Experiences and Lessons Learned from the AAPS Bioanalytical Community One Year after the Implementation of ICH-M10

February 7, 2024

15th JBF Symposium

Faye Vazvaei-Smith

on behalf of AAPS Bioanalytical Community

Disclaimer

- The opinions expressed by the speaker in this session are their own, they should not be taken as representing the views of their employer, AAPS, or of the ICH.

Biography and Contact Information

- Faye Vazvaei-Smith
  - Executive Director Regulated PK & ADA Bioanalysis at MSD
  - EWG Member of ICH-M10
  - AAPS Member
  - Email: Fataneh.Vazvaei-Smith@MSD.com

Outline

- Evolution of the bioanalytical guidelines
- AAPS Activities Post M10 Adoption
- M10 Implementation
- AAPS Activities Post M10 Implementation
- Summaries of Topics Discussed at Various AAPS Meetings
- Slides from the Hot Topic Session at the 2023 PharmSci 360 in Orlando, FL

Evolution of the BMV Guidance/Guidelines and The AAPS/Industry Contribution

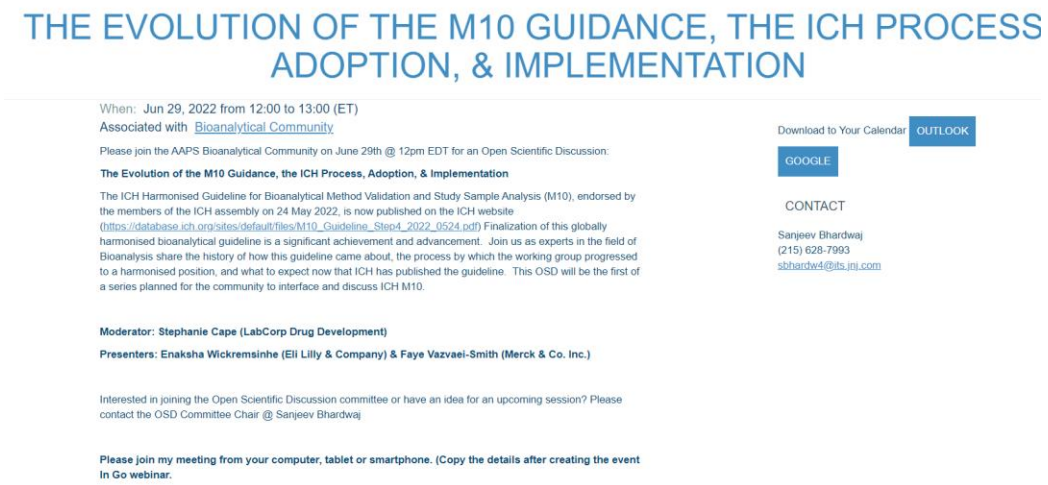
- Crystal City I (1990) – The first whitepaper on this topic
- Crystal City II (2000) – LC/MS assays
- FDA BMV (May 2001)
- ANVISA (2003) – Resolution
- Crystal City III (2006) – ISR & Matrix Effects/Factor introduced
- Crystal City IV (2008) – Discussion on ISR continued
- EMA BMV Guideline-(2009-) 2011
- ANVISA (2012) – Resolution
- Crystal City V (2013)
- MHLW Guideline (2013) Chromatography
- MHLW Guideline (2014) LBA
- NMPA (2014)
- Crystal City VI (2015)
- ICH picks up BMV as a topic for harmonization (2016)
- 1st Series of Joint AAPS/EBF/JBF Sister Workshops (2017)
- FDA BMV (2018)
- 2nd Series of Joint AAPS/CBF/EBF/JBF Sister Workshops (2019)—after public consultation
- ICH-M10 (May 2022)

AAPS Activities Post M10 Adoption

Link to slides and recordings provided and can be accessed by AAPS members

1st AAPS OSD—The Evolution of the M10 Guidance, The ICH Process Adoption & Implementation

- 1st Open Scientific Discussion (OSD) on June 29, 2022 –Slides
- Topics covered
  - ICH process
  - M10 journey
  - Next steps
  - Q&A



THE EVOLUTION OF THE M10 GUIDANCE, THE ICH PROCESS ADOPTION, & IMPLEMENTATION

When: Jun 29, 2022 from 12:00 to 13:00 (ET)
Associated with Bioanalytical Community

Please join the AAPS Bioanalytical Community on June 29th @ 12pm EDT for an Open Scientific Discussion:

The Evolution of the M10 Guidance, the ICH Process, Adoption, & Implementation

The ICH Harmonised Guideline for Bioanalytical Method Validation and Study Sample Analysis (M10), endorsed by the members of the ICH assembly on 24 May 2022, is now published on the ICH website (https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf) Finalization of this globally harmonised bioanalytical guideline is a significant achievement and advancement. Join us as experts in the field of Bioanalysis share the history of how this guideline came about, the process by which the working group progressed to a harmonised position, and what to expect now that ICH has published the guideline. This OSD will be the first of a series planned for the community to interface and discuss ICH M10.

Moderator: Stephanie Cape (LabCorp Drug Development)

Presenters: Enaksha Wickremsinhe (Eli Lilly & Company) & Faye Vazvaei-Smith (Merck & Co. Inc.)

