PQRI Technical Analytical Challenges Round 2 Interlaboratory Study: Progress and Early Findings

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Background

- 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
- Many labs expanding capabilities
  - Pharmaceutical labs adapting to ICP-MS analysis
  - Existing spectroscopy labs adapting to the requirements of <233>

Key Considerations

- Sample Preparation
  - Ensure appropriate and effective solution preparation
  - Total metal extraction implies clear solutions
- Instrumental Analysis
  - System suitability/data integrity
  - Options for sample introduction and interference reduction
    - Sample introduction accessories, reaction gasses & collision cells, correction equations, etc.
  - Calibration & LOQs
    - LOQ should be considered for large dose products and for raw material analysis
- Data review & interpretation
  - Recognition of issues
    - Drift, carryover/memory, interferences or element-specific pitfalls, non-ideal recoveries
  - Reportable data
    - Multiple modes of analysis possible
- No pharmaceutically relevant reference materials available

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)

First Round Study Outcomes

- Data for standardized samples allowed assessment of variation across laboratories
- 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

- Second round initiated
  - PQRI Sponsorship—allows wider participation
  - Study Administrator—RTI International

Second Round Enrollment Comparisons

General

- Digestion optimization performed with actual tablet samples
- Consistency in digestion conditions

ICP/MS	Uniform	Non-Uniform	Non-Uniform HF Methods
First Round	11 labs	15 methods	6 methods
Second Round	27 labs "exhaustive extraction"	?	16 labs "total digestion"

- Consistency among alternative techniques to ensure adequate data for comparison

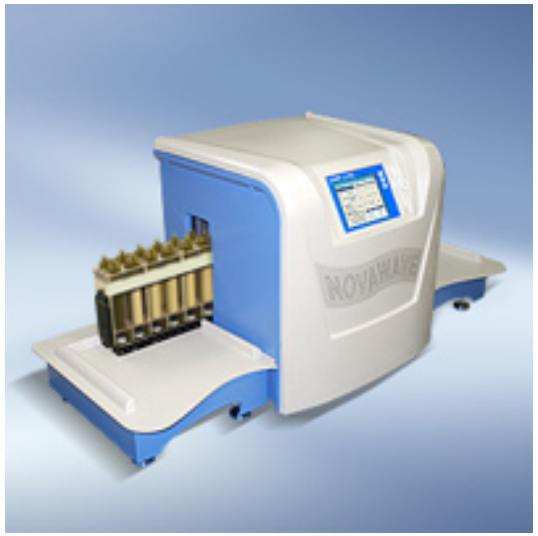
	ICP-OES	XRF
First Round	1	4
Second Round	16	7

- Raw materials to be distributed more widely for summation approach comparison
  - 2 labs ➡ 23 labs

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

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
- EI source from pharma materials wherever possible
- EI source from materials that are not easily solubilized

Formulation Design

- Pharmaceutical materials that contain significant, known levels have been elusive
  - Kauffman paper, Lhasa database participants, TAC team member experience
  - Considered non-pharma grades of pharma materials (talc, rice starch, etc.)
  - Small group of materials containing Pb & Cd identified
  - Few materials contain significant As & Hg
  - Class 2A elements present in iron oxides—
    - Low level usage in real pharma usage
    - Introduce Fe, a potential source of interferences
  - Physical/chemical properties eliminated some materials ($CaCO_3$, Na alginate, etc.)
- Key decision for solid formulations
  - Tablets similar to the first round tablets
  - Include small amounts of matrix XRF standards (silicon dioxide)
  - Some variation in materials used across three levels

Formulation Finalization and Tablet Manufacture

- All formulation materials gathered at LJMU from various donors
- Small test batches produced, digested and analyzed
- Results initially lower than expected for multiple elements
- Digestion tweaking resulted in good recoveries for most elements, but no detectable V.

