Drugs and Biologics

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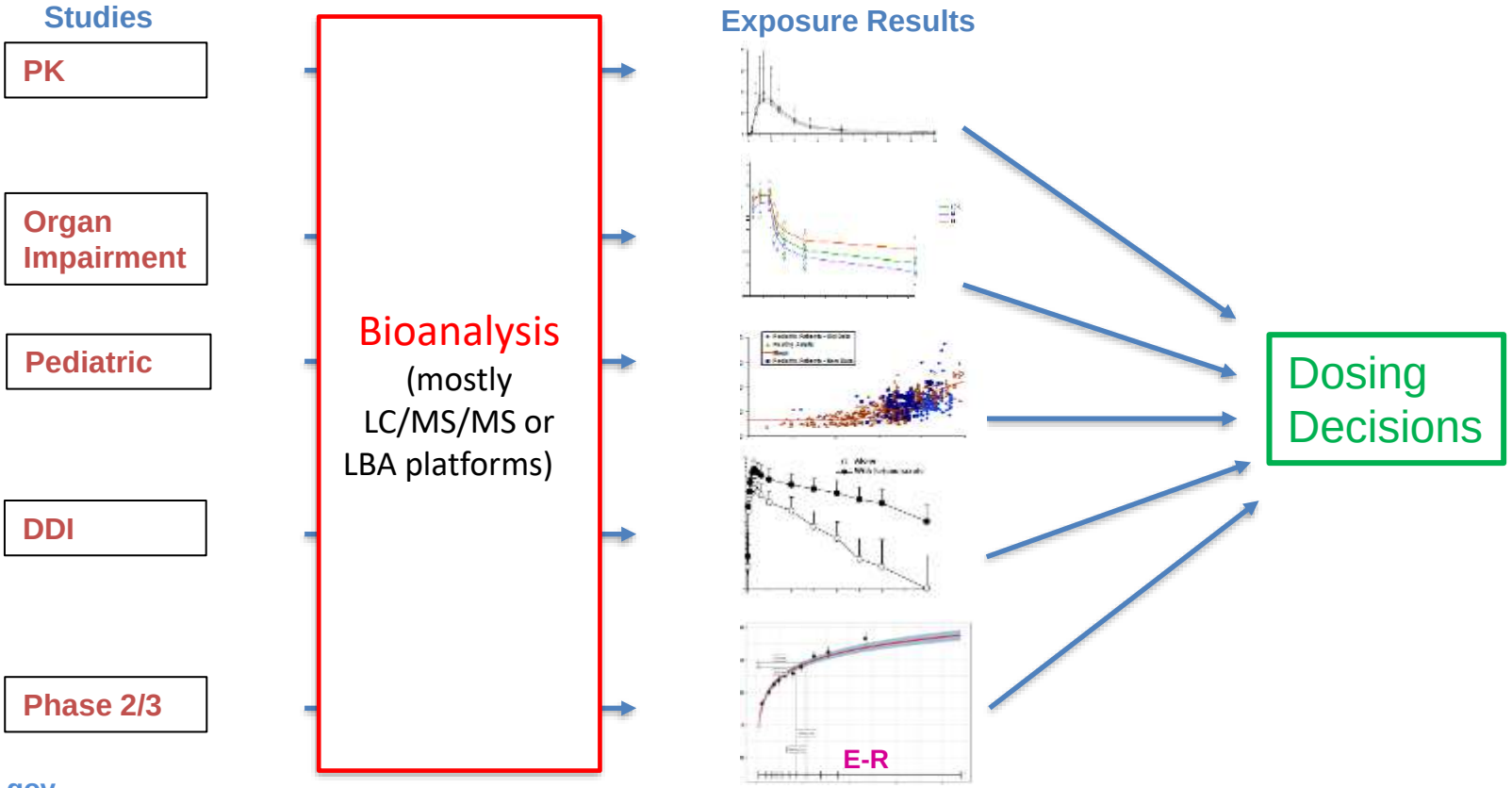
SBIA, June 30, 2020: Regulated Bioanalysis Workshop: Current Requirements and Expectations

Overview

- Why do we need BMV?
- What do we need to know about an assay?
- What do OCP reviewers look at?
- What issues do we often observe? Examples
- What can you do?

Why Do We Need BMV?



