Session 2 (BE): Bioanalytical Issues

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 15, 2024 – 9:00 – 9:40 AM

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Bioanalytical Issues from Recent FDA BIMO Inspections and Remote Regulatory Assessments

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A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 15, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

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This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Learning Objectives

- Familiarity with relevant laws and regulations
- Understand the basis for demonstrating bioequivalence (BE)
- Awareness of bioanalytical issues from recent FDA BIMO Inspections and Remote Regulatory Assessments (RRA)

Outline

- Relevant laws and regulations
- Basis for demonstrating BE
- Case studies
- Challenge questions
- References

Relevant US Laws and Regulations

The Federal Food, Drug, and Cosmetic Act (*FD&C Act*)

- The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments)
  - Section 505(b)(2), New Drug Application (NDA)
  - Section 505(j), Abbreviated New Drug Application (ANDA)

Code of Federal Regulations (CFR), Title 21

- Part 312, Investigational New Drug Application
- Part 314.54, Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug.
- Part 314.92, Drug products for which abbreviated applications may be submitted.
- Part 320, Bioavailability and Bioequivalence Requirements

Title 21 Part 320

	Part / Section
▼ **Title 21** Food and Drugs	
▼ **Chapter I** Food and Drug Administration, Department of Health and Human Services	1 – 1299
▼ **Subchapter D** Drugs for Human Use	300 – 499
▼ **Part 320** Bioavailability and Bioequivalence Requirements	320.1 – 320.63
▼ **Subpart A** General Provisions	320.1
§ 320.1 Definitions.	
▼ **Subpart B** Procedures for Determining the Bioavailability or Bioequivalence of Drug Products	320.21 – 320.63
§ 320.21 Requirements for submission of bioavailability and bioequivalence data.	
§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.	
§ 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.	
§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.	
§ 320.25 Guidelines for the conduct of an in vivo bioavailability study.	
§ 320.26 Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.	
§ 320.27 Guidelines on the design of a multiple-dose in vivo bioavailability study.	
§ 320.28 Correlation of bioavailability with an acute pharmacological effect or clinical evidence.	
§ 320.29 Analytical methods for an in vivo bioavailability or bioequivalence study.	
§ 320.30 Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration.	
§ 320.31 Applicability of requirements regarding an "Investigational New Drug Application."	
§ 320.32 Procedures for establishing or amending a bioequivalence requirement.	
§ 320.33 Criteria and evidence to assess actual or potential bioequivalence problems.	
§ 320.34 Requirements for batch testing and certification by the Food and Drug Administration.	
§ 320.35 Requirements for in vitro testing of each batch.	
§ 320.36 Requirements for maintenance of records of bioequivalence testing.	
§ 320.38 Retention of bioavailability samples.	
§ 320.63 Retention of bioequivalence samples.	

Basis for Demonstrating BE

Two drug products (Test and Reference Listed Drug/RLD) are considered bioequivalent if they are **pharmaceutical equivalents** or **pharmaceutical alternatives**

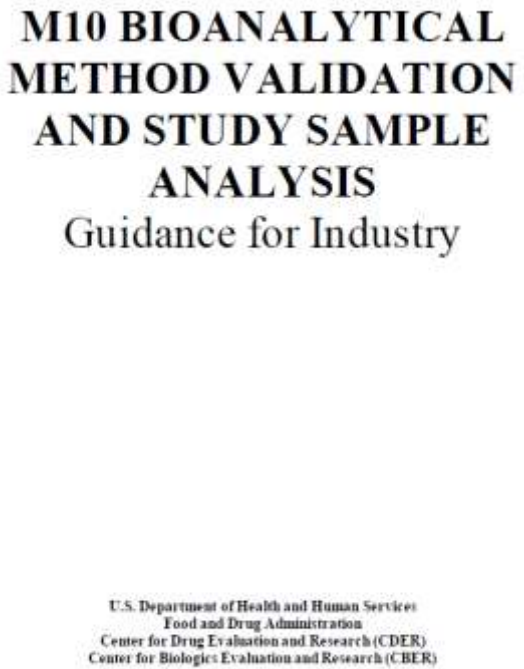
AND

- their **rate and extent of absorption** do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.
- their **extent of absorption does** not show a significant difference with different **rates of absorption** because such differences in the rate of absorption are intentional and are reflected in the labeling.

