

Breakout Session II

Topic: Analytical Testing Considerations

Facilitators: D. Seibert, T. Shelbourn, A. Teasdale, and K. Ulman

Discussion Points

- Best Practices
- Method Validation
- Dosage Form Considerations
- Acid Leach vs. Total Dissolution – Sample Preparation
- Inter-Laboratory Reproducibility – Coalition Collaborative Study Results
- Instrument Issues – Precision, Accuracy, and Corrections
- Matrix Interferences
- Potential Solutions

Top Takeaways

1. There are multiple paths to risk assessment or interpretation of what testing data (if any) is needed to support it. In the end, risk assessment must be scientifically defensible.
2. INPUT FROM REGULATORS IS NEEDED to know what types of data are acceptable for use in risk assessment
3. Methods and method validation are fit for purpose. When analytical methods are included for formal control purposes, full method validation is required. There is still some controversy about what level of validation is necessary for data used in risk assessment.
4. Overall, a need remains to understand the expected variation in ICP/MS data, given the sensitivity of the technique (possibility for contamination or interferences) and the complex matrices under evaluation (containing insoluble material, incompletely digested organic material, and potential for seasonal variations)

Questions:

1. How is screening for elemental impurities accomplished?
 - Which elements are being evaluated?
 - a. Per ICH and by dosage route
 - b. some routinely screen for all 24 elements
 - c. some include Big Four and Class 2(A/B)
 - d. screen to determine which elements are important (implies all 24)
 - e. customer-driven, tailored approach
 - f. no need to look at something that is not present; know process and know catalysts
 - g. if you do not expect an element, you still need to evaluate the risk of having it (two reports of finding “surprise” elements)
 - h. some looking for intentionally added elements
 - What justification is being leveraged for omitted elements?
 - a. No room addressed this point specifically
 - How is Osmium being handled?
 - a. Osmium is not included in screening by many labs, b/c of known recovery issues
 - b. Osmium is also not a common catalyst, nor can it be considered “ubiquitous”
 - c. Use of osmium should be known from supplier information
 - Are testing labs incorporating components of validation into the screening analysis?
 - a. Pre-digestion spike recovery? If so, at what level should spike recoveries be evaluated for screening analysis? 1J?
 - Some fully validate screening methods, although most agreed that screening methods are not fully validated
 - Spiked vs. unspiked samples included
 - Consider specificity, as samples containing high levels may have inter-element interactions; non-specificity may indicate other lab errors
 - Specificity checks include accuracy, verification of wavelengths/masses, known interferences
 - Linearity
 - b. “What is screening data?” came back as a question in multiple sessions.
 - A starting point where no other info is available
 - Can be used in risk assessment
 - Methods are typically not validated
 - Can be a hybrid—qualitative scans alongside quantitative data
2. What types of data are acceptable for use in risk assessment?
 - Screening data (implies unvalidated methods)?
 - Data from fully validated methods?
 - Combination of both?
 - When screening shows no elements at levels of concern?

- a. Literature data
 - b. Non-validated (screening) data as well as any fully validated data
 - c. Supplier data
 - d. Information in public databases
 - e. Other information available (knowledge of process, packaging materials)

 - f. INPUT FROM REGULATORS IS NEEDED to know what types of data are acceptable for use in risk assessment
 - g. Also need input on whether acid leach data is acceptable

 - h. Question: would the users value the data from non-validated lab?
Answer: Yes, a drug manufacturer would appreciate as a starting point to define the dose, etc. for analytical accuracy.
- 3. Which is preferred – finished product analysis or summation approaches?**
- a. Mixture/combination of both, case dependent
 - b. Informal poll (from a contract lab from fall 2014), 65% FP & 30% RM (remaining 5%?)
 - c. Before time extension, much finished product analysis as an initial approach
 - i. Follow hits back to RM source
 - d. RM/summation approach also common
 - i. Can help avoid costly ridding of product batches
 - ii. Longer path, and can be a more holistic approach
 - iii. For API & excipient testing, push down quantitation limits; would be incorrect to add zeroes in a summation
 - iv. May be preferred when good relationships with suppliers allow for open communication
 - v. Establishment of databases (internal & public) may make summation a more attractive approach over time
 - e. Comparison of summation values and finished product testing
 - f. Need to account for seasonal variation in natural products
 - g. Cost effectiveness and protection of IP factors into selection of approach
- 4. For raw material analysis—which elements are tested and to what concentrations or what dose?**
- a. Nature of materials determines which EIs are concerns
 - b. Some RM manufacturers check for presence of all 24 elements; most don't
 - c. Use <231> data as starting point if available for specific RM
 - d. How far down to push LOQs?
 - e. Partnership b/w customer & CL important—good, clear communication regarding needed LOQs is essential

