What meta-analysis can tell you about the performance of bioanalytical methods

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Learning Objectives

I. Describe bioanalytical data submitted to FDA

II. Explore the utility of meta-analysis on bioanalytical data

III. Show an example of FDA inspection that used meta-analysis

IV. Identify benefits and limitations of meta-analyses

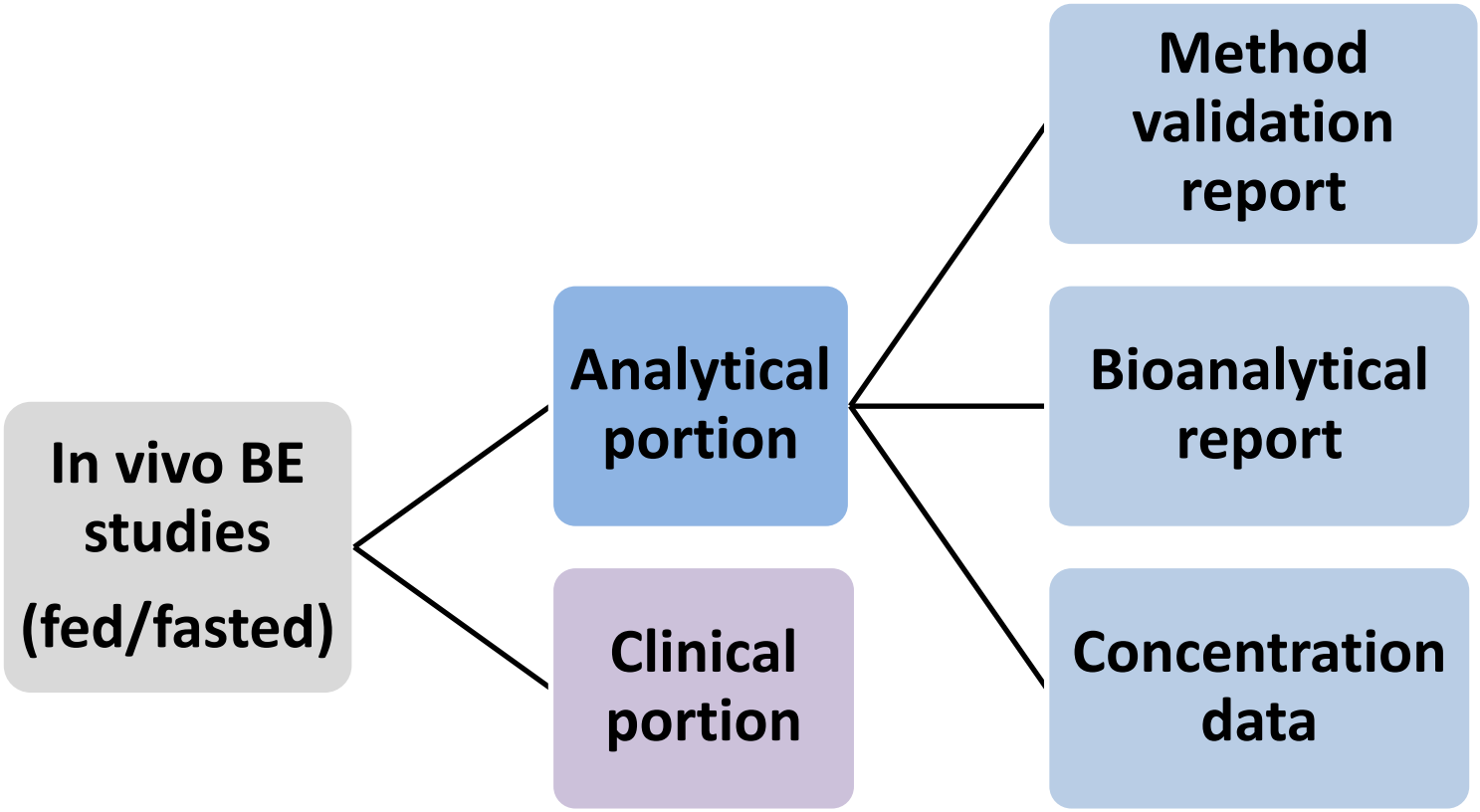
V. Discuss future steps

Bioanalysis in the Industry

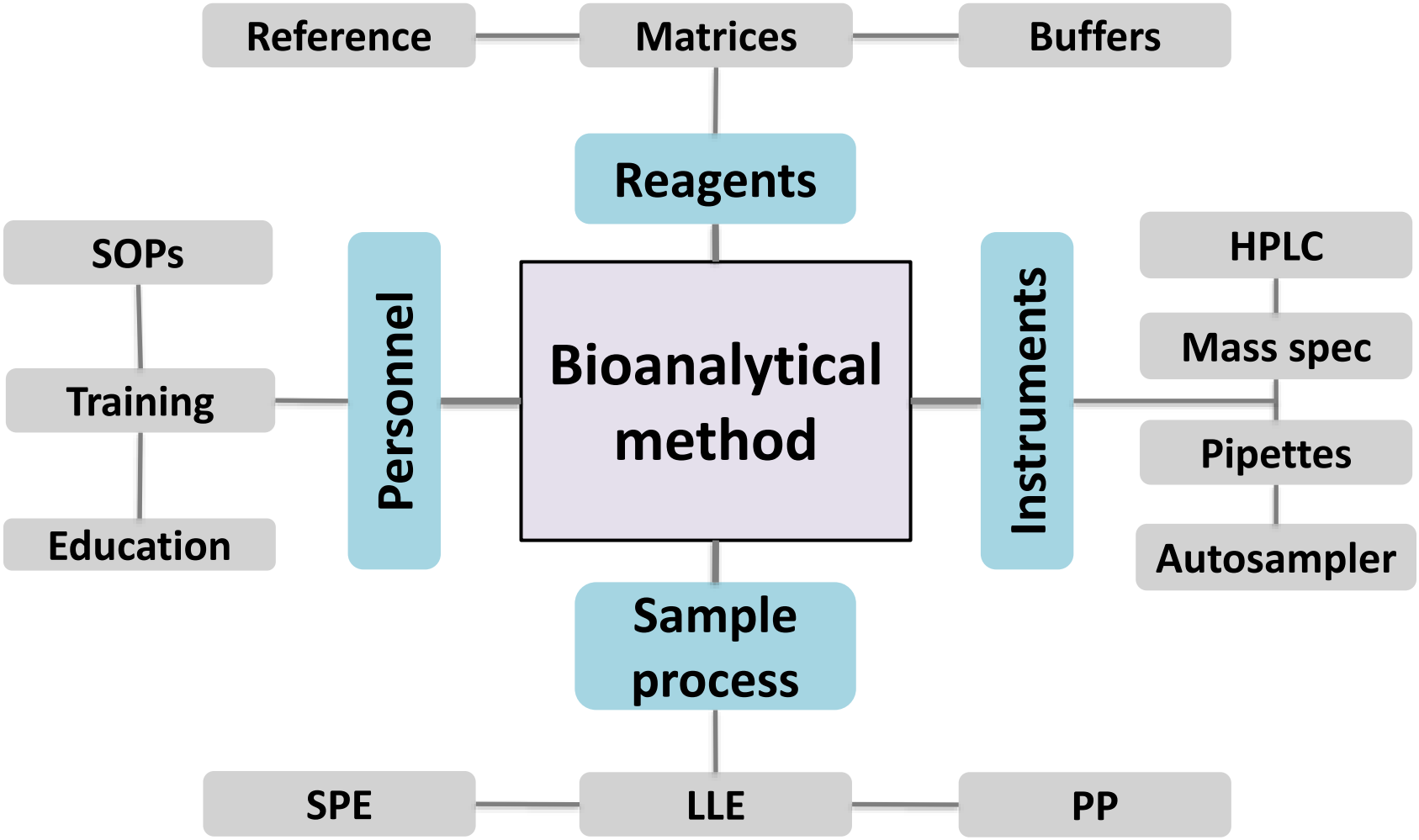
- Bioanalysis occurs in silo
- Companies create methods independently
- Published methods often lack details
- The FDA has a mountain of bioanalytical data from various companies
- Can we leverage the bioanalytical data?