	0.25 g 15 min hold at 210 °C		0.25 g 5 min hold at 210 °C		0.5 g 5 min hold at 210 °C	
Level 2 Tablets	%Recovery	RSD	%Recovery	RSD	%Recovery	RSD
^{75}As	82.7	3.0	89.1	4.2	38.3	8.7
^{111}Cd	102.3	3.0	71.1	2.3	54.4	3.0
^{202}Hg	100.9	5.9	101.3	12.7	102.5	7.0
^{208}Pb	89.2	2.3	88.3	5.5	76.8	5.8
^{59}Co	83.8	5.7	91.8	3.0	97.6	11.6
^{60}Ni	98.4	9.1	93.2	2.6	105.4	10.3
^{51}V	N/A	N/A	N/A	N/A	N/A	N/A

- Tested iron oxide—no detectible V!

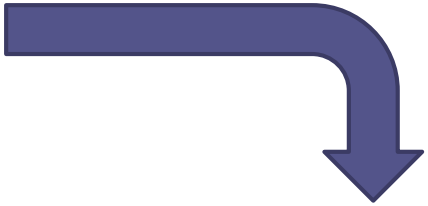
Formulation Finalization and Tablet Manufacture

- Replacement lot of red iron oxide obtained with known V content
- Manufactured additional small test batch with new source of iron oxide
- Additional digestions confirmed presence of V
- Produced actual evaluation samples at three levels

Key Decisions on Digestion Methods

Goal: Pre-define digestion approaches and clearly the define procedures.

- Highly aggressive microwave digestion
- Less aggressive microwave digestion
- Non-microwave acid leach methods (hot blocks/shakers/rotators/etc.)
- Non-uniform methods (choice of individual labs, variations in acid combinations, microwave programs, etc.)



- Not formally included in study
- Adequate tablets will be distributed to allow individual labs to generate data
- Allows intra-lab comparisons, and comparison to overall study results
- If critical mass is achieved, data mining is a possibility