Why Do We Need BMV?

To ensure the reliability of the concentration data

Make meaningful clinical decisions

What Do We Need to Know About An Assay?

- What is the purpose of this assay?
- Am I measuring what I think I am measuring?
- How much variability/error is in the measurement?
- What are the limits to these measurements?
- How do handling conditions affect the measurement?

What We Do & Review Time Line

Clinical Pharmacology-related Studies

- **PK**
- **Organ Impairment**
- **Drug Interaction**
- **Pediatric**
- **Population PK**
- **Exposure-response**
- **Bioanalytical**

Incomplete information reduces review time!

- Handicaps reviewers' evaluation.
- May result in discarding studies /complete response.

Source: CDER 21st Century Review Desk Reference Guide
https://www.fda.gov/media/78941/download#:~:text=The%20timelines%20for%20NMEs%20and,of%20submission%20of%20the%20application).

What do we look for?

- Potential assay issues in validation
  - Selectivity, Specificity, Sensitivity
  - Reasons for multiple changes to method
  - Several unsuccessful P&A runs
  - ‘Outliers’
  - Several missing runs
- In study assay performance

What do we look for?

- Complex assays, e.g., enzyme digestion, endogenous, free/bound:
  - do handling of QCs reflect study samples
- Stability: Robust? Multiple reanalysis?

  Does it adequately cover the study period?

  Are stability QCs made with the right entity?
- Multiple Methods: Cross-validated? Study results cross-compared?

What issues do we often observe?

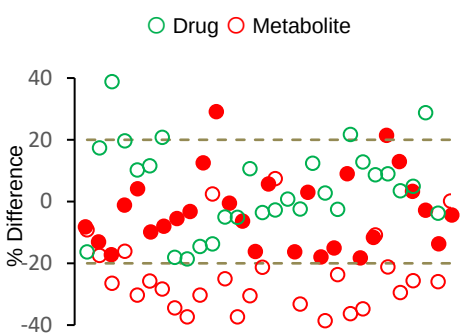
- Cross-validation issues
- Stability Issues
- Unexpected issues
  - Glossed over or impact not discussed.
- Cannot locate the analytical reports?
- At times only validation or analytical reports submitted.

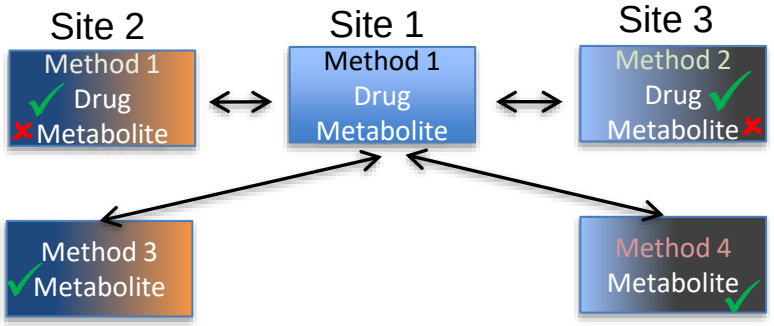
Some critical, some not!

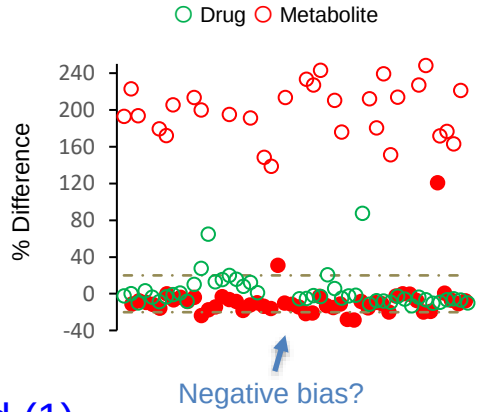
Example 1:

Prospective cross-validation with incurred samples

- 4 Methods: Developed at different stages
  - Modified: site changes, extraction, chromatography







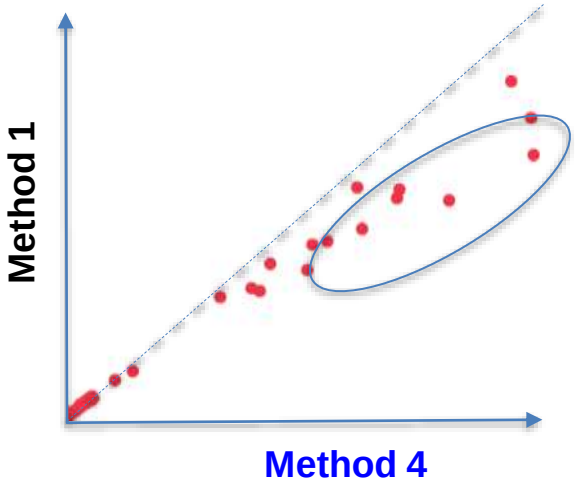
All methods cross validated to the original method (1)

Sufficient?