Interested in joining the Open Scientific Discussion committee or have an idea for an upcoming session? Please contact the OSD Committee Chair @ Sanjeev Bhardwaj

Please join my meeting from your computer, tablet or smartphone. (Copy the details after creating the event in Go webinar.

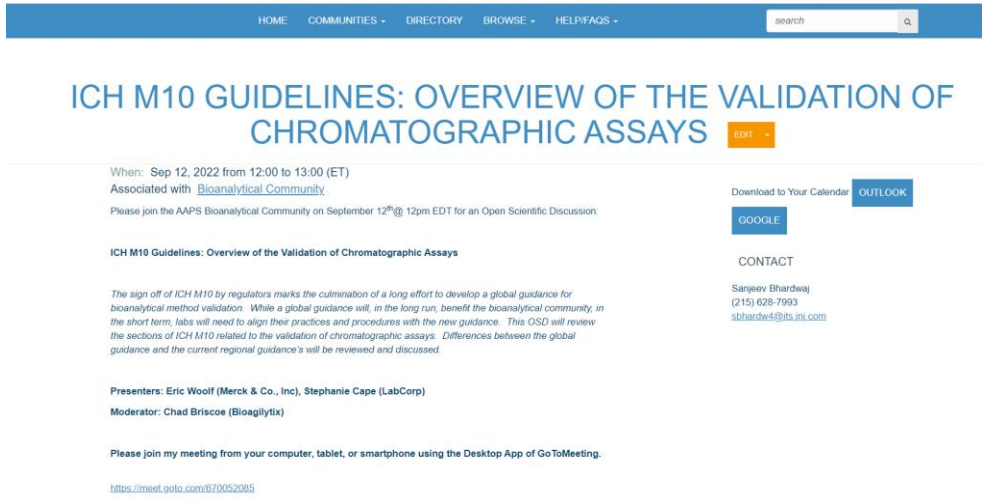
Download to Your Calendar OUTLOOK GOOGLE

CONTACT

Sanjeev Bhardwaj
(215) 628-7993
sbhardw4@its.jnj.com

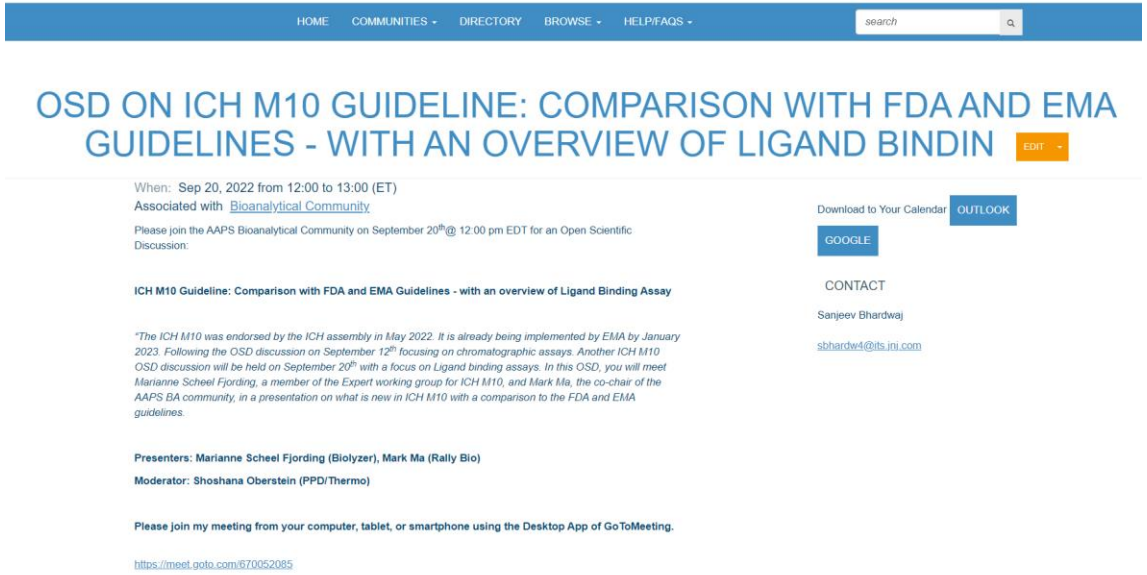
2nd OSD – Overview of the Validation of Chromatographic Assays

- 2nd OSD on September 12, 2022—Recording and Slides
- Topics covered
  - To review how M10 impacts how chromatographic assays are validated and utilized in regulated labs
    - Scope
    - Validation
    - Sample Analysis Q&A
  - Open Discussion



