4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements November 9-10, 2020

PQRI Phase 2 Elemental Impurities Collaborative Study Purpose and Design

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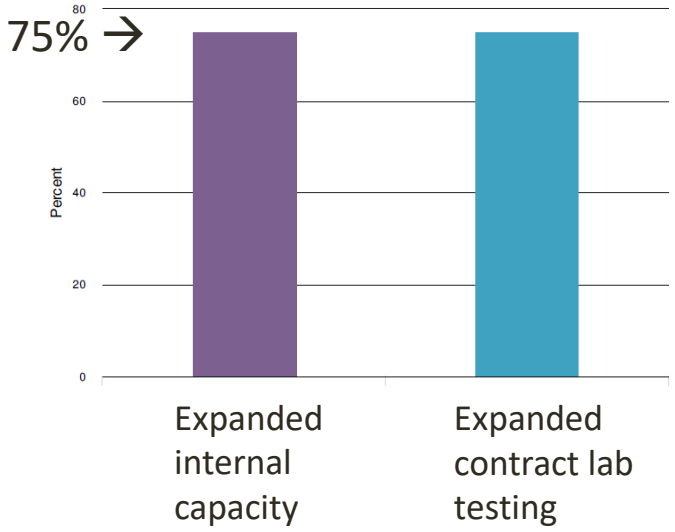
Learning Opportunities

- Risk assessment requires some basis in data
- Key question for industry and the regulatory community
  - –How reliably can we measure elemental impurities in drug products, APIs and excipients at the levels outlined in ICH Q3D and USP <232>/<233>?
- Variety and complexity of pharmaceutical samples and formulations
- Many labs expanding capabilities
  - –Pharmaceutical labs adapting to ICP-MS analysis
  - –Existing spectroscopy labs adapting to the requirements of <233>



Phase I Study and Outcomes

Completed in 2014-2015

Outcomes

- Data for standardized samples allowed assessment of variation across laboratories, between lab variation was higher than within lab variation
- Labs benefit from access to standardized evaluation samples
- Comparison of summation approach and finished product testing
  - Confounded by low levels of native elements and high influence of outliers
- Tighter variation among non-uniform methods
  - Suggests need for flexibility in methodology for testing labs
- XRF demonstrated as a complementary technique to ICP-MS
  - Bias from background levels in materials used to make standards (esp. Pb & V)

Second Round Study

- PQRI Sponsorship—allows wider participation
- Study Administrator—RTI International

Inter-laboratory Study Objectives

Objectives

- Address some key technical challenges faced by industry in preparation for compliance to ICH Q3D and USP <232>/<233>
- Provide a data-driven way to discuss technical aspects and expected variation of ICP-MS analysis of elemental impurities
- More specific objectives:
  - Inter-laboratory data comparison for standardized samples
  - Inter-laboratory evaluation of effectiveness of microwave digestion
  - Comparison of acid leach/extraction techniques to total metal extraction
  - Examination of the correlation (good or bad) between the analysis of individual components (summation) vs. the formulated tablet analysis
  - Comparison of ICP-MS and alternative techniques (ICP-OES and XRF)

Second Round Evaluation Samples

Liquid Sample

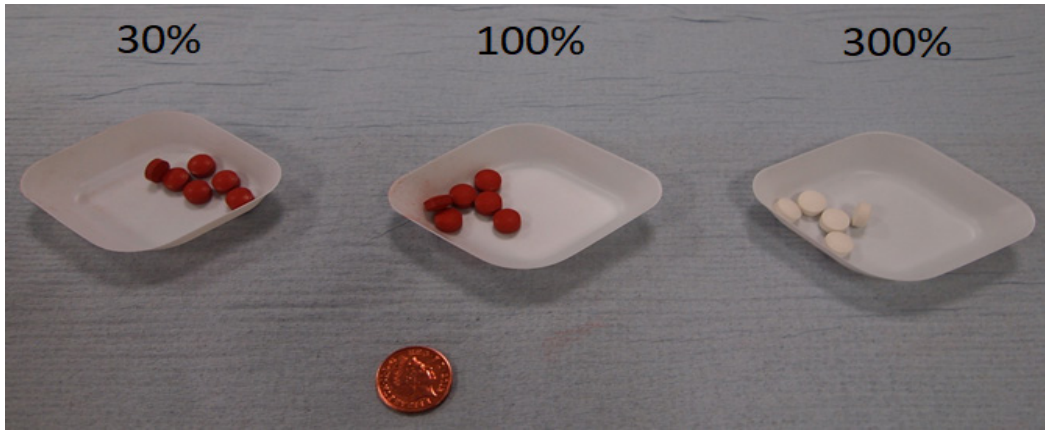
- Added to assess instrumental variation independent of sample preparation