Example 1: Contd.

Comparison of concentrations?

- Method 4 tends to have a negative bias at high concentrations compared to Method 1.
- Is this an issue?
- Not in this case.
  - Method 4 analyzed all samples from a single stand alone Phase 1 study.

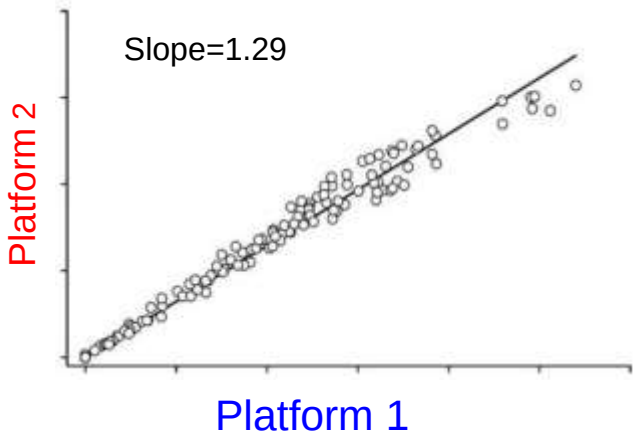


Potentially a problem if studies were cross-compared or analyzed by both methods, and used for dosing decisions or labeling.

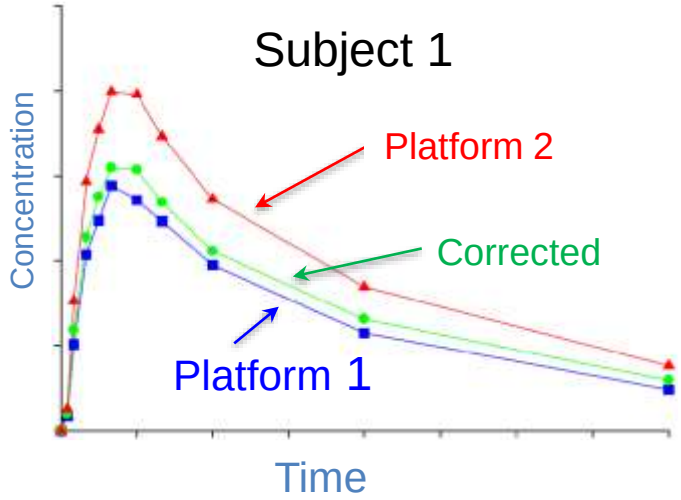
Example 2

Cross validation: Can we live with bias?

Cross-validation



Individual PK Comparisons



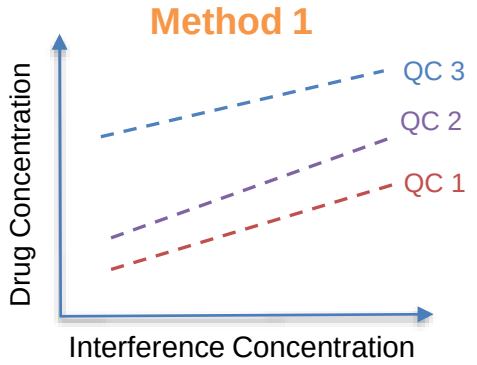
- Platform 2 produces higher concentrations
  - but bias appears constant
- Correcting for bias, shows overlap

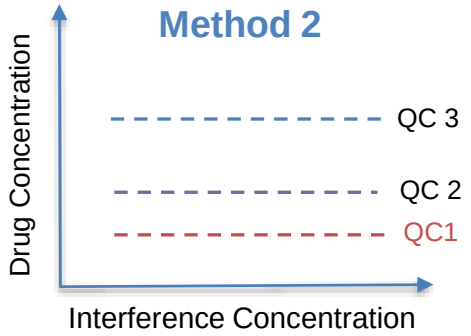
Source: Kothare PA, et al. (2016) AAPS J. 18(2), 519-527

Example 3

Important to monitor method accuracy

- **Method 1:** Analyzed samples from a pivotal and supporting clinical studies.
  - Investigations: Assay interference leading to bias in drug estimation.
- **Method 2**: Developed & validated a new method.
  - Established no assay interference.

