AAPS Feedback and Discussions Regarding ICH M10 Guidance and Implementation

Japan Bioanalysis Forum
March 1, 2023

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March 1, 2023

Goals for Today's Lecture

- Provide an overview of AAPS and how the organization is responding as primary association of USA Bioanalysis.
- Summarize current industry trends and discussions ongoing in USA.
- Highlight some new expectations (not comprehensive) included in M10.
  - Already many white papers/ webinars/ discussions comprehensively highlighting the differences.
- Think about next steps

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American Association of Pharmaceutical Scientists

- The American Association of Pharmaceutical Scientists (AAPS) is a professional, scientific organization of approximately 7,000 individual members and over 10,000 actively participating stakeholders employed in academia, industry, government, and other pharmaceutical science related research institutes *worldwide.*
- Over 40 communities with different focus
- AAPS is a global organization based in the USA. Japanese members WELCOME!

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AAPS Bioanalytical Community

- Over 1,000 scientists from around the world
- Community leadership includes co-chairs, vice-chairs, past chairs and secretary.
  - Vice-chair -> chair -> past chair
  - Ideally co-chairs have different expertise and CRO/Pharma mix
    - Rob Dodge – Novartis-Pharma, Ligand Binding Expertise
    - Chad Briscoe – Celerion-CRO, Mass Spectrometry Expertise
- 14 active discussion groups focused on specific key topics.
- Past Open Scientific Discussion Notes (OSDs) available to AAPS Members

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AAPS Bioanalytical Community Discussion Groups

Current Discussion Groups

Chromatographic Bioanalysis: Olga Kavetska, Fumin Li	PK Methodologies Biologics, Cell and Gene: Mark Ma, Tong-yuan Yang	Immunogenicity Assays: Boris Gorovits, Jim McNally	Immunogenicity of Cell and Gene Therapies (collaboration with TPI): Boris Gorovits	Neutralizing Antibody Assays: Lynn Kamen
Flow Cytometry (collaboration with BPM): Steve Eck, Jennifer Stewart	Microsampling and Patient-Centric Sampling: Enaksha Wickremsinhe, Shefali Patel	Data Storage and Processing: Scott Davis, Shibani Mitra-Kaushik	Vaccine Bioanalysis: Shara Dellatore, Andrea Bertolotti-Ciarlet	Non-Liquid Matrices: Faye Vazvaei, Wenkui Li
China Bioanalytical Support: Eric Woolf	qPCR Assays: Amanda Hays	Newly Formed: Critical Reagent, AI / Machine Learning	**All members welcome to bring new topics to incorporate into existing discussion groups or form new standing or ad-hoc discussion groups**	

Circled groups key to M10 work

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AAPS Community Resources

bookmarks

BIOANALYTICAL COMMUNITY

SETTINGS 1

COMMUNITY HOME | DISCUSSION 1.2K | LIBRARY 56 | EVENTS 0 | MEMBERS 1.2K

CREATE ENTRY

EXCEL PROGRAM FOR COMPUTATION OF…

Posted By **Maria Nadeau**
05-16-2019 07:53

133 187

SLIDES AND RECORDING FROM TODAY'S OSD ON…

Posted By **Sanjeev Bhardwaj**
09-20-2022 14:21

93 53

NEW MANUSCRIPT; "QUALITY CONTROLS IN…

Posted By **Mitra Azadeh**
12-11-2018 15:18

83 128

SLIDES FROM THE OSD PRESENTATION ON ICH M…

Posted By **Sanjeev Bhardwaj**
07-06-2022 10:23

65 51

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Filter By: File Type

Sort By: Date Created - Descending

Main (47)

Goals (3)

SLIDES AND RECORDING POSTED FOR THE OSD ON 18JAN2023- BIOANALYTICAL … APPROACHES AND CHALLENGES FOR LNP-MRNA THERAPEUTICS

Posted By **Sanjeev Bhardwaj**
01-26-2023 14:44

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AAPS Engagement Regarding ICH M10

- Conference calls with EBF and JBF
- Land O Lakes Bioanalytical Session (now Summer Scientific Forum)
- 3 Open Scientific Discussions
- PharmSci360 – 3 presentations
- Requested updates, thoughts and feedback from AAPS community leaders on what they are currently doing.
- Topic in 2023 Scientific Meetings
- Future Open Scientific Discussions Planned for 2023
- Active discussions in the community bulletin boards

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Status of Global Adoption

Japan not listed?