For drug products NOT intended to be absorbed into the bloodstream:

- BE may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the Test drug and the RLD in safety and therapeutic effect.

FDA's Current Thinking



M10 BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2022
ICH

Inspectional Coverage – Bioanalytical Conduct

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM PROGRAM 7348.004

CHAPTER 48 – BIORESEARCH MONITORING

SUBJECT:	IMPLEMENTATION DATE:
Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Analytical)	05/01/2018

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Product coding not required for biopharmaceutical establishments	48004A BIOANALYTICAL IN-VIVO BA/BE (ANDAS) 48004N BIOANALYTICAL IN-VIVO BA/BE (NDAS AND BLAS) 48004P BIOANALYTICAL PEPFAR ANDA BA/BE 48004Q BIOANALYTICAL PEPFAR NDA BA/BE 48004B BIOANALYTICAL BA/BE - BIOSIMILARS

Case Study #1

- Application type: ANDA
- Product: small molecule; endogenous compound
- Study design: *in vivo* (PK) BE
  - Randomized, two-treatment, two-sequence, four-period, cross-over, single-dose, full-replicate trial
- Bioanalysis methodology: LC-MS/MS

Case Study #1

Objectionable Conditions:

- Higher pre-dose analyte concentrations were observed prior to administration of Test product than Reference Listed Drug from multiple study subjects.
- The pre-dose analyte concentrations did not exhibit expected physiological variability in the subjects mentioned above.
- No adequate explanation or justification for the above observation was provided.

Case Study #1

OSIS Evaluation and Conclusion:

- No discrepancies in bioanalysis were identified.
- The finding impacts the reliability of data from the study. The firm did not offer any substantive explanation that would support the observed pre-dose analyte concentration differences between Test and Reference products.
- Therefore, OSIS concluded that the analytical data from the clinical study are not reliable for Agency review.

Case Study #2

- Application type: NDA
- Product: large molecule
- Study design: *in vivo* (PK) BA
- Bioanalysis methodology: LBA

Case Study #2

Objectionable Conditions:

- The assay did not demonstrate sufficient accuracy to measure analyte concentrations. Specifically, calibration standards and quality control samples were not created using a reference standard of known purity. Nonetheless, the calibration standards were used to back-calculate, assign, and report specific analyte concentrations for the subject samples. These specific concentrations were used to evaluate and support endpoints in clinical studies.

Case Study #2

OSIS Evaluation and Conclusion:

- The observation impacts the study data reliability of reported analyte concentrations. The site did not use analyte reference material of known purity to prepare calibrators and QCs of known concentrations. Thus, it is impossible to calculate and report accurate analyte concentrations of study subject samples.
- However, the percent-change from baseline analyte data should be reliable because the method demonstrated adequate precision when measuring instrument signals from QC samples. That is, the method consistently measured high signals in high QC samples and low signals in low QC samples with adequate reproducibility.
- It was verified that the instrument was properly maintained and calibrated according to site's SOP and CLIA requirements. Thus, the method showed adequate precision and percent-change-from-baseline analyte data are reliable.

Challenge Question #1

True or False?

You must follow all the recommendations listed in the FDA's Guidance for Industry for bioanalytical method validation and sample analysis.

A. True

B. False

Challenge Question #2

Which type of evidence may be used to establish BE?

A. Comparative PK

B. Comparative PD

C. Comparative clinical endpoint

D. in vitro-in vivo correlation (IVIVC)

E. All of the above

References

- M10 Bioanalytical Method Validation and Study Sample Analysis (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m10-bioanalytical-method-validation-and-study-sample-analysis)

- Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application, 2021 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug)
- Bioavailability Studies Submitted in NDAs or INDs – General Considerations, 2022 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations)
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, 2003 (www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-nasal-aerosols-and-nasal-sprays-local-action)

- Product Specific Guidance (www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development)

- Applications Covered by Section 505(b)(2), 1999 (www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2)
- Determining Whether to Submit an ANDA or a 505(b)(2) Application, 2019 (www.fda.gov/regulatory-information/search-fda-guidance-documents/determining-whether-submit-anda-or-505b2-application)

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  - PMT and CREST

Questions?