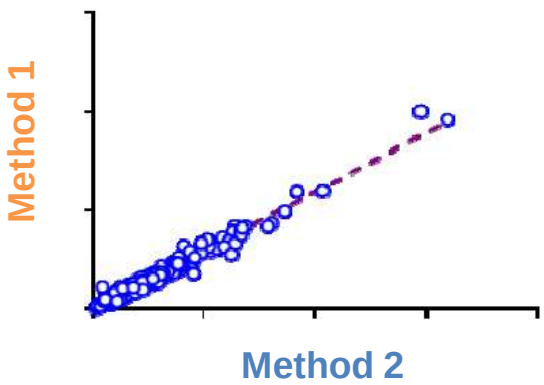




Example 3: Contd.

Performance in study samples?

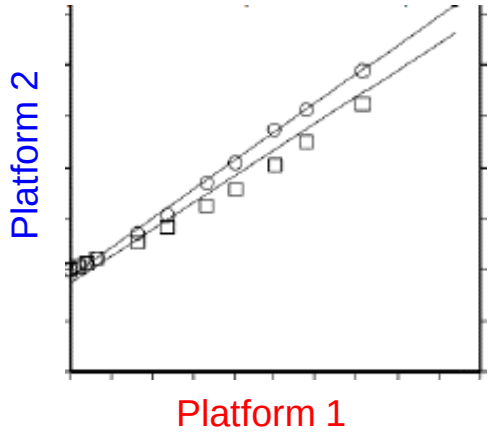
- Subset of clinical samples analyzed by both methods
  - Correlation observed.
  - Positive bias in concentrations from **Method 1** vs. **Method 2**.
- Pivotal Study: Reanalyzed with Method 2.
- Supporting Study: Correction factor used because study samples cannot be reanalyzed for potential sample integrity issue due to long sample storage.



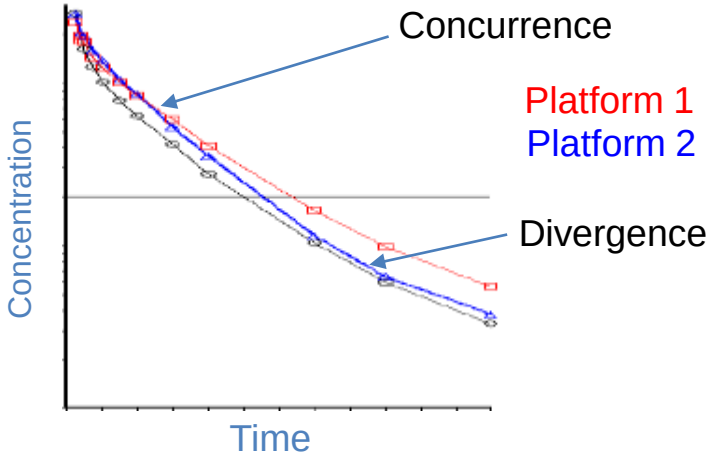
Example 4

Cross validation: When bias is not constant?

Cross-validation



Individual PK Comparisons



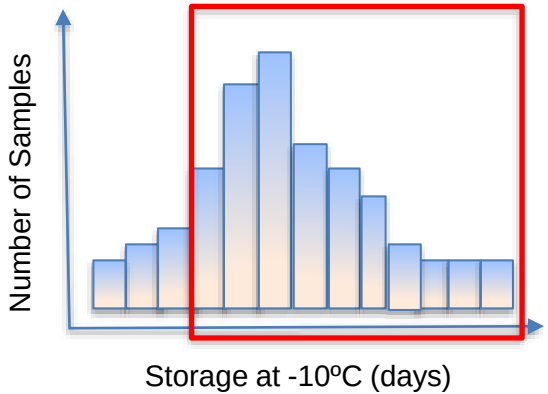
Are the methods comparable?