BIOANALYTICAL DATA SUBMITTED TO THE FDA

Usual Bioanalytical Data in Drug Applications



Available Method Information*



*Not an exhaustive list

UTILITY OF CONDUCTING META-ANALYSES ON BIOANALYTICAL DATA

Assess Intra and Inter-Method Performance

Benchmark results

- Dynamic range
- Sensitivity
- P&A

Profile analytes

- Stability
- Matrix effects

Compare methods

- Good outputs
- Areas of concern

RECENT EXAMPLE OF FDA INSPECTION AND META-ANALYSES

Inspection

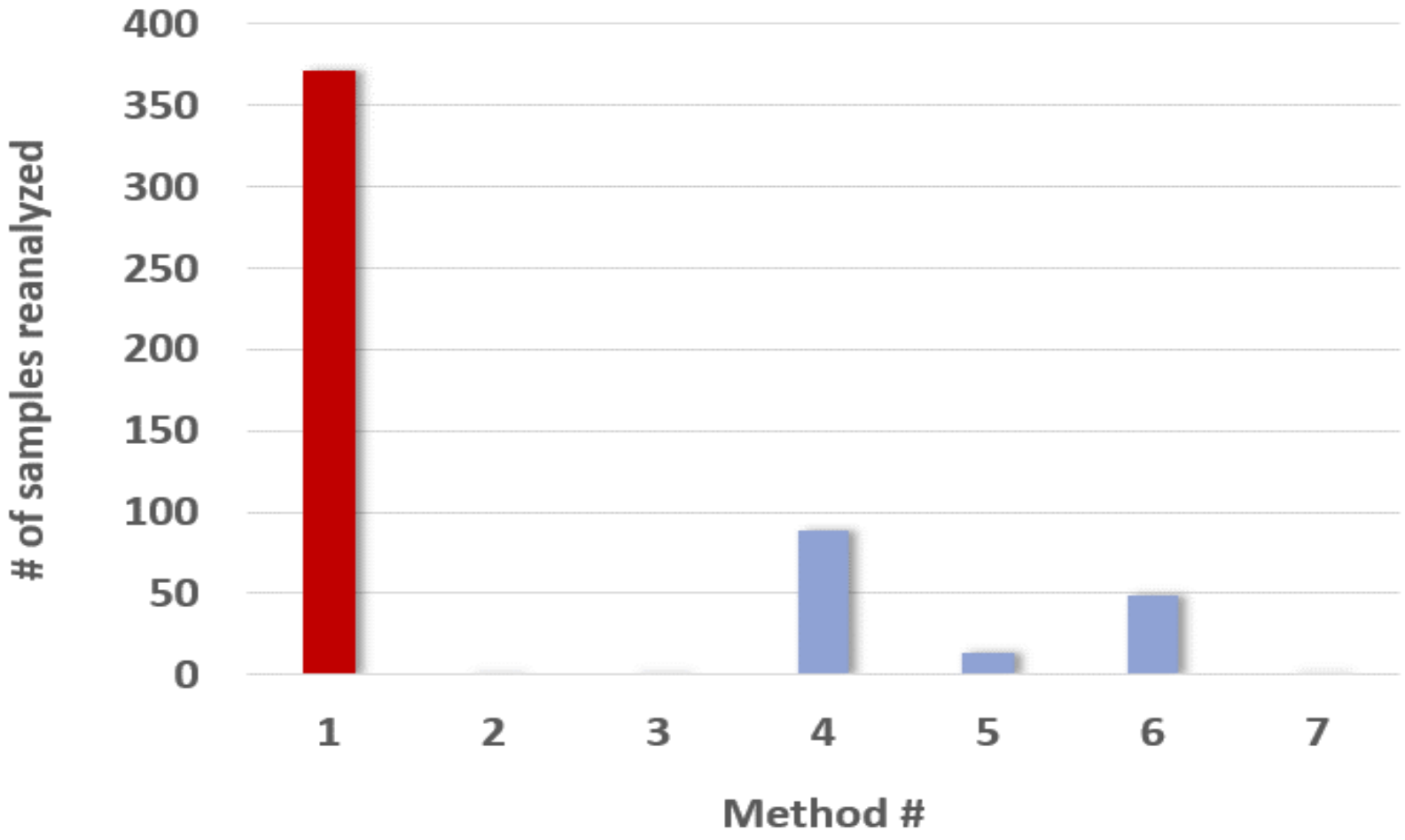
- One BE study (n=60), crossover, fed conditions, PK endpoint