Digestion Optimization

- 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

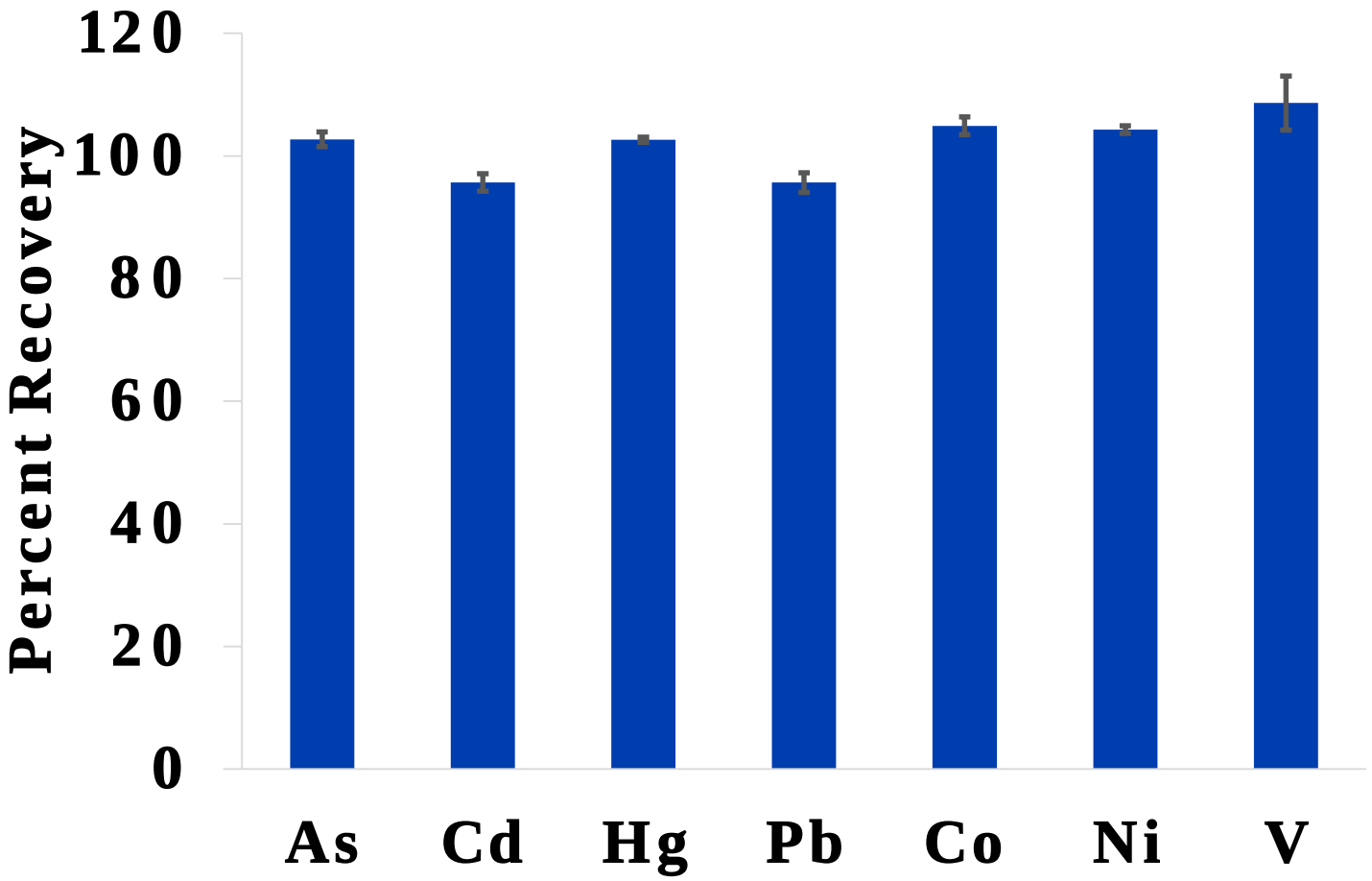
Total Digestion Procedure

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

- Sample size: 1 tablet (0.25 g)
- Acid matrix: 0.5 ml H_2O, 2.5 ml HNO_3, 0.5 ml HCl, 0.5 ml H_3PO_4, 1 ml HBF_4
- Microwave program (SRC, UltraWAVE with ECR, HCl compatible):
  1. Ramp to 250 ^oC for 25 min
  2. Hold at 250 ^oC for 20 min
- Dilute to 50 ml → Intermediate solution
- Additional 50X dilution w/ additional HCl and HNO_3
- Analysis by ICP-QQQ-MS/MS using multiple detection scheme for maximum selectivity

Total Digestion – Accuracy Assessment



Replicates (n=3) spikes using 30% tablet and neat-standards
Typical RSDs are <15%, and most are <5%