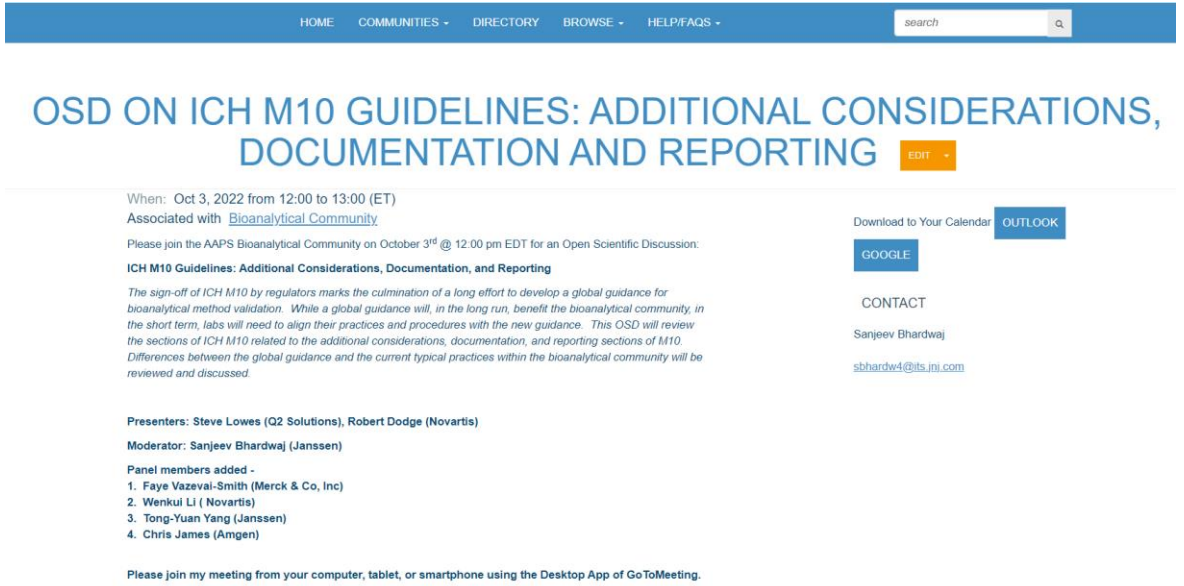
3rd OSD – Overview of Ligand Binding Assays

- 3rd OSD on September 20, 2022—Recording and Slides
- Topics covered
  - ICH M10 Guideline: Comparison with FDA and EMA Guidelines
  - Q&A



4th OSD – Additional Considerations, Documentation and Reporting

- 4th OSD on October 3, 2022—[Recording and Slides]
- Topics covered
  - General Principles \ Incurred Sample Reanalysis
  - Partial and Cross Validation
  - Additional Considerations
  - Biomarker (absence from ICH M10)
  - Documentation
  - Q&A



Contributors to the 1st through 4th OSDs

- Speakers and Moderators
  - Stephanie Cape
  - Faye Vazvaei-Smith
  - Enaksha Wickremsinhe
  - Chad Briscoe
  - Eric Woolf
  - Mark Ma
  - Shoshana Oberstein
  - Marianne Scheel Fjording
  - Steve Lowes
  - Sanjeev Bhardwaj
  - Wenkui Li
  - Tong-Yuan Yang
  - Chris James

- With Special thanks to the BA Community Leads, Stephanie Cape, Mark Ma, Chad Briscoe, Robert Dodge

- AAPS Staff

  And

- OSD Chair
  - Sanjeev Bhardwaj

Topics Covered at PharmSci 360 - October 2022

- 3 Rapid-Fire presentations
  - ICH Process and the M10 Journey (Faye Vazvaei-Smith)
  - The Mass Spec Topics That are New/Different from the Previous Guidelines (Enaksha Wickremsinhe)
  - Comparison of ICH-M10 to previous BMV guidelines/LBA (Mark Ma)

- Speaker Spotlight: Ask a regulator
  - Brian Booth, PhD, FDA

A few areas with questions from the “Ask a Regulator” session

- Scope of the guidance
- The need for dilution QCs (ultra-high QC above the curve)
- Use of fresh calibrators and QCs (fresh/frozen QCs)
- Cross-validation – Acceptance criteria?
- Co-med stability—What are FDC[1] regimen?
- Stability QCs (QC above the curve)
- Documentation for cBA/BE studies—what are cBA studies?

1- FDC: Fixed Dose Combination

M10 Implementation Schedule

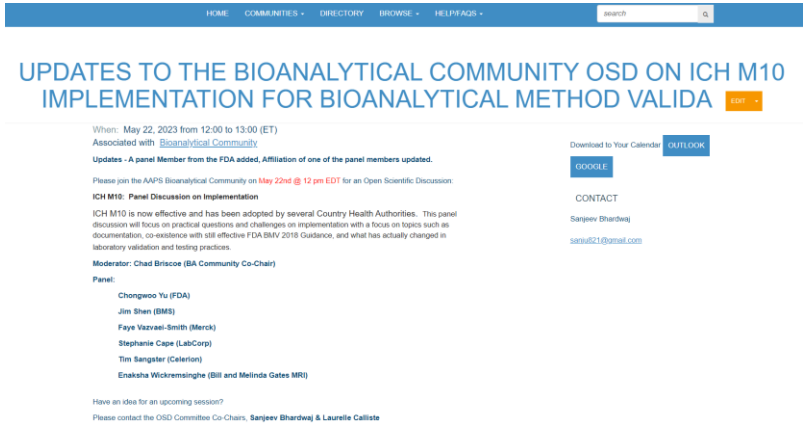
ICH Member	Implementation Status	Implementation Date
EC, Europe	Implemented	21-Jan-23
FDA, United States	**Implemented**	**7-Nov-22**
Health Canada, Canada	Implemented	20-Jan-23
MFDS, Republic of Korea	In the process of implementation	31-Oct-23
NMPA, China	Implemented	29-Jul-23
SFDA, Saudi Arabia	Implemented	10-Aug-23
Swissmedic, Switzerland	Implemented	25-May-22
TFDA, Chinese Taipei	Implemented	30-May-23