- Compared analytical data from 7 similar methods submitted to FDA
- Meta-analyses focused on in-study performance
    - Subject sample reanalysis
    - Failed runs
    - ISR
    - QC performance

LC/MS-MS Method Characteristics*

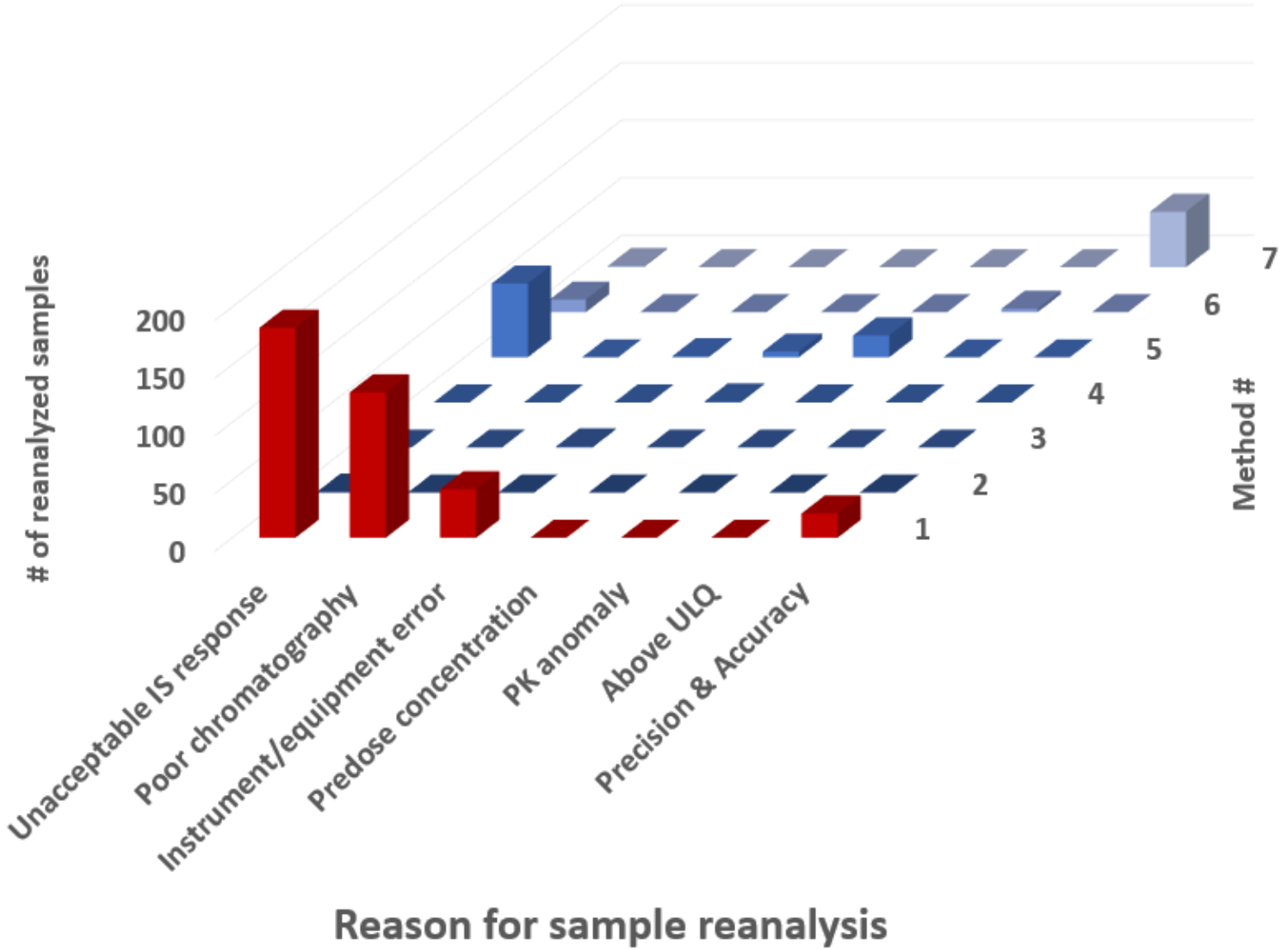
Method	Internal standard	Sample process	Range (ng/mL)	Mobile phase (organic:buffer)
1	**Isotope**	**LLE**	**5-1500**	**70:30**
2	analogue	SPE	5-1500	Not reported
3	Isotope	LLE	5-3000	Not reported
4	Isotope	SPE	2-2000	70:30
5	Isotope	LLE	10-1500	80:20
6	Isotope	LLE	2-1400	80:20
7	Isotope	LLE	10-1500	80:20