5. What defines total metal extraction and how can it be demonstrated?

▪ *Total metal extraction is the preferred sample preparation approach to obtain an indirect solution.* ▪ *1S (USP38)*

- **Do digestates need to be clear solutions with no solid material/particulates?**
 - a. **Some say no, but clear digestates are required by EMA guidance**
 - b. **Production of clear solutions is the most “satisfying” outcome**
- **Is a digestate that passes through a clear, dissolved state and later forms precipitates acceptable? Can spiked recoveries help justify this?**
 - a. **No, spiked recoveries are not useful to justify...some previous work showed that sample prep can affect the result obtained for spiked recovery**
- **Can equivalency data generated between laboratories with differing microwave capabilities be used to justify the use of a digestion method that does not produce a clear solution?**
 - a. **No direct answers to this question were included in the notes**
 - **For example, an end user’s microwave method/system produces a cloudy solution whereas a contract laboratory’s microwave method/system produces a visually clear solution. Both laboratories produce the same final result for elemental impurity content in the sample. Can the end user subsequently justify the use of the method and system that did not produce a visually clear solution?**
 - **If this scenario were acceptable, what criteria would be used to evaluate the final elemental impurity results?**
 - **Robustness, sample size, solvents, pressurization...all considered to achieve the best extraction**
 - b. **Acid conditions (concentrations & identity) needed to achieve total digestion may be too harsh and could cause problems with instrument**
 - c. **Need to define total dissolution, total extraction, acid leach**
 - d. **Acid leach methods are designed to mimic biological processes and to assess bioavailable or bioaccessible fractions**
 - e. **Simply having solids remaining or the formation of a precipitate does not mean it’s an acid leach method (i.e., acid leach and total extraction are not direct opposites)**
 - f. **Total dissolution has a defined endpoint, while acid leach does not.**
 - g. **If acid leach methods had a defined protocol (standardized methods), the approach would be more acceptable.**

6. What studies are needed to leverage acid leach data?

- a. **No direct answers to this question were included in the notes**
- b. **Standardized reference material would be useful to qualify acid leach approaches**
- c. **FASSIF vs. acid leach (are these correlatable?)**
- d. **Some rooms interpreted this question to refer to leaching from packaging material...it was intended as estimation of bioaccessible or bioavailable fractions.**

- 7. What are the main challenges to producing precise and accurate data?**
- a. Spectral interferences, especially at low levels
 - b. Matrix interferences are a big challenge
 - c. Environmental contaminants pose an issue b/c of great sensitivity of ICP-MS (clean room, PPE)
 - d. Spiking studies may or may not be reflective of accuracy
 - e. Stir bars include Al, Ni, Sn...can leach if surface is damaged
 - f. Large molecules often have unexpected analytical results
 - g. Need to understand what variability is to be expected

Outstanding Issues/Concerns

1. INPUT FROM REGULATORS IS NEEDED to know what types of data are acceptable for use in risk assessment. Specific guidance is needed from ICH IWG and from regulators in each region as to what the regional expectations will be.
2. We need to determine the appropriate level of method validation for screening data used in risk assessment.
3. Clear definitions are needed for “total metal extraction” and “acid leach” methodology. Some protocols need to be established to support the use of acid leach methodology. Further research may be needed to adequately develop these protocols.
4. Analytical challenges with ICP-MS methodology still exist. Further Round robin studies are still needed to address many outstanding questions and to understand variability.
 - a. Momentum for second round, with some re-designs
 - b. Inclusion of alternative methods (XRF, others?)
5. Lack of availability of standardized comparator samples may be an issue although there was no consensus on whether these types of samples should exist since they may have limited value across material types.
 - a. There was no desire to see prescriptive regulatory or compendial standards.
 - b. Standardized reference material could be useful to qualify acid leach approaches
6. Relevant literature references gathered in one industry-accessible place would be useful (i.e.; website). Including an annotated bibliography concerning the data covered in an article would be beneficial.