AAPS-sponsored ADA Validation and Reporting Harmonization (ADAH Team)

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ADAH Membership

- Established in September 2017
- Biweekly Meetings and F2F at WRIB 2018
- Planned: Workshop PharmSci360 2018; Publication 2019

US:

- Heather Myler, PPD/LBABFG chair
- An Song, Immuneonc/TPIFG chair
- Jim McNally, Shire
- Susan Richards, Sanofi
- Shobha Purushothama, Biogen
- Mark Ware, Jannsen
- Jennifer Cummings, BMS
- Vibha Jawa, Merck
- Marta Manning, Amgen
- Lakshmi Amaravadi, Shire

US:

- Theresa Goletz, EMD Serono
- Meina Liang, MedImmune
- Charles Hottenstein, GSK
- Cecil Chen, MedImmune
- Kelli Phillips, PPD
- Valerie Theobald, CRL
- Carol Gleason, BMS/stats
- Viswanath Devanaryan, CRL/stats
- Ron Bowsher, B2S/stats
- Jad Zoghbi, Sanofi

EU:

- Jo Goodman, MedImmune/EBF
- Robert Nelson, NovImmune/EBF
- Szilard Kamondi, Roche
- Paul Chamberlain, NDA Advisory Board
- Daniel Kramer, Sanofi

FDA Representatives

- Susan Kirshner, FDA
- Joao Pedras-Vasconcelos, FDA
- Steve Bowen, FDA
- William Hallett, FDA
- Haoheng Yan, FDA
- Mohsen Rajabiabhar, FDA
- Zhenzhen Liu, FDA

ADAH Objectives

- Provide recommendation for ADA validation and data reporting
  - Alignment with FDA/EMA
  - Publish recommendations as a manuscript in 2019
- Promote collaborations across industry
  - Increase consistency
- Streamline communications with regulatory agencies
  - Include FDA as core contributors/HA advisors
  - Partner with EBF for EU alignment
  - Engage ROW HA during review process
  - Reduce data reporting-related HA queries

ADAH Sub Teams

- Assay sensitivity
- Study specific (in-study) cut point
- Drug interference with ADA assessment
- Target interference with ADA assessment
- Assay selectivity to matrix components
- System suitability criteria for in-study plate acceptance
- Sample stability for sample storage and handling conditions
- MRD and sample processing for titer reporting
- ADA domain specificity for multi-domain drug

Assay Sensitivity

Objectives:

Define and recommend methods to assess assay sensitivity

- Harmonize method for sensitivity evaluations
  - Sensitivity requirements, screening and confirmatory
  - Experimental design
  - Positive control (polyclonal vs. monoclonal)
- Provide recommendations for validation and data reporting
  - Sensitivity report: mass unit of undiluted matrix (not titers)
  - Sensitivity calculations
  - LPC concentration selection

Study Specific (In-study) Cut Point

Objectives:
When and how to estimate in-study SCPF

- When in-study CP may be necessary
  - Putative positives in baseline study samples: not in 2-11%
- Sample size and approach
- Statistical methods to compare in-study with validation results
  - Whether to implement a population-specific SCPF
- Possibility to use common SCPF across multiple patient populations
- Evaluate in-study titer cut point factor (TCPF) if needed

Drug Interference with ADA Assessment

Objectives:

Harmonize drug tolerance validation and reporting

- How to assess and report drug tolerance during validation
- What is the highest drug level that the method should tolerate
- Risk assessment for drug tolerance requirement
- Evaluate drug tolerance in various diseases

Target Interference with ADA Assessment

Objectives:

Validate and report target interference

- Evaluate the risk of target interference
- Experimental design to validate target interference
- How to report target tolerance

Assay Selectivity to Matrix Components

Objectives:

Assay specificity to the components of the sample matrix

- Assessing selectivity in screening and confirmatory assay tiers
- Matrix considerations
  - Hemolyzed and lipemic samples, pre-existing antibodies
- The need to assess in buffer
- Handling of selectivity when changing populations
- Application of acceptance criteria

System Suitability Criteria for Plate Acceptance

Objectives:

Monitor tiered ADA method performance during clinical sample testing using plate acceptance criteria

- Selection of adequate controls
- Determine the acceptance criteria
- When and how to apply each acceptance criterion
- Considerations:
  - Screening assay: LPC, HPC and NC
  - Confirmatory assay: NC, LPC
  - Titer assay: titer control

Sample Stability

Objectives:

Validate the process of handling clinical samples during collection, storage and bioanalysis to ensure their integrity

- Which stability conditions need to be evaluated
  - Room temp
  - 2-8^{o}C
  - Freeze/thaw cycles
  - Long term
- The optimal testing approaches
  - Number of testing tubes for each condition
  - Which control levels should be tested, e.g. LPC, HPC, titer controls

MRD and Sample Processing for Titer Reporting

Objectives:

How to integrate MRD into titer reporting in the less straightforward extractions methods, e.g. SPEAD/BEAD

- Necessity of harmonization
  - Currently inconsistent across industry

Example: In a traditional bridging assay

Samples	→	1:10 dilution	→	1:5 dilution by conjugate mix
Min Titer	1		10	50

  - Improve transparency to assist submission review by HA
- Provide guidance for multi-step methods on how to include MRD

ADA Domain Specificity

Objectives:

Provide guidance for how to assess ADA domain specificity for multi-domain drug

- How to evaluate domain specificity
- Cut point approaches
- Necessity for an in-study cut point
- Validate precision, drug tolerance and assay sensitivity
- Assess accuracy of ADA specificity classification

Summary

- Immunogenicity is a critical aspect of biotherapeutics development
- Lack of consistency in ADA validation and data reporting
- Necessity of harmonization of ADA validation and data reporting
- ADAH, sponsored by AAPS, established in 2017
  - Provide guidance for ADA validation and data reporting
  - Promote across industry collaboration
  - Streamline communication with HA
    - Include FDA as core team members
    - Partner with EBF
    - Engage ROW HA during review process for alignment
  - Publish recommendations as a manuscript in 2019

Thank You

Presenter

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