

Breakout Session I

Topic: Assessment of Ingredients – Excipients and APIs

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Discussion Points

- Sourcing and Use Considerations
- Variability of Natural & Mined Ingredients – Excursions
- Lack of Predictability for Risk Assessment
- Acid Leach vs. Total Dissolution – Data Interpretation
- Appropriate Supplier-User Communication
- How to Assess what is “*Likely to be Present*”?
- Data Sharing – Development of an Excipient Elemental Impurity Database

Top Takeaways:

1. Some non-analytical factors for pharmaceutical companies to consider in their risk assessment might include: product intended use/duration/route of delivery; process steps where catalyst is added or removed; excipient source and source location; excipient concentration in finished drug product and historical excipient published reference and literature information.
2. Additional assessment of excipient elemental impurities might be necessary when a natural disaster and/or environmental event (fire) occurs near the source of the ingredient.
3. Some suppliers are providing elemental impurity information using the IPEC-Americas Elemental Impurity template; however, some users have commented that the template approach resulted in qualitative information, some quantitative information, and often more questions. Regardless, information from the form could be used to trigger a dialog between the maker and supplier on elemental impurity issues and needs.
4. Mined excipients were most frequently identified as having the highest potential for variability (vs. synthetic and plant sourced ingredients) and it was suggested that excipients with known potential levels of elemental impurities may need to include some type of screening or testing to mitigate the potential for elemental impurity excursions.
5. Some suppliers expressed concerns that pharmaceutical companies set unreasonable elemental impurity limits on them without sharing their intended use/application/formulation information.
6. Some information that helps drug companies assess elemental impurity risks include: known excipient elemental impurity variations and/or use of catalyst, number of excipient sources used, historical compendia/supplier/literature information, etc.

7. Contract labs reported that many of their clients had little to no involvement in defining the testing or specifications for gathering data. A standard template of questions could help establish an appropriate dialog between the contract lab and the client.
8. Acid leach results are harder to assess because they don't have a common method or end point. Many excipient suppliers that also supply into the food industry have historically performed acid leach testing (for food additives and California Prop 65 compliance), but pharmaceutical companies are not familiar with nor have they had experience with acid leach. It appears that some type of standardization of methodology/endpoint determination and guidance in this area would be beneficial.
9. Although pharmaceutical companies tended to be in-favor of a public database of excipient elemental impurity information, some pharmaceutical companies and suppliers expressed concern over potential miss-use of information from a public database (e.g. use of information from database without understanding the source of the ingredient). This database is not intended to replace the need for organizations to conduct a specific risk assessment for the product in question. The instigators of the database have categorically stated that information cannot be used as the sole basis of a risk assessment since the elemental impurity levels may be quite different from grade to grade and supplier to supplier. Each pharmaceutical company must assess the specific grades and different supplier of excipients they use in their drug products with data relevant to that grade/supplier.

Breakout Questions:

1. What non-analytical factors are you considering in your risk assessment?

- **source type (mineral, plant, other)**
 - **sourcing from multiple suppliers,**
 - **quantities used in product**
 - **reference/literature information**
- a. Product use (e.g. shampoo/wash-off vs parenteral vs oral vs topical) /duration (systemic/chronic use, dose frequency - life/time exposure)
 - b. Step in process where catalyst is added/removed
 - c. Source of materials (mineral/plant/synthetic)
 - d. Level of ingredient used in finished drug product
 - e. published reference and literature information (e.g. supplier routes of manufacture/testing/sample preparation and testing conditions/ summation option)
 - f. source location of supply, including impact of known natural disaster (fire, flood, spill, etc.)

2. What testing (if any) have suppliers performed and shared with drug manufacturers?

- a. Supplier shared data
 - Suppliers who have provided elemental impurity information to their customers most frequently used the IPEC-Americas elemental impurity template
 - Based on feedback from users, the template approach resulted in qualitative information, some quantitative information, and often more questions.