ICH Member	Implementation Status
ANVISA, Brazil	In the process of implementation
COFEPRIS, Mexico	Not yet implemented
EDA, Egypt	In the process of implementation
HSA, Singapore	In the process of implementation
MHLW/PMDA, Japan	Not yet implemented
MHRA, UK	In the process of implementation
TITCK, Türkiye	Not yet implemented

ICH Official web site : ICH -- Inforamtion as it appears on the ICH website as of January 28, 2024

5th OSD – Post M10 Implementation by the FDA

- 5th OSD on May 22, 2023—Recording and Slides
- Topics covered
  - Panel discussion focusing on practical questions and challenges on implementation
  - Focus on chromatographic assays



Example questions and discussion topics:

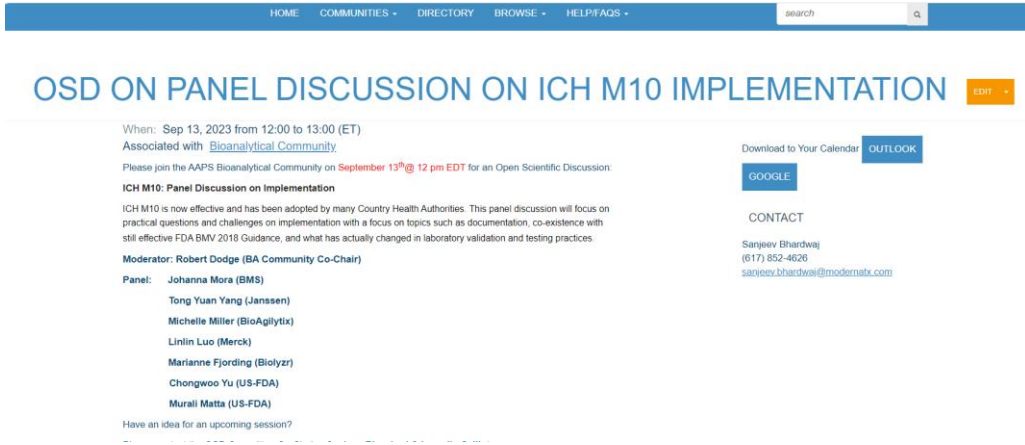
- FDA Reviewers perspective (early and clear communication is key)
- Is it necessary to do the stability with all co-drug administered. If not, in which cases it is necessary to prove stability with the co-drugs.
- What ultra high stability QCs should be included (i.e., one at Cmax)?
- How to place ultra-high QCs for SAD/MAD studies where a range of doses used?
- When and where should dilution QC be used as an acceptance criteria?
- Is it required to provide 100 Chromatograms for Validation and study report?

6th OSD – Post M10 Implementation by the FDA

- 6th OSD on September 13, 2023—

[Recording and Slides]

- Topics covered
  - Panel discussion focusing on practical questions and challenges on implementation
  - Focus on LBA assays



Example questions:

- If I started a study prior to ICH M10 becoming effective in my country or finished a study but not yet written the report, will there be any additional work I need to do to update previous testing to meet a new requirement listed in ICH M10.
- I am just about to prepare the submission documents for my project. I have not performed any studies after M10 was implemented. Should I update my validation report prior to submission?
- I am switching matrix from mouse to monkey plasma. Do I need to perform a full or partial validation? If partial which parameters to assess? Is it different for chromatographic and LBA?

Contributors to the 5th and 6th OSDs

- Speakers and Moderators
  - Chad Briscoe
  - Chongwoo Yu (FDA)
  - Jim Shen
  - Faye Vazvaei-Smith
  - Stephanie Cape
  - Tim Sangster
  - Enaksha Wickremsinhe
  - Robert Dodge
  - Johanna Mora
  - Tong-Yuan Yang
  - Michelle Miller
  - Linlin Luo
  - Marianne Fjording
  - Chongwoo Yu (FDA)
  - Murali Matta (FDA)