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UK MHRA Bioanalytical Observations and Findings from recent Inspections

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MHRA Bioequivalence (BE) Inspections

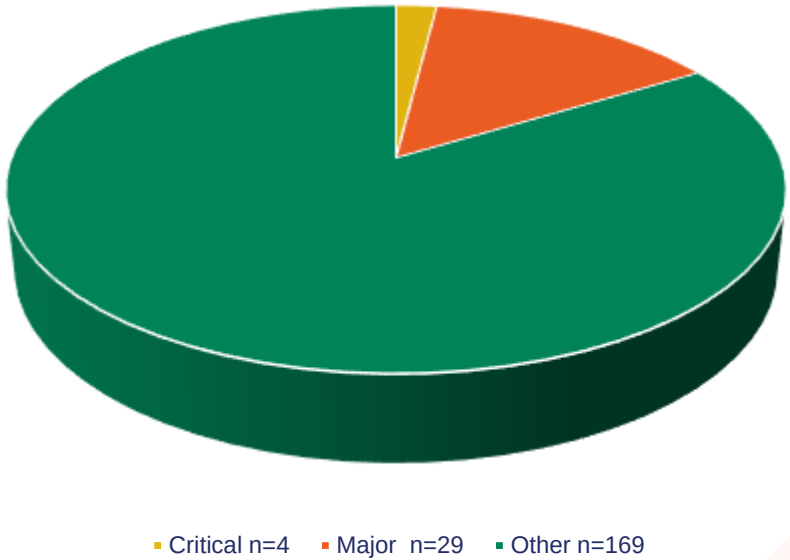
24 inspections performed since 2019

Remote (office based) inspections between October 2020 and June 2022.

Combination of inspections approaches since June 2022

- Remote
- On-Site
- Hybrid

Distribution of Findings 2019 - 2023



Critical Findings (n=4)

Subject Eligibility**

Method Validation**

Data Integrity**

Clinical Sample Analysis**

**Ineligible subjects recruited into studies

**Related to clinical sample analysis

Major Findings (n=29)

CRF/Source Data (n=3)

Subject Eligibility (n=2)

IMP Management (n=2)

Quality Assurance

Subject Safety

Facilities and Equipment

Archiving

Medical Oversight

Method Validation (n=4)

Data Integrity Controls (n=4)

Clinical Sample Analysis (n=5)

Quality Systems

Competent Authority

Reporting

Data Management

MHRA Key Messages

- Method Validation
  - Stability
- Clinical Sample Analysis
  - Run Acceptance Criteria
- Data Integrity Controls
  - Dynamic data

- Make effective use of regulatory guidance
- Transparency
- Data security and control

Method Validation - Stability (1)

- A number of laboratories have failed to analyse the prepared stability samples intended to generate long term stability immediately after preparation.
- Instead opting to store all samples generated.

Method Validation - Stability (2)

ICH

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS
M10

Final version
Adopted on 24 May 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Stability of the analyte in the matrix is evaluated using low and high concentration QCs.

Aliquots of the low and high QCs **are analysed at time zero** and after the applied storage conditions that are to be evaluated.

Section 3.2.8 (Stability)

Method Validation - Stability (3)

Laboratory procedures did not contain a requirement to analyse stability samples immediately following initial preparation. Therefore, there was no assurance that stability samples met acceptance criteria prior to storage.

What can be done at this stage?

Clinical Sample Analysis - Run Acceptance Criteria (1)

- Inclusion of company specific acceptance criteria
- These additional criteria are not always applied consistently
- Limited documentation supporting use of additional criteria

Clinical Sample Analysis - Run Acceptance Criteria (2)

If the rejected calibration standard is the LLOQ, the new lower limit for this analytical run is the next lowest acceptable calibration standard of the calibration curve. … If the highest calibration standard is rejected, the ULOQ for this analytical run is the next acceptable highest calibration standard of the calibration curve

Section 3.3.2 Acceptance Criteria for an Analytical Run

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ICH HARMONISED GUIDELINE

BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS
M10

Final version
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Clinical Sample Analysis - Run Acceptance Criteria (3)

- Considerations:
  - Are the additions necessary?
  - Have you documented your rationale?

Laboratory procedures were found to contain issues with respect to analytical run acceptance criteria, where requirements were not in accordance with regulatory guidance

As a consequence of the policy, analytical runs which would otherwise have been considered acceptable were being repeated and the original results obtained not considered for pharmacokinetic analysis.