- ICP-MS appeared to be a common method for analysis
 - b. Supplier issues with drug manufacturers
 - Often drug manufacturers set unreasonable Elemental Impurities limits for excipients and don't understand the issue with so many requests for data
 - Often, drug manufacturers don't share enough information with suppliers about their application (% in drug, type of drug, etc.)
- 3. What other type of information (e.g. source of raw material, potential for elemental impurity variability and/or excursions) are or have suppliers been willing to share with drug manufactures?**
- a. Most breakout groups did not capture what other types of information suppliers were providing to drug manufacturers; however, they did acknowledge that additional information/specifications could require confidentiality agreement or special purchase agreements.
 - b. Some drug manufacturers stated that they were not sure what to ask or how to ask their suppliers for elemental impurity information and they were not aware of the IPEC-Americas Elemental Impurity template.
 - c. Some suppliers won't share information on testing/control because there is no compendial requirement for them to do so.
- 4. What type of information have drug manufacturers shared with their suppliers (type of products to be used in, expected concentration levels, etc.)?**
- a. Suppliers stated that they need to know how excipients are used. This information is critical especially if there are excipients that are normally used in oral products but might also be used in specific parenterals
 - b. Drug manufacturers should give suppliers enough time to respond, especially those suppliers who are less aware of recent changes in the regulation.
- 5. What information will a drug manufacturer use to assess whether an Elemental Impurity is "likely to be present" in a material:**
- **sample preparation (acid leach vs total digestion), test method and source of data (supplier vs contract lab vs public database vs internal),**
 - **excipient variability, including potential excursions**
 - **sourcing from multiple excipient suppliers,**
 - **known levels of ingredient processing,**
- a. Variability in **Elemental Impurities** for raw materials from various suppliers.
 - b. Variability in sample preparation
 - c. Review of current compendial specifications for elements/heavy metals. Even if only a limit test, can still provide qualitative information.
 - d. Information from supplier/literature on use of catalysts and other potential sources of **Elemental Impurities**

- e. Reference to data from other regions (e.g. China) where **Elemental Impurities** requirements exist
- f. Lot to lot variability and seasonal variability of published data

6. If working with a contract lab for Elemental Impurities data, how involved are you in specifying their sample preparation, type of and settings for equipment/instruments, reporting requirements?

- a. Contract labs indicated a lack of communication between requester and contract lab with regards to sample preparation, test method/analysis, validation expectations.
- b. Many of the labs that perform elemental analysis are environmental labs; they have limited understanding of cGMP; they are used to testing with prescriptive procedures
- c. Industry may need to provide relevant guidelines, templates/protocols, validation expectations, etc. to contract labs and audit them for compliance
- d. Whereas some contractors only specify the reporting requirements, not the procedure/method, others oversee all development and validation activities, sign-off, approvals of all transfers
- e. 40-50% of industry are using contract labs

7. Would you consider acid leach data acceptable?

- a. Half of the room perform acid leach and believe that acid leach data should be accepted.
- b. Within ICH guideline; acid leach is acceptable when justified; however, caution should be taken to understand fate of ingredient in the human body
- c. Although total digestion has a common end-point it was recognized during the break-out discussions that due to the variability in methods and end-points, defined protocols and end-points should be established for acid leach methods.

8. Would you see any value in having a public database of elemental impurity data for drug ingredients?

- a. Two separate camps on the value of a public database
- b. Suppliers were concerned about confidentiality of information, variability in data from different sources and potential miss-use of the data.
- c. Drug companies believe that the value of such a database could be used to supplement the lack of historical elemental impurities in most commonly used excipients and APIs and be useful for initial risk assessments.
- d. Database developers agree that it is critical to define ground rules for database, including details of sample preparation, test method/conditions, equipment/validation state. In addition, they understand the need for a third party to blind and ensure the validity of the data.
- e. Regulators may benefit from having access to such a database of information.

Outstanding Issues / Concerns

1. Industry is still not sure what to expect from regulators (especially FDA and EMA) and believe that it is important to know more about what regulators really expect and how they will use/review the information.
2. General concern on how quickly Japan and non-ICH regions will implement transition to ICH Q3D and their elemental impurity expectations in the interim....especially as historical USP and EP compendial monographs are made obsolete.
3. Also concerned about type and level of information from non-ICH regions where variability and economically motivated adulteration could have higher concerns. Both testing capabilities and data integrity for materials from these regions should be included in the sourcing section of the risk assessment.
4. General concern by suppliers that added testing of all their products could significantly increase their characterization costs (extensive sample preparations, expensive equipment, technical expertise to perform sample preparation and analysis), yet pharmaceutical companies may be reluctant to have these costs passed on to them.
5. Consider creating a list of the most common excipients, their typical sources (mined, plants, synthetic, etc.) and their typical uses in order to help support drug companies during their risk assessments.