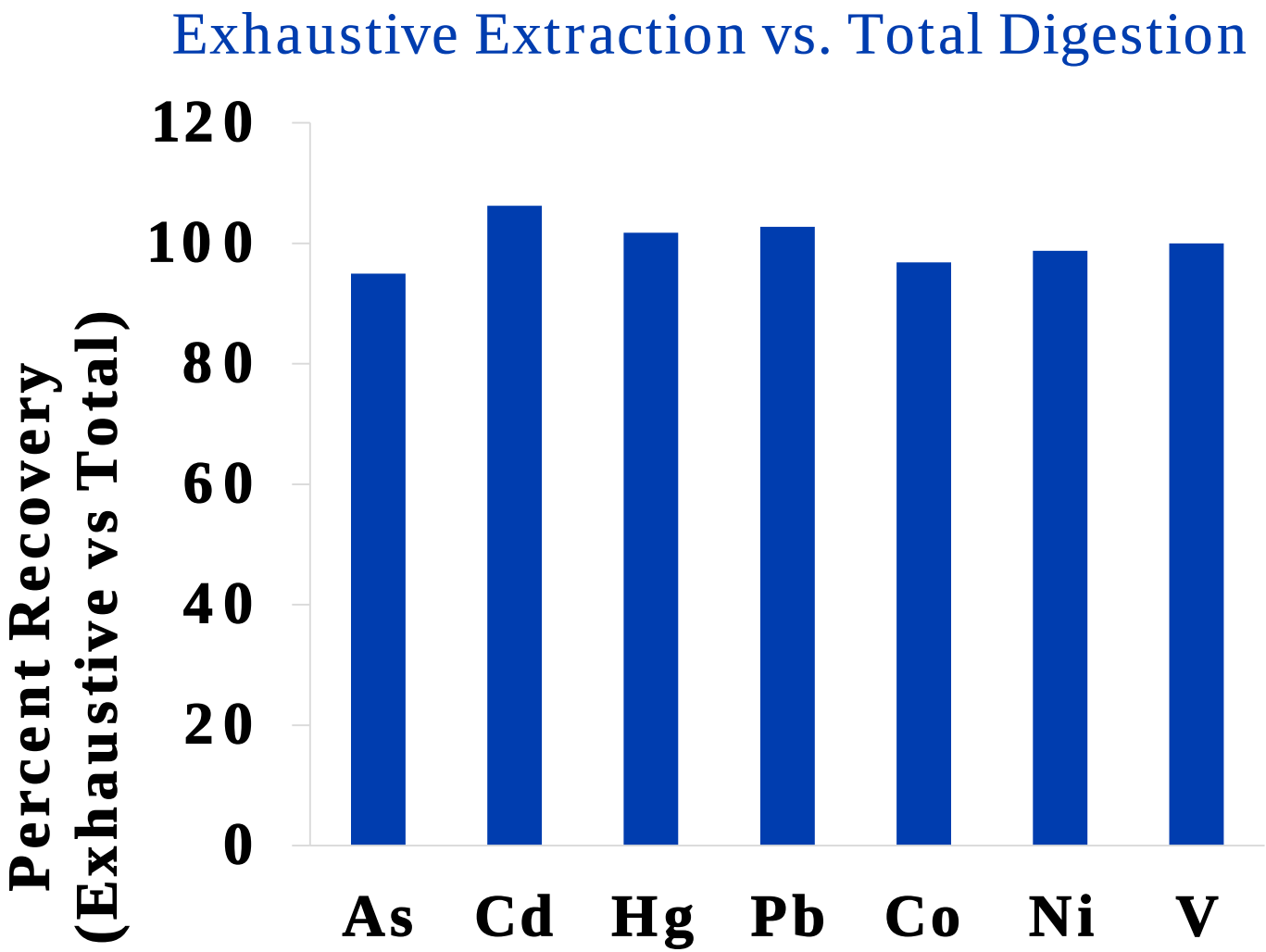
Exhaustive Extraction

Exhaustive extraction:

- Less aggressive microwave digestion (based on 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