Solid Samples

- Tableting is preferred to preserve homogeneity
- Material combination must have favorable mixing & flow properties, and must be compressible
- Multiple tableted evaluation samples targeting three different levels (30%, 100%, and 300% J)
- EI source from pharma materials wherever possible
- EI source from materials that are not easily solubilized

Formulation Design

Raw Material	Tablet Level 1 (30% J, µg/g)	Tablet Level 2 (100% J, µg/g)	Tablet Level 3 (300% J, µg/g)
Microcrystalline Cellulose	0.150	0.150	0.150
Magnesium Aluminum Silicate Clay, USP/NF	0.050	0.100	0.100
Lactose monohydrate, NF	0.5305	0.465	0.478
Pregelatinized Starch	0.200	0.200	0.200
Stearic Acid	0.012	0.012	0.012
Ferric Oxide Red, BC	0.050	0.050	0.000
Silicon Dioxide Standard (As, Co, Hg)	0.0060	0.0180	0.0450
Silicon Dioxide Standard (Cd, Ni, Pb)	0.0015	0.0050	0.0150
Total	1.00	1.00	1.00



Digestion Optimization for ICP/MS

- Total digestion:
  - Highly aggressive microwave digestion (using HF or HBF_4)
  - Complete digestion that is stable (no re-precipitation)
  - Achieves clear solution with no insoluble material

- Exhaustive extraction:
  - Less aggressive microwave digestion (e.g., EPA 3051A)
  - Acid extraction that is equivalent to the total digestion results
  - Achieves totally recovery of EIs from tablet matrix, but does not necessarily achieve a clear solution

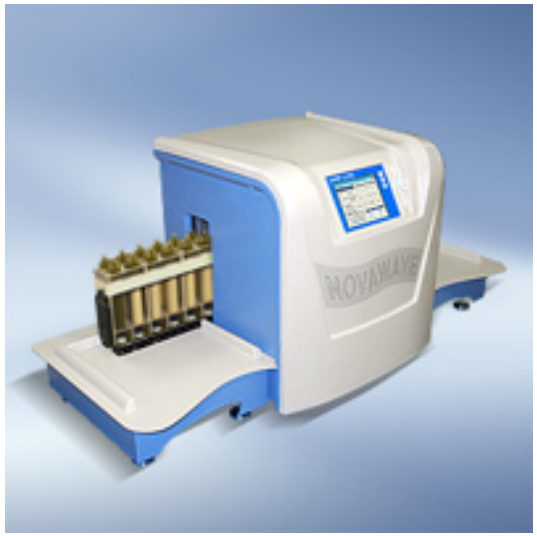
- Test the variability of the analytical method across the labs
  - Minimize the differences in sample preparation between labs

- Limitations:
  - HCl – Not all microwave systems are compatible
  - HF/HBF_4 – Not all labs equipped for use

Second Round Design Improvements & Best Practices

Uniform Sample Preparation

- Specify parameters such as sample size, sampling technique, replicates, acid mixtures, and digestion temperature/pressure
- Document type of digestion vessels and microwave model used
  - IPV vs. SRC



Second Round Design Improvements & Best Practices

Uniform Analysis

- Define isotopes used for quantitation
- Define procedures around units, LOQs, calibration, system suitability and data reporting
- Document interference management (reaction/collision gases, correction equations, etc.), internal standards, and any additional isotopes monitored
- Document instrument type
  - Single Quad vs. Triple Quad vs. High resolution systems