- With Special thanks to the BA Community Leads

- AAPS Staff

  And

- OSD Committee Co-Chairs
  - Sanjeev Bhardwaj
  - Laurelle Calliste

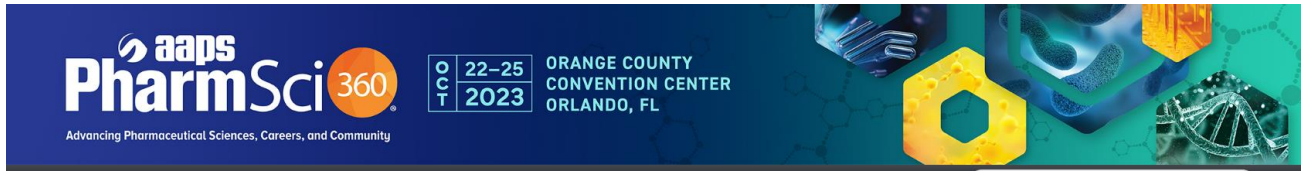
In-Person Meetings in 2023

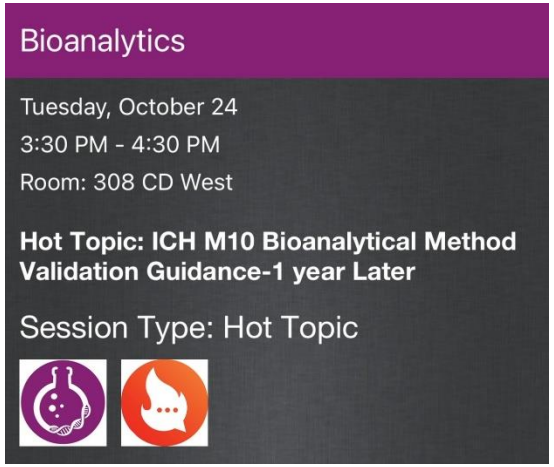
Summer Scientific Forum July 2023

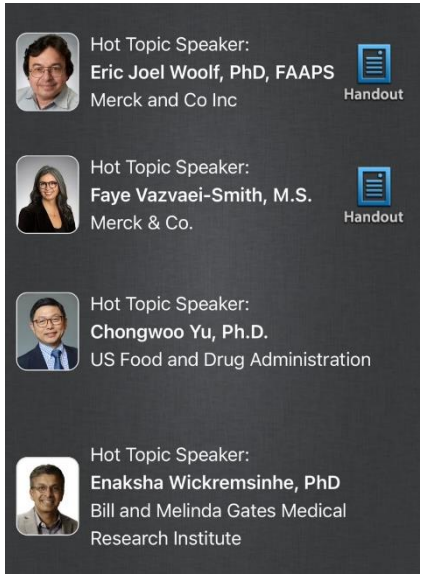
- ICH M10 - CRO Experience (Beth Hyer, Labcorp)
- Pharma's Experience on Implementing M10 (Christopher A. James, Ph.D., Amgen Research)

PharmSci 360 October 2023

- Hot topic session







Focus of Next Slides—Hot Topic Session

Areas identified by the bioanalytical community needing further clarification – discussed at **2023 PharmSci 360** in Orlando

- Cross-Validation
- Parallelism
- Dilution QCs
- Implementation inconsistencies across labs
- cBA/BE studies definition and associated documentation
- Co-med stability
- Analytes with endogenous counterpart

The following 5 slides were presented by

Faye Vazvaei-Smith, MSD

at

2023 PharmSci 360 in Orlando

October 24, 2023

Cross Validation—What/When

- Cross-validation is about measuring the potential **bias** between data sets produced when multiple labs or methods are involved
- **No pass/fail criteria** (e.g., ISR) is necessary

Section 7.6 - New or Alternative Technologies

When a new or alternative technology is used as the sole bioanalytical technology from the onset of drug development, cross validation with an existing technology is not required.

- Use of two different BA technologies during drug development requires cross-validation

Section 7.6.1

When DMM is used for clinical or nonclinical studies in addition to typical liquid approaches (e.g., liquid plasma samples) in the same studies….

Section 2.2.3

Cross validation is required to demonstrate how the reported data are related when multiple bioanalytical methods and/or multiple bioanalytical laboratories are involved

Section 6.2

Cross validation is required under the following situations:

- Data are obtained from different fully validated methods within a study.
- Data are obtained within a study from different laboratories with the same bioanalytical method.
- Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

DMM=Dried Matrix Methods

Cross Validation—The How

Section 6.2

Cross validation should be assessed by measuring the same set of QCs (low, medium and high) at least in triplicate and study samples (if available) that span the study sample concentration range (n≥30) with both methods, or in both laboratories

Section 6.2

Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two methods (e.g., concordance correlation coefficient) may be used too. Alternatively, the concentration vs. time curves for study samples could be plotted for samples analysed by each method to assess bias.

Cross-validation of assays with different analytical ranges (non-overlapping)

- Should be avoided within a study
- Samples/QCs can be diluted to fall in the low range assay

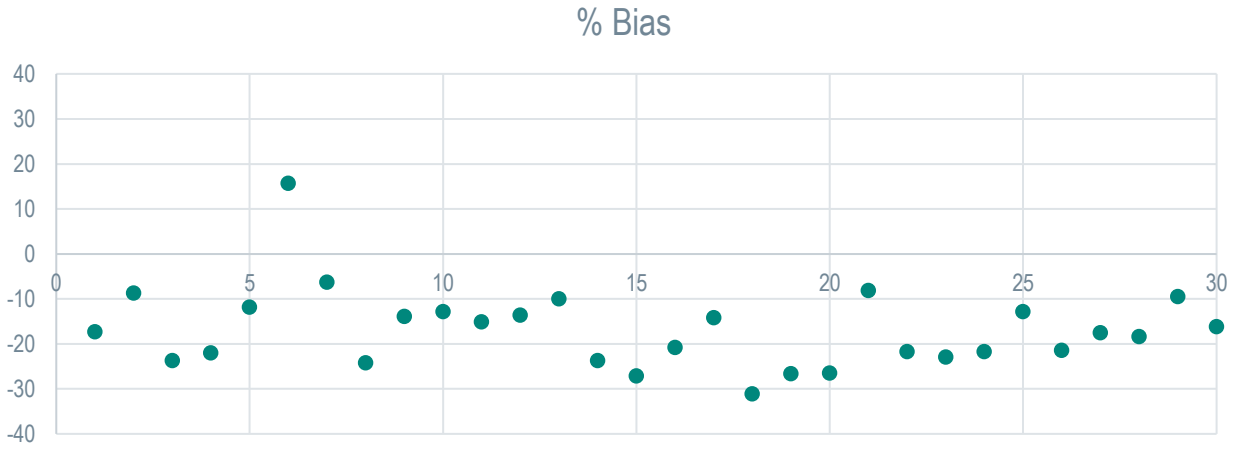
Cross-Validation Example 1 (mAb) –2017
ISR Criteria not Accepted – Question Regarding Bias Raised