***Not an exhaustive list**

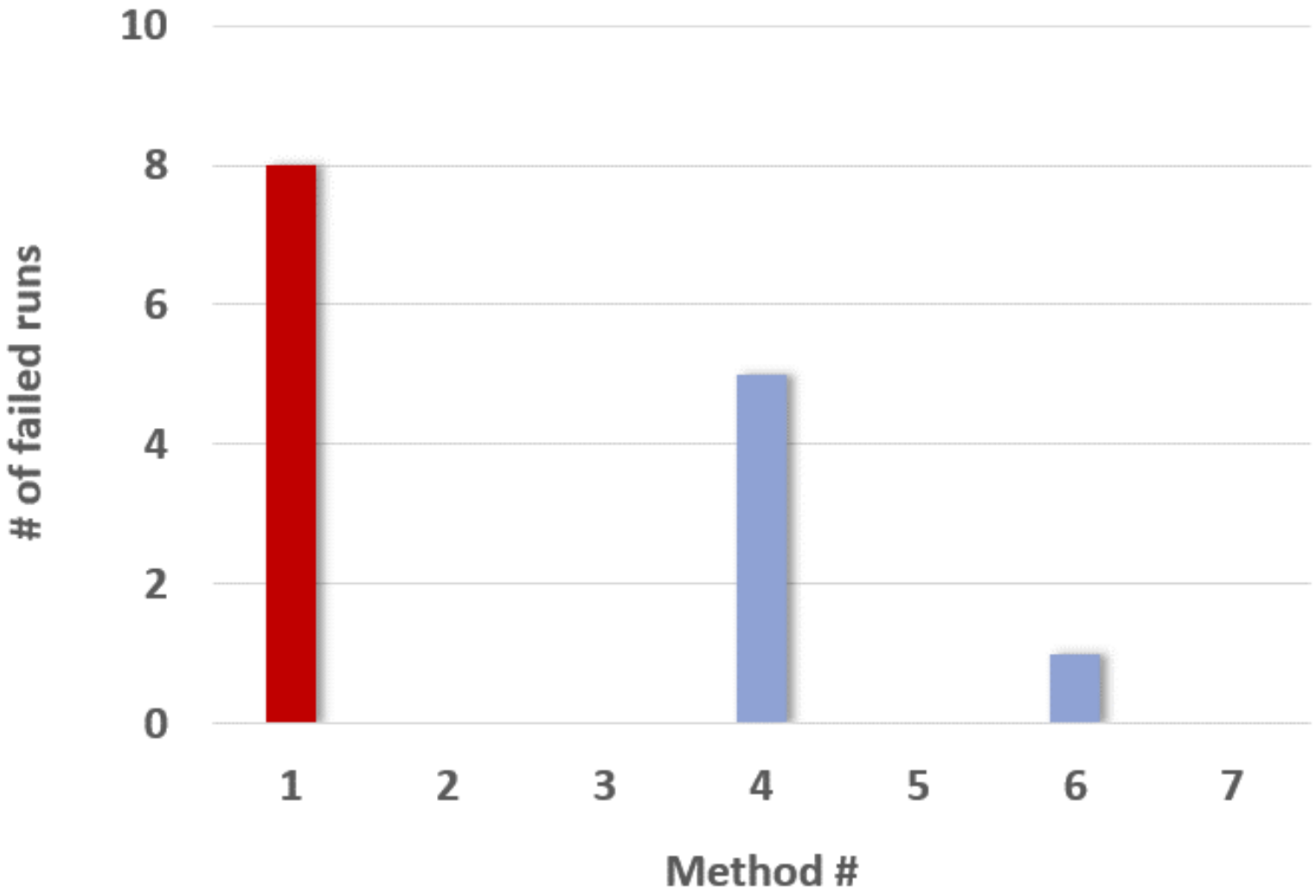
Results – # of reanalyzed samples



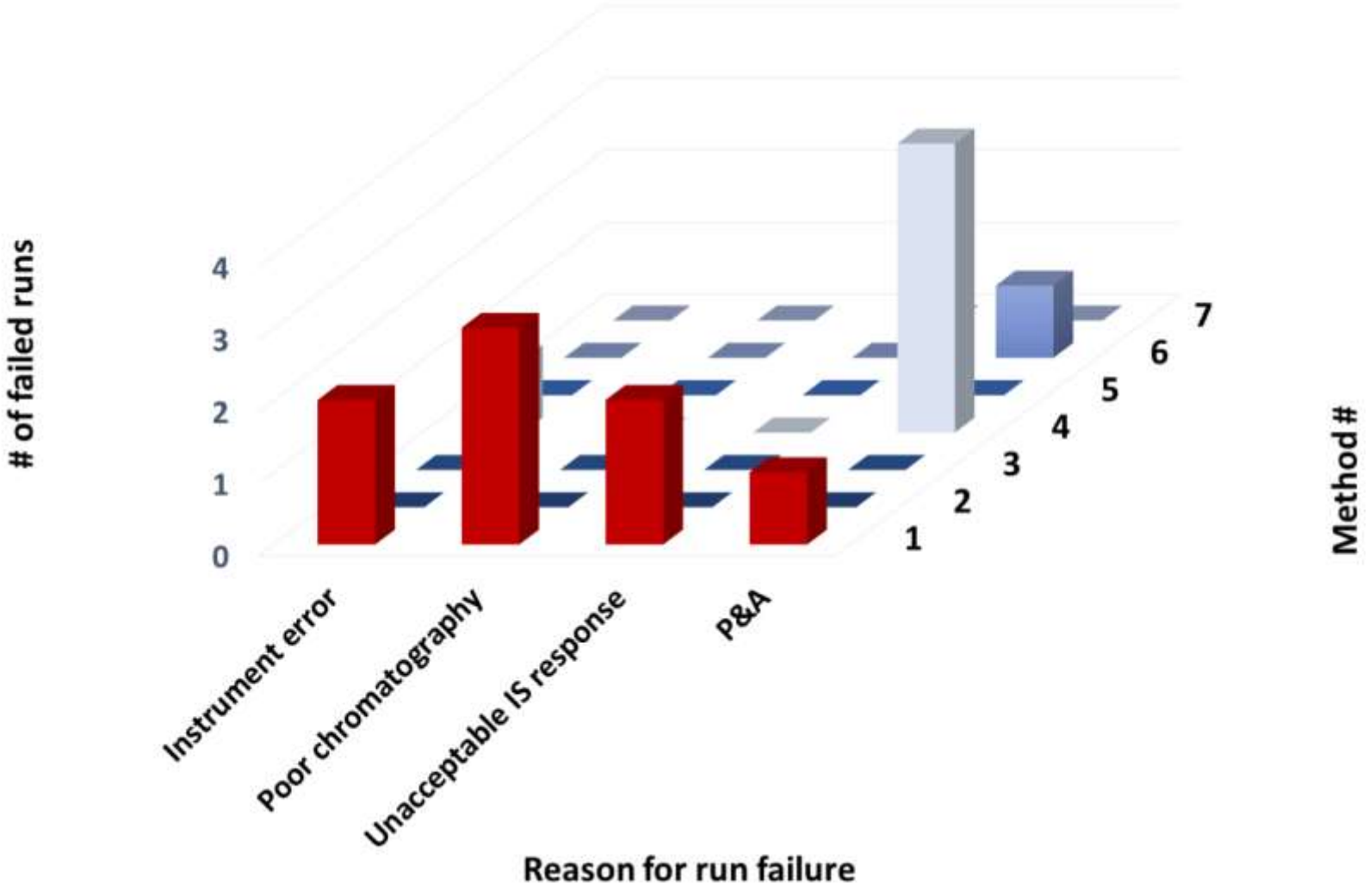
Results – Reason for sample reanalysis



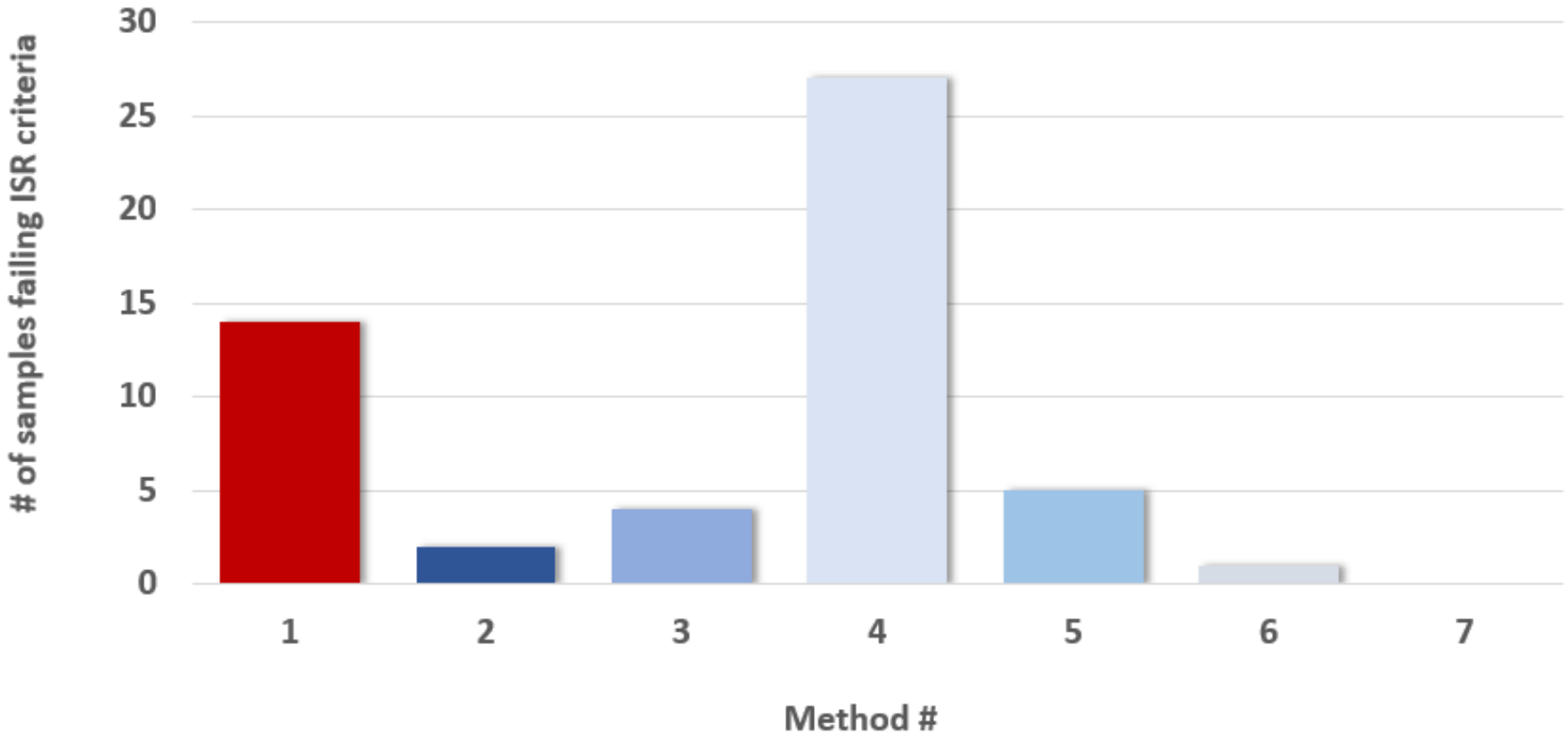
Results - # of failed runs



Results – Reason for run failure

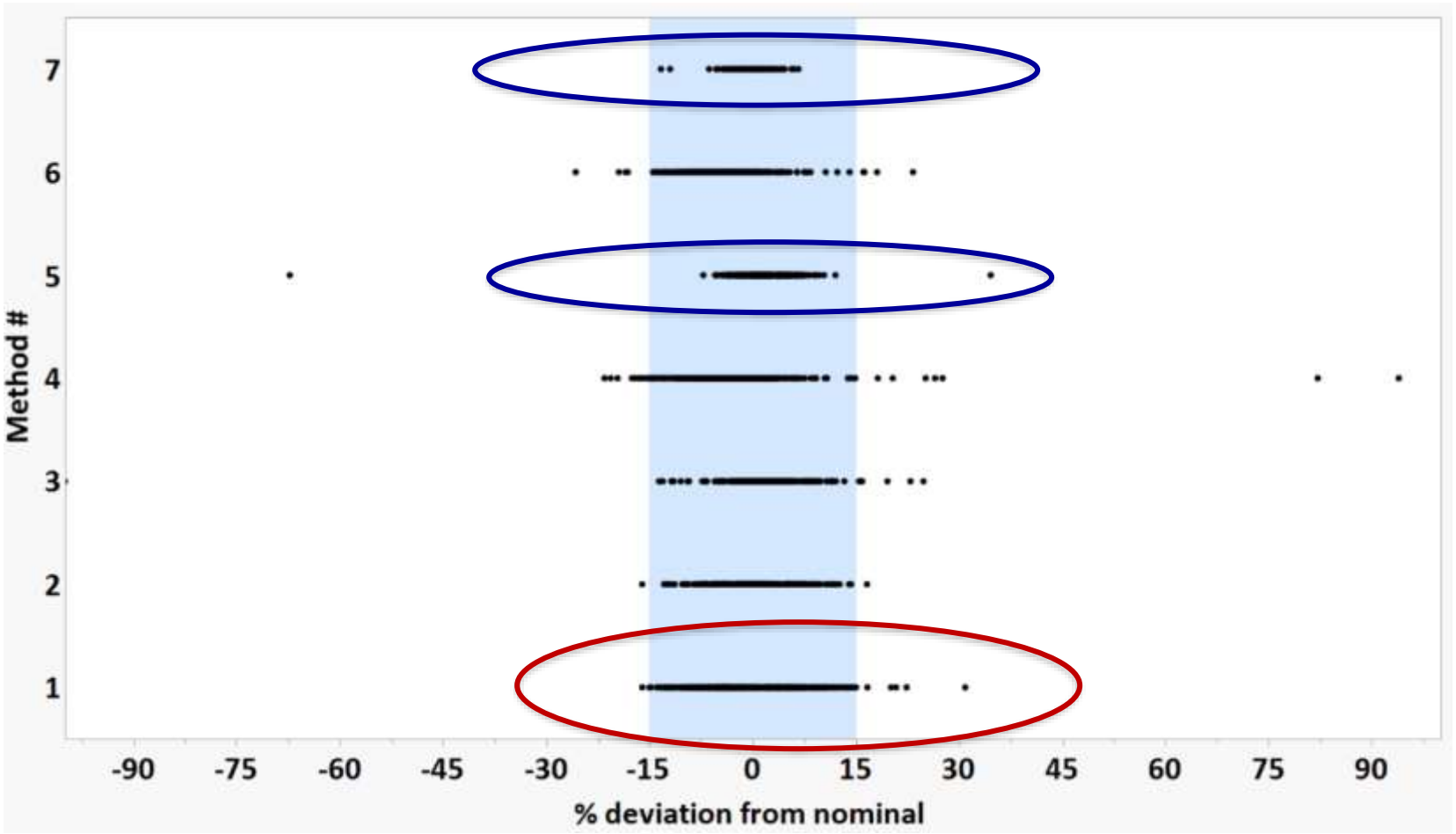


Results – Samples failing ISR Criteria*

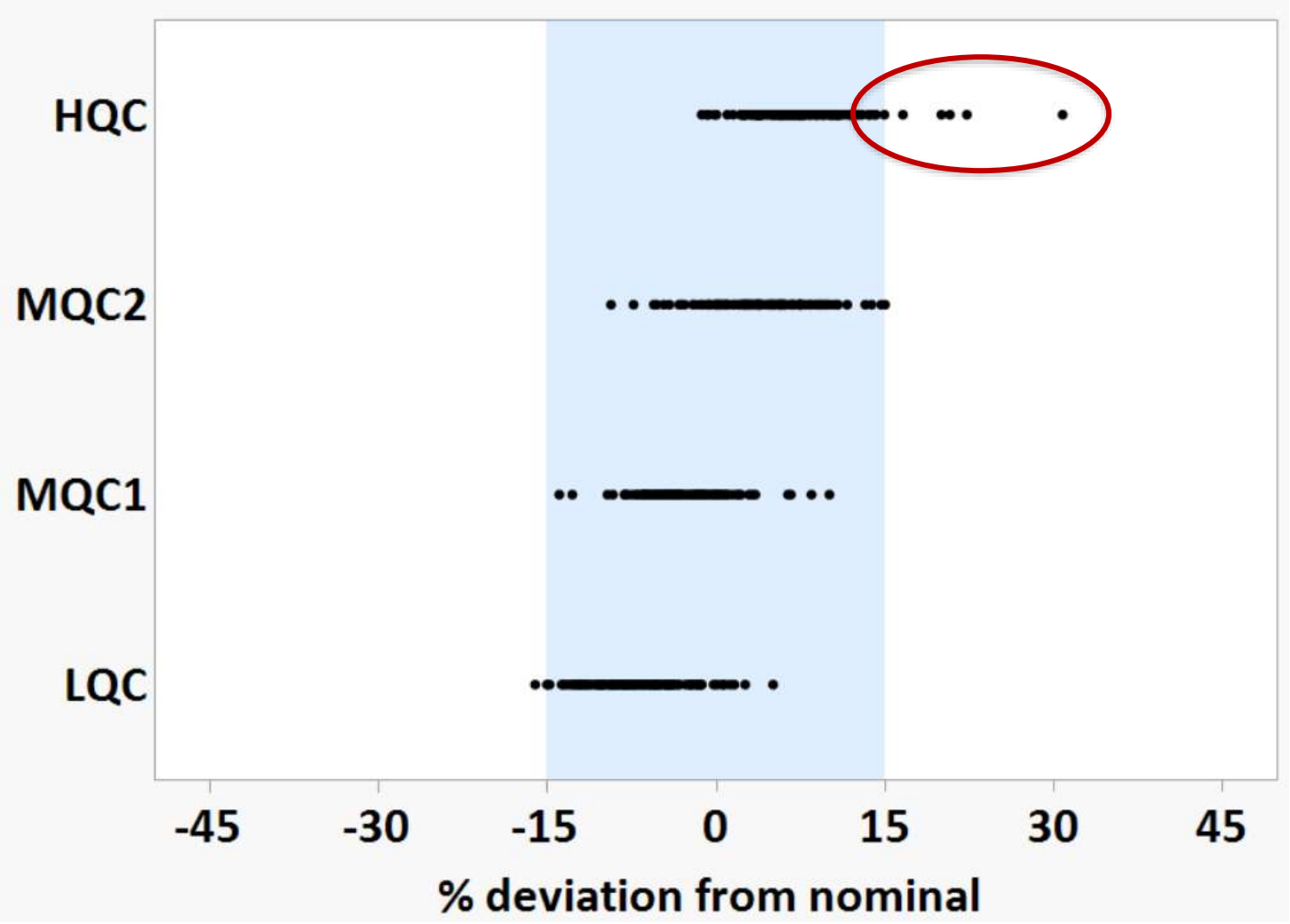


*Same trend observed for % of samples repeated for ISR

Results - QC performance among methods