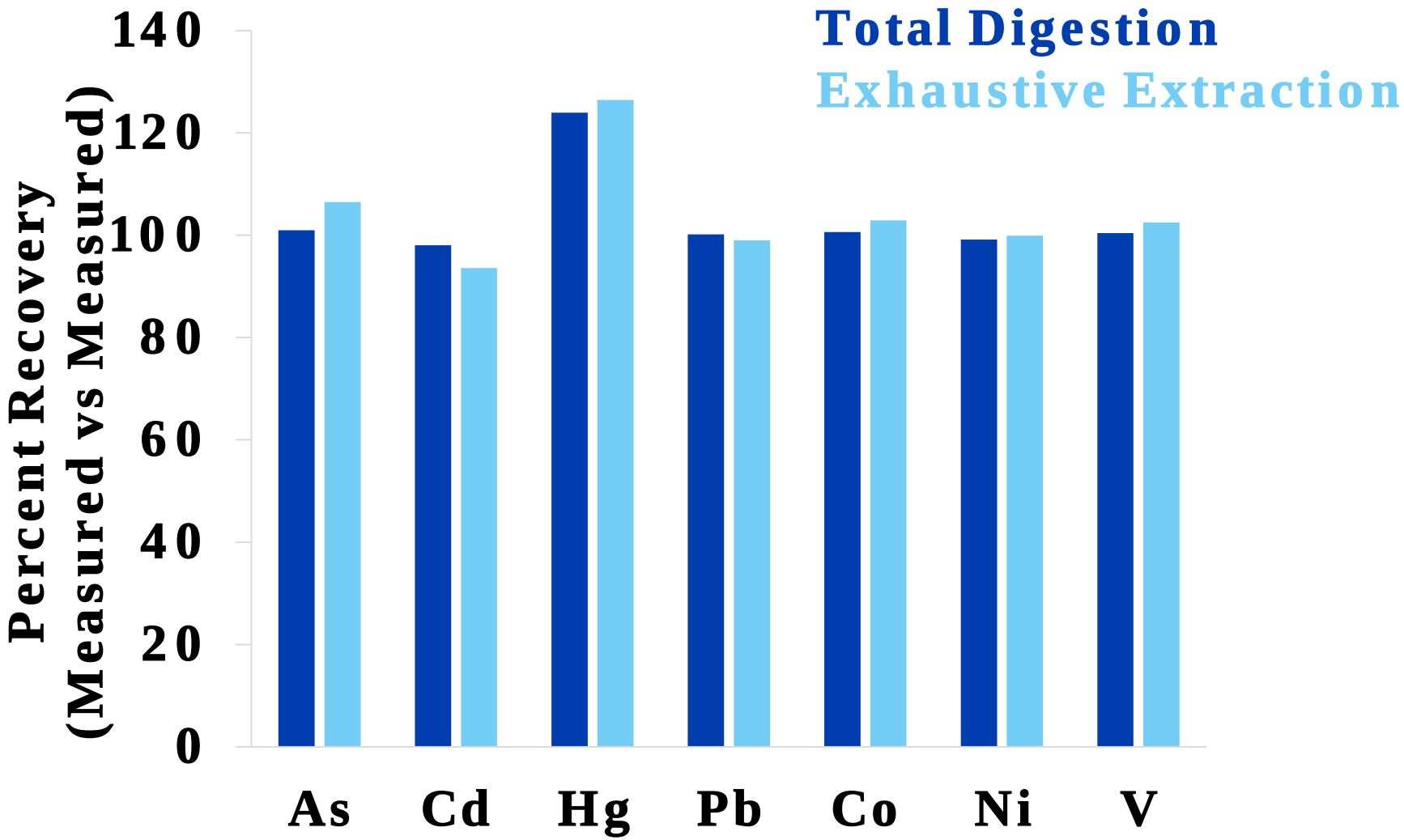
- Sample size: 1 tablet
- Acid matrix: 10 ml HNO_3, 5 uL 10,000 ppm Au
- Microwave program (IPV, Ethos):
  1. Ramp to 175 ^oC for 3 min
  2. Hold at 175 ^oC for 7 min
- Dilute to 50 ml → Intermediate solution
- Centrifuge to remove remaining particulate
- Additional 50X dilution w/ additional HCl and HNO_3
- Analysis by ICP-QQQ-MS/MS using multiple detection scheme for maximum selectivity

Comparison of Digestion Approaches



Replicates (n=9, triplicate at each tablet level)

Mass Balance: Comparison to Measured Value



Replicates (n=3) for all tablet levels (30%, 100%, 300%) and RMs

The XRF story

- First Round Findings
  - Results generally comparable to ICP-MS
  - Bias from background levels in materials used to make standards
    - Apparent in Pb and V results
    - Standard additions in calibration setup could correct for this bias
  - When sample is not limited, XRF offers quick and economical analysis
    - Once calibration is established, only check standards need to be analyzed

- Key Decisions for Second Round XRF Study Design
  - Calibration: Empirical or Standard Additions?
  - Because of multiple tablet levels, fundamental parameters option was explored

Empirical vs Fundamental Parameters (FP)

Empirical

- Each analyte calibrated independently
- Each level of tablet requires its own set of standards

Fundamental Parameters—

- Calibration of all analytes and the inorganic components of the matrix (Al, Fe, Si, etc.) through interdependent calibration to describe 100% of the formulation
- Once prepared, FP calibration can be used across tablet levels
- Set of 8 calibration levels has been proposed

Remaining Steps

- Reporting template—in review
  - ICP-MS and XRF reporting templates
- Package assembly & shipment—in progress
  - RTI distributes packages to US
  - Phil Riby distributes packages to UK/EU
  - Separate shipments will be needed for ICP/MS and XRF
- Requested data delivery timeline
  - End of March

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