- QCs prepared and analyzed at reference lab + 30 pooled post-dose samples prepared and analyzed at reference lab
- Acceptance criteria
  - QCs: Bias: ±20% at each level with 50% of QCs at each level meeting requirement
  - Pooled Post-Dose: Relative % difference between reference lab and China lab must be ±30% for 2/3 of the samples tested (ISR)

Cross-validation spikes QC results

Run ID	Run Date	Sample ID	Nominal Conc. (ng/mL)	Determination	Mean Conc. (ng/mL)	Accuracy (%)
40	21-Jul-2016	Reference lab HQC	600	1	523	87.2
				2	516	86.0
		Reference lab MQC-	150	1	130	86.7
				2	131	87.3
		Reference lab LQC	70.0	1	60.3	86.1
				2	60.6	86.6

Cross validation pooled samples result



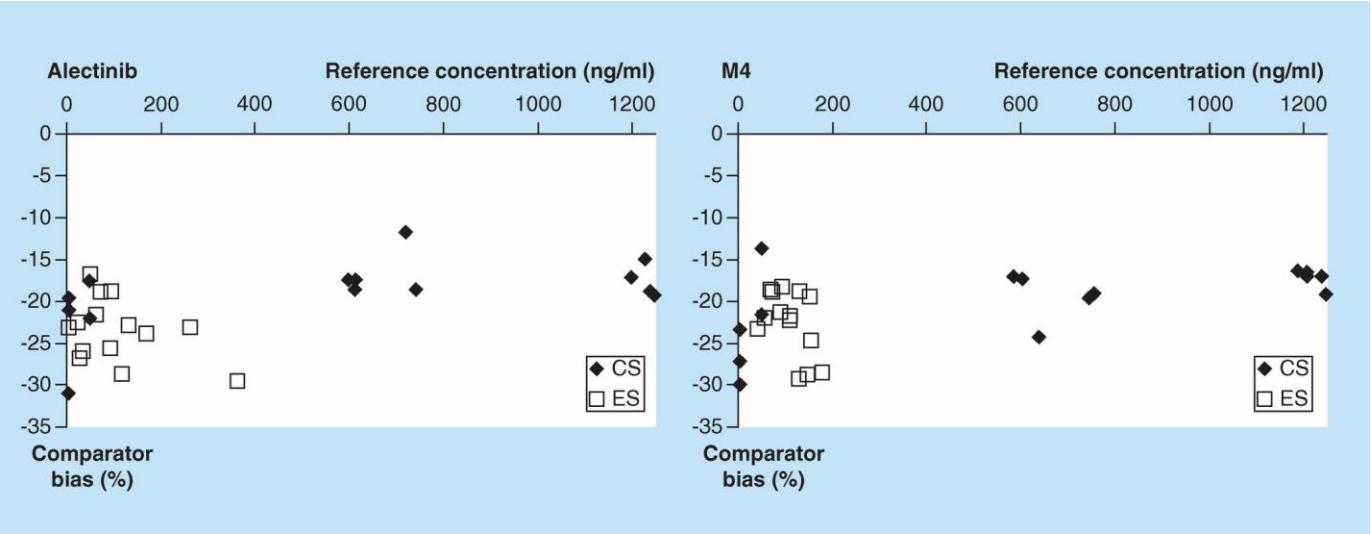
Annex 1: Rapporteur proposed Request for Supplementary Information

Query: In the submitted cross-validation method, the difference between the two values were within 20% only for 17 pooled study samples out of 30 (56,7%). Data demonstrate that the concentration data obtained at XXX laboratories were lower when compared to the concentration data obtained at the reference lab, the MAH should discuss on this issue and extensively justify deviation from relevant guideline.

MAH- Marketing Authorization Holder

Example 2 – Alectinib + M4 metabolite (Published 2016)

- Methods:
  - Method 1a/1b LC-MS/MS (1a for alectinib, 1b for M4) supported early phase studies
  - Method 2: Simultaneous method supported later studies
- Cross-validation samples: 30 cross-validation samples in total
  - 15 pooled study (*ex vivo*) samples (ES) and
  - 15 spiked check samples



Approach: PK data from pivotal Phase I/II studies were analyzed by applying a correction factor to account for the bias using a population PK. This was done by correcting the relative bioavailability by a mean factor of 0.8

Bias (%) of comparator lab concentrations *versus* reference lab concentrations for alectinib and M4

The overall combined bias for CS and ES samples was -21% (with 21.6% CV) for alectinib and -21.2% (20.5% CV) for M4

Heinig K, Miya K, Kamei T, et al. *Bioanalysis*. 2016;8(14):1465-1479.

Parallelism

Parallelism is defined as a parallel relationship between the calibration curve and serially diluted study samples to detect any influence of dilution on analyte measurement. Parallelism is a performance characteristic that can detect potential matrix effects.

