive modeling, machine learning, bioanalytical methods, Immunogenicity and clinical biomarker qualification. He was inducted as a Fellow of the American Association of Pharmaceutical Scientists (AAPS) in 2014. He is currently employed at Charles River Laboratories and is also serving as an Adjunct Professor at the University of Illinois in Chicago.

FDA Cut Point Perspective

The assay cut point distinguishes anti-drug antibody (ADA) positive samples from ADA negative samples. The cut point is typically set to minimize the risk of false-negative samples by including an estimated frequency of false positives. Multiple statistical approaches for the determination of assay cut points have been described. This presentation will provide a regulatory perspective on the cut point calculation approach and statistical methods.

Steven Bowen, U.S. Food and Drug Administration

Biography unavailable.

Immunogenicity Studies; Recently Issued 483s

This session will provide examples of the observations that were made during the audit of antidrug antibody (ADA) assays in support of immunogenicity assessments.

Mohsen Rajabi Abhar, Ph.D., U.S. Food and Drug Administration

Mohsen Rajabi is a Pharmacologist in the Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance, Office Translational Science, Center for Drug Evaluation and Research, US FDA, Silver Spring, MD. He received his Ph.D. from University of Maryland in Baltimore, MD. After completing a research fellowship, he joined the Office of Study Integrity and Surveillance in 2015. He conducts study-directed and comprehensive surveillance inspections of firms that conduct pharmacokinetic, bioavailability/bioequivalence (BA/BE) in support of human drug applications. He also participates in working groups to develop and refine strategies to improve inspections planning, execution, evaluation and to provide recommendations to CDER review divisions, while focusing on human subject safety and data integrity. In his free time, he enjoys outdoor activity and traveling.

Defining Assay Sensitivity

The presentation will summarize the recommendations from the ADA Validation Harmonization team for the validation of sensitivity in ADA assays. This session will address the challenges associated with defining assay sensitivity, potential approaches that are commonly used when reporting sensitivity and identification of the critical information required by regulators when reporting assay sensitivity.

Kelli Phillips, Ph.D., PPD

Kelli began her career in biologics in 2006, as a Principal Investigator in the Immunochemistry Research and Development department at PPD. In her current role as a Laboratory Manager, she provides oversight to method development and validation of quantitative (PK), immunogenicity (ADA), and biomarker methods. During her tenure at PPD, her focus has been on the development of robust, drug-tolerant immunogenicity assays and the life-cycle management of extended-use methods. Recently, Kelli has expanded her focus to include method development and validation for biosimilar drug products.

Defining Assay Drug Tolerance

Summary of recommendations of the ADA Validation Harmonization team for the validation of drug tolerance.

Marta Starcevic-Manning, Ph.D., Amgen

Marta Starcevic Manning, PhD is a Principal Scientist in the Pharmacokinetics and Drug Metabolism department at Amgen. Marta received her B.S. in Cell and Molecular Biology from Tulane University in New Orleans, and her PhD in Human Genetics at the University of California, Los Angeles. Since joining Amgen in 2005, Marta has supported immunogenicity testing efforts for various types of protein therapeutics, including monoclonal antibodies, antibody-drug conjugates, peptides, and BiTEs. She is experienced in designing risk-based immunogenicity testing bioanalytical strategies, assay optimization and validation, and interpretation of anti-drug antibody results.

FDA Perspective on Assay Sensitivity and Drug Tolerance

Session description unavailable.

Haoheng Yan, U.S. Food and Drug Administration

Haoheng Yan, M.D., Ph.D., Chemist, FDA-CDER Dr. Haoheng Yan is a biologics product quality and immunogenicity reviewer in the Office of Biotechnology Products (OBP) in CDER/FDA. Haoheng joined FDA in 2014 as a full-time reviewer. She is the primary reviewer for numerous INDs and several BLAs. Dr. Yan has also gained extensive experience in immunogenicity assay review for monoclonal antibodies, pegylated proteins, fusion proteins, antibody drug conjugates, polypeptides and polynucleotides. She is a member of OBP immunogenicity working group and CDER Center of Excellence in Infectious Disease and Inflammation. Dr. Yan received her M.D. from Peking Union Medical College, Beijing China and her Ph.D in Molecular and Cellular Biology from the University of Massachusetts, Amherst.

Defining Assay Domain Specificity/ Selectivity

This is a subsection of the overall ADA Reporting Harmonisation activity. The goal here is to help attendees understand what assay parameters need to be evaluated for multi-domain biologics and how these parameters should be reported. Generation of the appropriate controls will remain out of scope. In the realm of selectivity, we will discuss how selectivity is assessed, at what levels and how these data should be reported.

Shobha Purushothama, Biogen

Shobha Purushothama, Ph.D., is a scientist at Biogen with extensive bioanalytical knowledge for the development of biologics from the pre-IND phases to the post marketing stage. In her current role, she is responsible for overseeing bioanalytical strategy across the large molecule portfolio as well as critical reagent generation for the support of the large molecule projects. Her particular interests pertain to the assessment of technology platforms to solve challenging bioanalytical problems of sensitivity and matrix effects. In addition, she has a keen interest in understanding immunogenicity of biologics - from risk assessment to assessing clinical impact. She has published extensively; on bioanalytical and biomarker topics as well as presented at national and international meetings. She is an active member of several AAPS groups and currently co-chairs the Immunogenicity Discussion Group. Shobha obtained her Ph.D. in Analytical Chemistry from the University of Cincinnati.

MRD, Titer Reporting and Stability

This presentation will cover topics such as calculating and incorporating the MRD in titer reporting as well as performing sample stability per regulatory expectations. Examples of MRD calculations will be shown for less straight forward methods such as SPEAD, ACE and PandA.

Jad Zoghbi, Sanofi

Jad Zoghbi is a Principal Scientist in the Boston-Biomarker and clinical Bioanalyses group at Sanofi. The group is responsible for preclinical and clinical bioanalytical strategy and implementation which includes Immunogenicity, PK, and Biomarkers on multiple technical platforms. Jad holds a MS degree from California State University and more than 15 years of experience in immunogenicity assay development and validation with various companies.

Organizing Committee Biographies

Heather Myler, Ph.D., PPD

Heather received her PhD in Biochemistry and Cell Biology at Rice University and completed her post-doctoral training at Pfizer in Drug Safety Evaluation, later holding positions of increasing responsibility at Amgen, Ambrx, Merck and BMS where she has contributed to the growth of the bioanalytical discipline, supporting PK, immunogenicity and biomarker bioanalysis with an expertise in biologics. Heather currently serves as the Director of R&D, Immunochemistry at PPD leading a group scientist responsible for PK, ADA and neutralizing antibody bioanalytical method development, tech transfer, validation and automation supporting biosimilars and novel biologics. Heather has a strong external science presence, currently serving as co-Leader of the Bioanalytical Community within AAPS and actively participating on multiple bioanalytical and cross-functional initiatives. Specifically, Heather is currently leading a team focused on the Harmonization of ADA validation testing and reporting, comprised of over 30 KOL from across industry and from various health authority agencies with a strong FDA presence.

An Song, Ph.D., Genentech

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