Data Integrity Controls – Dynamic Data (1)

- We continue to see static data being used for review of bioanalytical data which has been acquired in a dynamic format

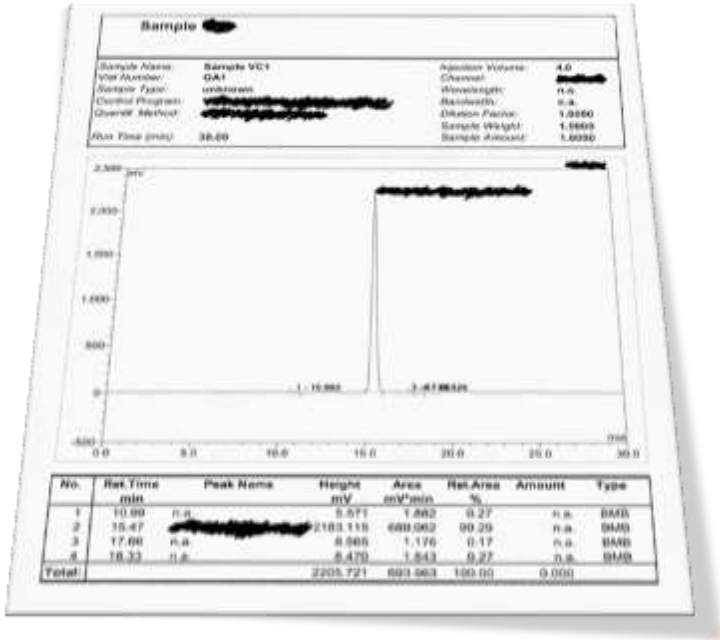
Data Integrity Controls – Dynamic Data (2)

Raw data must permit full reconstruction of the activities. Where this has been captured in a dynamic state and generated electronically, paper copies cannot be considered as ‘raw data’.

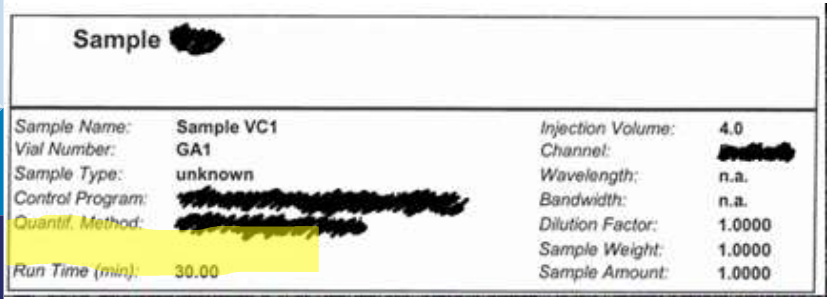
Definitions section 6

Data Integrity Controls – Dynamic Data (3)

- Chromatogram for stability assessment.
- Generated in a system assessed for DI controls.



Data Integrity Controls – Dynamic Data (4)



Sample [redacted]

Sample Name:	Sample VC1	Injection Volume:	4.0
Vial Number:	GA1	Channel:	[redacted]
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	[redacted]	Bandwidth:	n.a.
Quantif. Method:	[redacted]	Dilution Factor:	1.0000
		Sample Weight:	1.0000
Run Time (min):	30.00	Sample Amount:	1.0000

- Chromatogram print out modified for prior to review stage
- Removal of acquisition date and time

Data Integrity Controls – Dynamic Data (5)

The review of data from the bioanalytical department was not performed on the dynamic data but flat files (PDF or paper prints outs) which was inappropriate. Data from the software was acquired electronically in a dynamic state and static paper/PDF copies of the data, in isolation, cannot be considered raw data as the dynamic nature was lost upon printing.

- Considerations:
  - Why would you move data out from your secure systems?
  - Removal of opportunities is only part of the puzzle
    - Look to achieve the ‘right environment’ where mistakes can be discussed.

Critical Findings (n=4)

Subject Eligibility**

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Method Validation (n=4)

Data Integrity Controls (n=4)

Clinical Sample Analysis (n=5)

Quality Systems

Competent Authority

Reporting

Data Management

Summary

- Please make effective use of guidance.
- Documentation to support decision making is crucial.
- Exercising control over your data important, don’t let your hard work go to waste.
- Act before issues escalate.

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