- **2.2.1 Full Validation**

- For LBAs …. If necessary, parallelism can be conducted when appropriate study samples are available, e.g., when necessary:
  - Interference caused by a matrix component (e.g., presence of endogenous binding protein) is suspected during study sample analysis.
  - Parallelism investigations, or the justification for its absence, should be included in the Bioanalytical Report.
  - Some methods may demonstrate a lack of parallelism in different patient population

- **7.1 Methods for Analytes that are also Endogenous Molecules**

Parallelism assures that observed changes in response per given changes in analyte concentrations are equivalent for the surrogate and the authentic biological matrix across the range of the method

- Surrogate analyte/recombinant protein
- Surrogate matrix

The following 3 slides were presented by

Enaksha Wickremsinhe Ph.D., Bill & Melinda Gates Medical Research Institute

at

2023 PharmSci 360 in Orlando

October 24, 2023

Slides included here with permission

Comparative BA studies

- ICH adopted the term Comparative BA *(term used 13 times in text and 7 times in Table)*
- What are comparative BA studies?
- FDA uses the term Relative BA*

Examples:

- RBA studies comparing formulation changes
- Definitive food effect studies

Exclude:

- Early clinical trials, comparing formulations for internal decision making
- Early food effect for internal decision making

BE: to establish equivalence between two preparations of a drug – typically between a branded vs a potential to-be-marketed generic.

**FDA Guideline: Bioavailability Studies Submitted in NDAs or INDs — General Considerations Guidance for Industry, April 2022*

Combination Drug Stability

"For fixed dose combination products and specifically labelled drug regimens, the freeze-thaw, bench-top and long-term stability tests of an analyte in matrix should be conducted with the matrix spiked with all of the dosed compounds" (page 16)

"For fixed dose combination products and specifically labelled drug regimens, the freeze-thaw, bench-top and long-term stability tests of an analyte in matrix should be conducted with the matrix spiked with all of the dosed compounds, on a case-by-case basis" (page 29)

- What are FDCs?
- What are "specifically labelled drug regimens"
- Conc of spiked combination drugs: Cmax, solubility limitations, Css
- Timing: for FDCs – can be performed during method validation
- Timing for combination regimen: may not be known till later in development (i.e., oncology)
- Some combinations – i.e., a platinum drug and a mAb, may be able to justify using scientific rationale

Dilution QCs Stability, DQCs & Sample Analysis

"Stability of the analyte in the matrix is evaluated using low and high concentration QCs" (page 15)

"Stability of the analyte in the studied matrix should be evaluated using low and high concentration QCs" (page 29)

- What about dilution QC stability?
- Do you? or don't you?
- Including dil QCs in stability may behoove you in certain situations

  e.g., large number of samples are >ULOQ and must be diluted

"If multiple dilution factors are used in one analytical run, then dilution QCs need only be diluted by the highest and lowest dilution factors" page 20.

- *These will be in addition the run QCs (and requirements)*
- *If DQCs fail, then data for samples with corresponding dilution in that batch/run can be questionable*

The following 7 slides were presented by

Chongwoo Yu, Ph.D., FDA

at

2023 PharmSci 360 in Orlando

October 24, 2023

Slides included here with permission

aaps PharmSci 360

OCT 22–25 2023

ICH M10: Do You See What I see?

(Hot Topics Session: ICH M10 Bioanalytical Method Validation Guidance - 1 year Later)

October 24, 2023

Chongwoo Yu, PhD

FDA U.S. FOOD & DRUG ADMINISTRATION

Disclaimer

Dr. Yu contributed to this presentation in his personal capacity. The views expressed are his own and do not represent the views of the Food and Drug Administration or the United States Government.

Highlights of What's New in ICH M10?

- The bioanalysis of biomarkers and bioanalytical methods used for the assessment of immunogenicity are not within the scope.
- Detailed recommendations on study sample analysis in addition to method validation
- New dedicated sections on chromatography, ligand binding assay (LBA), parallelism, recovery, and minimum required dilution (MRD)
- More specific recommendations on partial validation (for LBA), cross validation, and endogenous analyte bioanalysis
- Additional reporting requirements for comparative bioavailability (BA) / bioequivalence (BE) studies

Partial Validation and Cross Validation

- Partial validation: ICH M10 added a list of typical bioanalytical method modifications for LBAs that require partial validation.
- Cross validation: Provided detailed recommendations
  - When: (1) Different methods within study; (2) Same methods from different labs within a study; (3) Different methods across studies that data will be combined/compared to support regulatory decisions
  - How: “Cross validation should be assessed by measuring the same set of QCs (low, medium, and high) at least in triplicate and study samples (if available) that span the study sample concentration range (n ≥ 30) with both methods, or in both laboratories.” (p. 29)

Endogenous Analyte Bioanalysis: Common Issues Found

- While surrogate matrix was used to prepare calibration standards (CSs) and quality controls (QCs), the endogenous concentration of the analyte was not accounted for in the study sample analysis.
- Absence of parallelism test addressing the potential matrix effect and differences in recovery between the surrogate matrix and the authentic matrix
- The stability of the analyte during sample collection and handling was not adequately demonstrated during bioanalytical method development and validation.
- Study samples went through a different sample preparation method compared to the CSs and QCs resulting in an uncertainty of the accuracy and precision.

Yu *et al*., ***Bioanalysis*** 16(3), 171-184 (2024) Yu *et al*., ***2023 AAPS PharmSci 360*** Poster M1330-06-39

Perspective: Do You See What I See?