- **ANVISA, Brazil** - In the process of implementation;
- **COFEPRIS, Mexico** - Not yet implemented;
- **EC, Europe** - Implemented; Date: 21 January 2023; Reference: EMA/CHMP/ICH/172948/2019
- **FDA, United States** - Implemented; Date: 7 November 2022; Reference: Vol. 87, No. 214, Docket No. FDA-2019-D-1469, p. 67037-67039
- **Health Canada, Canada** - Implemented; Date: 20 January 2023; Reference: File #: 22-108195-929
- **MFDS, Republic of Korea** - In the process of implementation; Date: 1 October 2023;
- **MHRA, UK** - Not yet implemented;
- **NMPA, China** - In the process of implementation; Date: 29 July 2023; Reference: NMPA, China Announcement No. 16 (2023)
- **SFDA, Saudi Arabia** - Not yet implemented;
- **Swissmedic, Switzerland** - Implemented; Date: 25 May 2022; Reference: ICH Guidelines apply in Switzerland automatically upon reaching Step 4: Swissmedic Journal 05/2006, p. 504
- **TFDA, Chinese Taipei** - In the process of implementation;
- **TITCK, Turkey** - Not yet implemented;

https://www.ich.org/page/multidisciplinary-guidelines

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Why isn't FDA BMV Guidance inactive now?

- FDA's 2018 BMV Scope
  A. Non-clinical and clinical development for human medicine
  B. Veterinary (animal) medicine development
  C. Biomarkers
- ICH M10 Scope
  A. Non-clinical and clinical development for human trials
- FDA currently needs 2018 BMV to address veterinary and biomarkers

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Status of Company Implementation Across Industry

- Wide ranging status at companies due to many factors
  - Initially unclear adoption timeline from regulators
  - Differing corporate structures
    - small vs big companies
    - many sites/geographies versus single sites
    - Stricter procedures for updating SOPs
  - Wide number of documents impacted
    - SOPs, Validation protocols, Reporting templates, IT Systems, Training systems
- Will this be a problem with regulators?
- If you are a CRO will it be a problem with sponsors?

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What can you do?

- Ideal scenario – your company would have fully updated and implemented SOPs launched or waiting for your country's adoption to launch.
- If your company is acting slowly?
  - Conduct your own gap analysis.
  - Know the differences from your SOPs to M10 and you will be prepared to discuss the differences.

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Challenges to implement M10

- Words Matter
  - Concomitant, co-meds, fixed dose, etc.
  - Rejected and reinjected run reporting
  - Proper translation and understanding certainly difficult as it can even be confusing for native speakers.
- Clarifications reduce conflicts between docs but create short-term conflicts in process
- You don’t know if you got it right until inspection or review
- Auditors may interpret changes differently.

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Concomitant

- Co-meds, co-dosed, co-formulated, concomitant, fixed dose combinations. Are these all the same? Some yes, some no.
- Two definitions below – there are more
  - Concomitant - something that accompanies or is collaterally connected with something else (www.webster.com)
  - Concomitant - In medicine, it may refer to a condition a person has or a medication a person is taking that is not being studied in the clinical trial he or she is taking part in. (www.cancer.gov)

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ICH M10 - Concomitant

3.2.2. Specificity

Specificity is the ability of a bioanalytical method to detect and differentiate the analyte from other substances, including its related substances (e.g., substances that are structurally similar to the analyte, metabolites, isomers, impurities, degradation products formed during sample preparation, or **concomitant** medications that are expected to be used in the treatment of patients with the intended indication). **If the presence of related substances is anticipated** in the biological matrix of interest, the impact of such substances should be evaluated during method validation, or alternatively, in the pre-dose study samples. In the case of LC-MS based methods, to assess the impact of such substances, the evaluation may include comparing the molecular weight of a potential interfering related substance with the analyte and chromatographic separation **of the related substance** from the analyte.

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ICH M10 - Concomitant

- 5. Incurred sample reanalysis (ISR)

The performance of study samples may differ from that of the calibration standards and QCs used during method validation, which are prepared by spiking blank matrix. Differences in protein binding, back-conversion of known and unknown metabolites, sample inhomogeneity, **concomitant medications** or biological components unique to the study samples may affect measured concentrations of the analyte in study samples. ISR is intended to verify the reliability of the reported sample analyte concentrations

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3.2.8 Stability

For **fixed dose** combination products and specifically labelled drug regimens, the freeze-thaw, benchtop and long-term stability tests of an analyte in matrix should be conducted with the matrix spiked with all of the dosed compounds.

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FDA 2018 - Concomitant

Section 4 - Selectivity and Specificity

When using liquid chromatography/mass spectrometry (LC/MS) methods, the sponsor or applicant should determine the effects of the matrix on ion suppression, ion enhancement, or extraction efficiency. Internal standards should be assessed to avoid interference with the analyte. **Potential interfering substances in a biological matrix include endogenous matrix components such as metabolites, decomposition products – and from the actual study – concomitant medications and other xenobiotics**….