- Platform 2 AUC ~30-40% < Platform 1 AUC.

Platform 2 would have resulted in higher dose.

Example 5: Stability

- Freezer conditions of clinical study samples altered mid-way during storage (-10°C → -80°C).
- Validated stability for the initial frozen storage conditions does not cover sample storage period.
- Only 30% of study samples from pivotal study within confirmed stability.



Insufficient study samples for PK M&S.

Example 6: Stability

Address unexpected findings

- Study X: Phase 2 - Measured Drug and Metabolite.
- Analytical Report: Samples from 40% of patients for metabolite were analyzed beyond validated storage stability.
- Report did not address impact.
- Information Request: Identify the samples, and compare concentrations versus samples within the validated stability period.

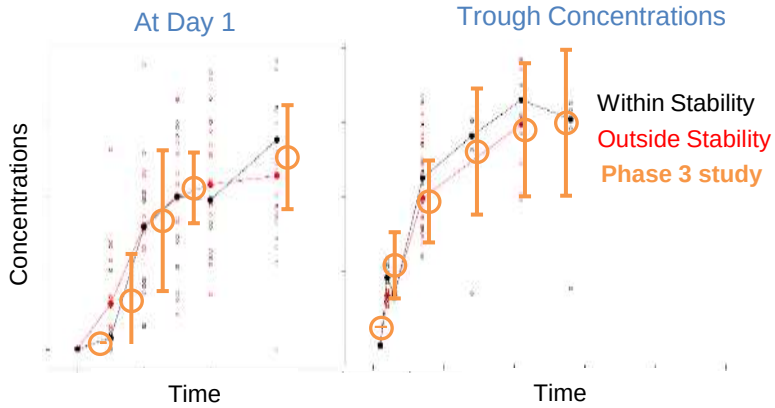
Example 6: Contd.

Assess Impact

- Mean metabolite levels similar and with overlapping variability in Study X.
  - Also, similar to concentrations in the Phase 3 study.

Not an issue in this case: Metabolite has relatively low activity.

Conclusions were based on parent drug.



Potentially a problem when results are used for dosing decisions or labeling.

What can you do?

- Understand the purpose of the assay.
  - i.e., questions you are trying to answer in validation.
- Unexpected findings during validation & in-study analyses.
  - Report in the analytical/validation reports
  - Address the impact in the analytical/validation reports.
- Incomplete information reduces review time.
    - May result in discarding studies or complete response!
- Include analytical reports in Module 5.3.1.4 or clearly label as an appendix to CSR

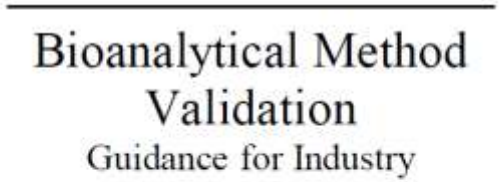
Early FDA interaction recommended for….

- Novel Technologies.
  - Comparison to established approaches recommended.
- Assay-related Issues.

Last, but not the least……

Follow the FDA BMV guidance

https://www.fda.gov/media/70858/download

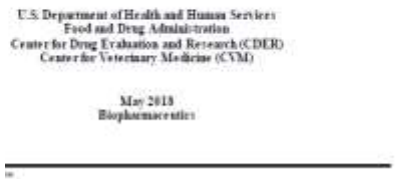

Bioanalytical Method Validation
Guidance for Industry

Summary templates for bioanalytical methods used in clinical pharmacology studies

https://www.fda.gov/media/131425/download


Bioanalytical Methods Templates

Guidance for Industry
Technical Specifications Document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Challenge Question 1

- You repeated L-T stability assessment as the first assessment failed due to a ‘suspected’ conduct issue.
- In the validation report, do you report:
  1. L-T data from only the 2nd assessment? ☐
  2. #1 and Mention the reason the reassessment? ☐
  3. #2 and data from 1st assessment ☐
  4. #3 and pooled data from both assessments ☑

Challenge Question 2

- You decided to switch to a high throughput method during late clinical development of Drug X.
- You have sufficient volumes of study samples
- You plan to cross validate the methods with:
  - ❑ Blinded QCs
  - ☑ Blinded QCs and subset of study samples
  - ❑ Blinded QCs and pooled study samples

Thank you