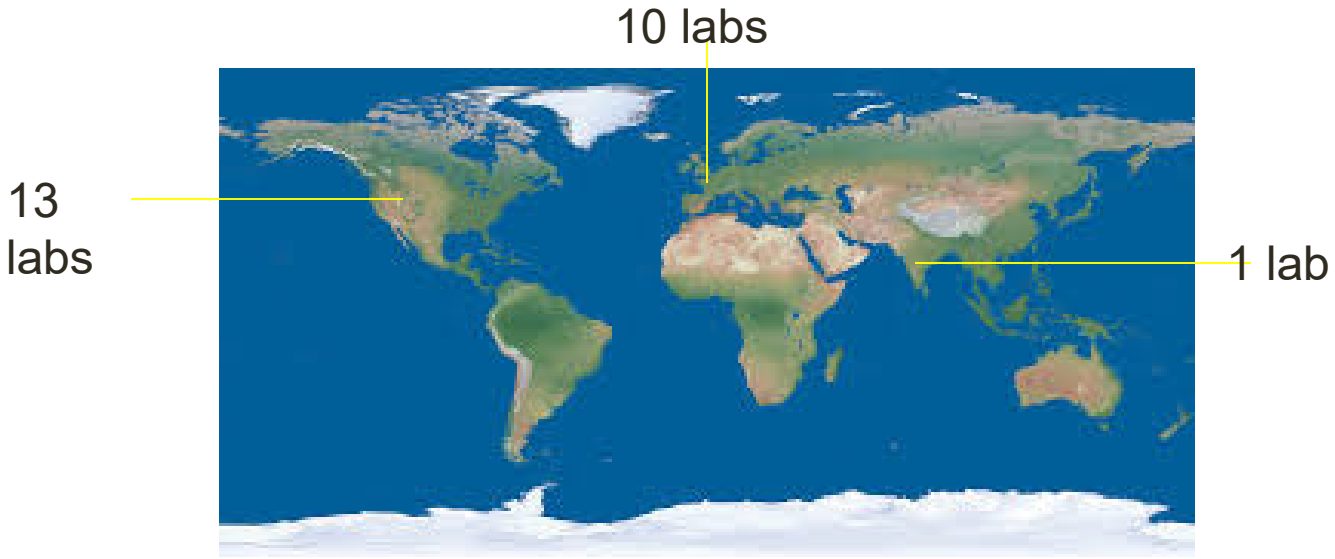
Sample Preparation and Calibration for XRF

Key Decisions for XRF Study Design

- Calibration type
  - How to minimize bias for Pb & V?
  - Considered use of standard additions
  - Because of multiple tablet levels all with similar composition, fundamental parameters option was utilized
- FP approach had implications on sample preparation
  - Additional, clean source of silicon dioxide required

Recruiting

- 24 laboratories participated
  - Pharma manufacturers or suppliers: 16 laboratories
  - Contract/CRO: 3 laboratories
  - Instrument manufacturers: 3 laboratories
  - Government/compendial: 2 laboratories



Acknowledgements

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- Glenn Williams, Thanh Nguyen, Rigaku
- Frank Flynn, Peter Ciullo, Vanderbilt Minerals
- Josh Foote, Perrigo
- Gary Hayes, Colorcon
- TAC Team members
- All participating labs

PQRI Product Quality Research Institute

Perrigo

Colorcon

RTI INTERNATIONAL

Rigaku

Vanderbilt

LIVERPOOL JOHN MOORES UNIVERSITY

P&G

MANCHESTER 1824 The University of Manchester

Today's Agenda

Method Development and Laboratory Participant Perspective

- Denise McClenathan – P&G

Results Review and Publication

- ICP-MS - Donna Seibert - Perrigo
- XRF - Glenn Williams and Thanh Nguyen - Rigaku

12:30 – 1:00 pm **Lunch**

Main Take-aways

- Statistician Interpretation - Steven Erickson - RTI
- Key Findings - James Harrington - RTI

Implications for Analytical Testing in Laboratories for EI/Participant Perspective

- Francine Walker – SGS Chemical Solution Laboratories, Inc.

Implications on Risk Assessments/Industry Perspective

- Xiaoyi Gong - Merck

3:00 – 3:30 pm **Break**

Breakout Sessions—Explore the impact of the study on industry and regulators