Sponsors should make a scientific judgment about the need to assess these (and any other) potential interferences during method development. During validation, the sponsor should confirm that the assay is free of potential interfering substances including endogenous matrix components, metabolites, anticipated concomitant medications, etc. If the study sample contains more than one analyte and the analytes are intended to be quantified by different methods, the sponsor should test each method for interference from the other analyte

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FDA 2018 – Concomitant / co-meds

Section 7 Stability

For drugs administered as **fixed combinations**, or part of a specific drug regimen, the stability of the analyte should be assessed in the presence of the other drug. The sponsor should also consider the stability of the analyte in the presence of **other co-medications that are known to be regularly administered to patients** for the indication of the drug under development.

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Concomitant / fixed dose – Now What?

- Concomitant – 2 or more xenobiotics that a participant has taken on a trial within a reasonable time period.
  - How to address late phase trials with thousands of pages of patient data?
- Fixed dose – 2 or more drugs that are made together and taken as one product.
  - How about co-dosed but not fixed dose? Eg. Two or more separate pills
- Unfortunately I don't have a definitive answer.

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Reanalysis and reporting of rejected and reinjected runs – 1 of 2

- 3.3.4 Reanalysis of study samples (also in table 1)

  For comparative BA/BE studies, a separate table should report values from rejected runs.

- Table 1: Analysis

  Table of reinjected runs with results from reinjected runs and reason(s) for reinjection

- 3.3.2. Acceptance criteria for an analytical run

  At least 2/3 of the total QCs and at least 50% at each concentration level should be within ±15% of the nominal values. If these criteria are not fulfilled the analytical run should be rejected. A new analytical batch should be prepared for all study samples within the failed analytical run for subsequent analysis. In the cases where the failure is due to an assignable technical cause, samples may be reinjected.

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Reanalysis and reporting of rejected and reinjected runs – 2 of 2

- Careful review of the wording is critical.
- What is required versus what is said? Multiple opinions.
  - Reporting of failed run results only necessary for BA/BE studies.
  - Report failed runs but don't report the failed run results.
  - Report all failed runs and results.
  - Don't report failed run results but have them available upon request.
- Will different regions take a different interpretation?
- Will different companies expect a CRO to approach it differently?

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Reporting

- Significant changes in reporting expectations.
- Assist regulators in understanding the data
- We'll only know for sure if the changes we make are acceptable once submissions are made
- On-going experience sharing will be critical

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Reporting – Big Changes

- Summary of re-assay reasons
- QC graphs and trending
- Reason for reintegration
- Reporting of rejected run values for BA/BE
  - QC/Stds and/or unknowns? Will someone compare valid with invalid data?
  - What happens with differences from valid and invalid data?

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Summarizing Reporting Expectations

- All relevant documentation necessary for reconstructing the study as it was conducted and reported should be maintained in a secure environment.
- Regardless of the documentation format (i.e., paper or electronic) follow the principles of ALCOA-C Attributable, Legible, Contemporaneous, Original, Accurate, and Complete
- Documentation should be readily available for inspection.

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A few more important points to highlight….

- Highlighting deficiencies
  - Assessing back-conversion in MD. Reporting on potential
  - Extrapolated stabilities allowed for small molecule
- Clarifying and updating requirements
  - Dilutions QCs – bracket or match every dilution
    - Bracketing is acceptable, DQCs required in LC/MS but not LBA
  - All study samples should be bracketed by QCs in a run
  - Reinjection reproducibility standard practice now formalized
  - Cross-validation approach clarified – statistical approaches
  - Internal standard stability approach clarified

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Future Considerations

- Interpretations varying across the globe?
- Will countries / regions take their own interpretations or make a supplemental guidance?
- Regulatory bodies will watch what we do in the industry.
- What about technologies outside of scope?
  - qPCR, Flow Cytometry, ELISpot, ???
- AAPS Bioanalytical community discussion groups to monitor and planning OSD's in 2023

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References

- ICH M10 Final Guideline: M10_Guideline_Step4_2022_0524.pdf (ich.org)
- ICH M10 Guideline: BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS Questions and Answers (ich.org)
- BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS M10 Frequently Asked Questions (FAQs) (ich.org)
- European Bioanalysis Forum feedback on draft ICH M10 guideline on bioanalytical method validation during the Step 2b public consultation period Bioanalysis 2020 Mar;12(6s):1-11. doi: 10.4155/bio-2020-0065.
- ICH M10: History, publication and initial perspectives on global implementation Bioanalysis Zone, August 2022 ICH M10: Publication & global implementation - Bioanalysis Zone (bioanalysis-zone.com)
- ICH guideline M10 on bioanalytical method validation and study sample analysis – Frequently Asked Questions (FAQ) 25 July 2022 EMA/CHMP/ICH/660315/2022 European Medicines Agency (M10_Guideline_Step4_2022_0524.pdf (ich.org))

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