Results - QC Performance for Method 1



Summary

- **Meta-analyses**
  - Among all 7 methods, method 1 had:
    - ↑ # reanalyzed samples
    - ↑ # failed runs
    - 2nd ↑ # samples with failed ISR criteria
    - Issues with HQC, but all sample concentrations < HQC
- **Inspection**
  - No objectionable conditions were observed
  - Confirmed instrument errors, poor chromatography, and excessive ISV

BENEFITS AND LIMITATIONS OF META-ANALYSES

Limitations

- Different companies
- Different materials and method parameters
- Technological advances

Benefits

- Allows for focused FDA inspections
  - Meta-analyses revealed troublesome spots with method 1
  - Time was allocated to audit those spots
  - FDA inspection was not conducted in silo
  - High return on investment – 7 methods were reviewed!

Benefits (Cont.)

- Industry outreach
  - Company visually reviewed meta-analyses results
  - Company identified possible causes for inspectional findings
  - Company may use a different instrument brand and refine method parameters for future studies with same analyte

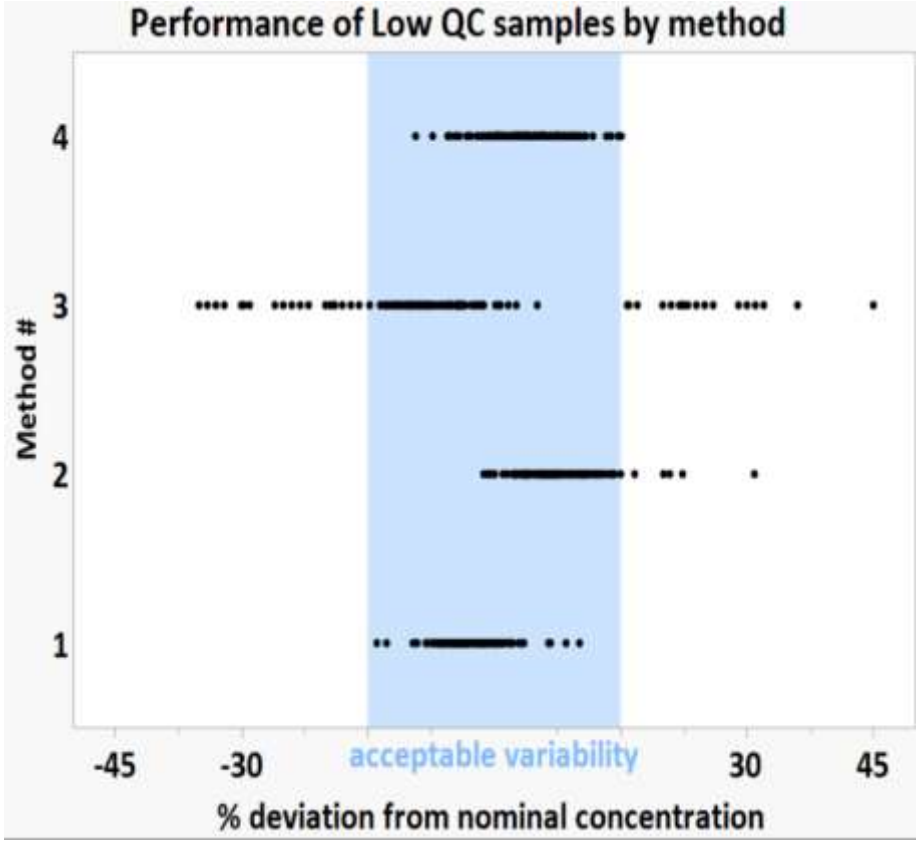
Future steps

- May build a library of methods for LC/MS-MS, in vitro, and immunoassays
- May encourage FDA inspectors to conduct similar meta-analyses before inspections
- May share non-confidential information with industry to refine or reaffirm method performance

CHALLENGE QUESTION

- Fill in the blank

- Method # **3** may have issues measuring low QC samples



Acknowledgements

- DNDSI Staff and management
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