- Main principles of the ICH M10 Guidance remains the same
- Reliable and reproducible bioanalytical methods are essential in drug development:

  "Can you trust & rely on the numbers/peaks/data?"
- Understand the impact of the data/issue on regulatory decisions
- Is your bioanalytical method answering the question?
- Utilize the guidance/tools available
- Early communication is critical!
- Challenges provide us with opportunities!

Bioanalysis:
The Firm Foundation of Drug Development

To have confidence in the clinical implication of the data, need to have confidence in:

- PK & PD parameters
- Concentration values
- Bioanalytical methods

Yu and Bashaw, ***Bioanalysis*** 6(4), 505-510 (2014)

Acknowledgments

- Tina Morris, Maria Nadeau, Mark Arnold, Chad Briscoe, Robert Dodge
- 2023 AAPS PharmSci 360 Organizing Committee
- 2023 AAPS Hot Topic session on ICH-M10 contributors:
  - Eric Woolf, PhD
  - Chongwoo Yu, PhD
  - Enaksha Wickremsinhe, PhD
- AAPS Bioanalytical community leads and members, OSD organizers, moderators, speakers, participants
- AAPS Staff
- AAPS Board of Directors

References

- ICH-M10 https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf
- Heinig K, Miya K, Kamei T, et al. Bioanalysis. 2016;8(14):1465-147
- Gleason CR, Ji QC, Wickremsinhe ER. Evaluation of correlation between bioanalytical methods. Bioanalysis. 2020;12(6):419-426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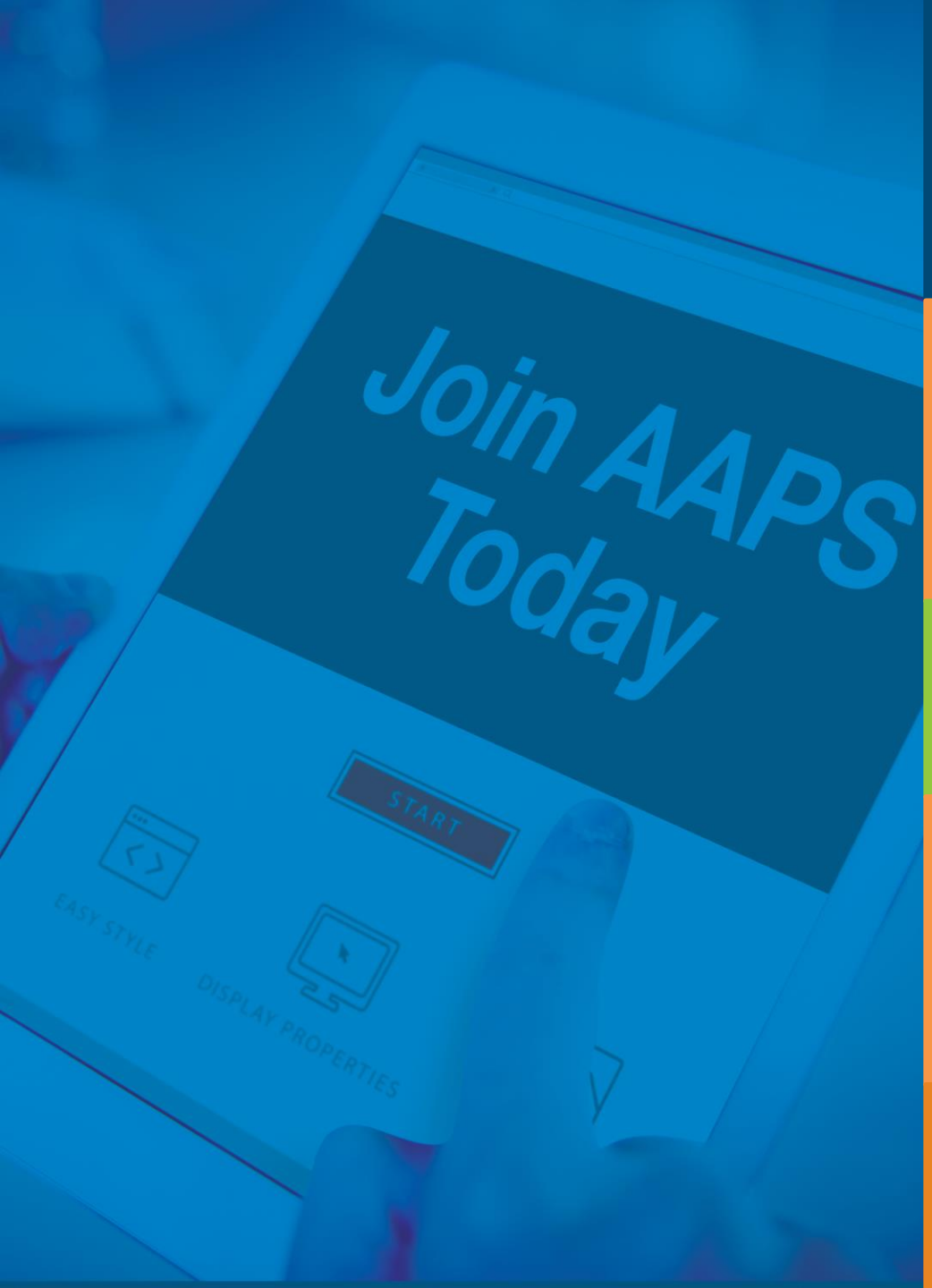
from around the world!



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