Breakout Session III

Topic: Successful Risk Assessment Methodologies

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Discussion Points:

- Key Considerations and Tools
- Predictability
- How to Address Levels Present in Water?
- How to use a Control Threshold (i.e.; 30%)?
- When is Testing Needed and When is it Not?
- Case Studies to Demonstrate Appropriate Control Strategies

Top Takeaways:

1. General consensus that the 30% PDE was the threshold for routine control.
2. Elemental Impurities will need to be managed as a complete Quality Program / System. Full documentation, change control, and lifecycle assessments.
3. Risk Assessments must be all encompassing: Supplier Statements, Supplier provided assessments, literature information, Specifications/C of A, Drug Manufacturing Process assessment, risk associated with similar materials/products, packaging assessments, equipment assessments, and data. Test results from materials and/or products.
4. Screening data should include Pre-digestion spiked recovery and visual digestion assessment.
5. When moving to a control strategy that includes testing, full Analytical TM Validation is required.
6. Control Strategies would typically be applied to the RM source material as opposed to control strategies based only on finished product. Ingredients used in Drug Product Manufacturing are normally the focus in control strategy development since having a failure on the final drug product would create major issues and not allow easy prevention on future batches.
7. A general acceptance that some Analytical data will be needed to support the Risk Assessment and defining of the Control strategy. There was no specific consensus on the level of analytical data that would typically be needed for ongoing control.
8. A documented Elemental Impurity Product Assessment will be needed for every Drug Product/Drug Product Family with an appropriate rationale.
9. Each Company will need to define a periodic monitoring program for materials or processes that have a variability risk (i.e. mined or naturally occurring materials). There was no real consensus on how exactly this should be done but there will need to be a scientific justification for the approach used.
10. A general unknown that remains important and may need clarification is: “How much information is enough to justify a low risk or no risk scenario”?

Questions:

1. **Where does your Company plan to apply control? At the excipient, APIs, Bulk Product, Finished Dosage Form, Stability**
    a. Varied responses from Drug Product Manufacturers: Incoming Materials, Finished Products, and Stability (routine &/or stressed studies). Risk Assessment needs to include contribution assessment from packaging (leachable/extractable) and manufacturing equipment.
    b. Consensus was that with the correct application of GMP the risk from manufacturing equipment was low and the risk from packaging still lower still. The Jenke article (*Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review PDA J Pharm Sci Technol. January/February 2015 69:1-48*) showed that the extractive levels from common materials was extremely low (based on a very low level presence in the base material) and that the leachable risk was lower still. There also has to be a viable mechanism for migration.
    c. Control should be applied to the source (the "at risk" ingredient or processing phase). Primarily the incoming raw materials however all "at risk" sources will need to have a control.
    d. General consensus that the 30% ICH PDE was the threshold for routine control.

2. **How do you plan to utilize non-analytical factors in your risk assessment?**
    - **source type (mineral, plant, other)**
    - **sourcing from multiple suppliers,**
    - **quantities used in product**
    - **reference/literature information**

    a. All aspects need to be considered. The level of detail with each will depend upon the perceived risk.
        i. Supplier Statements, Supplier provided assessments, literature information, Specifications/C of A, Drug Manufacturing Process assessment, and risk associated with similar materials & products.
        ii. Difficult to assess risk without some data. Some level of minimal screening on product and/or materials.
    b. Overall water was considered a low risk but did need to be included in the risk assessment. Referenced article relative to the risk of water in pharmaceutical products is listed below.
        i. *Elemental Impurities in Pharmaceutical Waters*, coauthor with Dr. Anthony Bevilacqua, Stimuli to the Revision Process, Pharmacopeial Forum 39(1):Online (Jan-Feb, 2013).

3. **Is there a threshold above which your company plans to require routine testing on each batch (i.e. the recommended 30% Control Threshold listed in the ICH Q3D Guideline)?**
    a. 30% of the PDE. Could be lower depending upon the analytical method capability (LOQ) and/or material variability.
    b. Individual Company Risk Assessments and FDA feedback from ANDA/NDA's may drive a company's strategy.

4. **How would your company plan to justify a "no risk" position?**
    a. A "no risk" position would be difficult to qualify therefore the recommendation would be a "low risk" position. A status analogous to "not likely to be present".
    b. An assessment would be at a point in time that would include supplier statements and screening data (materials &/or product). A robust change control process must be implemented, linked to the **Elemental Impurity** Assessment – both internal and externally driven changes.

5. **What is your plan for evaluation of:**
    - **excipients and/or product for all listed Elemental Impurities ?**
    - **your water systems, control and/or monitoring?**
    - **your processing systems contribution?**
    - **your packaging components contribution**

    a. Elemental Impurities that will be evaluated: Just those that need to be controlled. Class I and II. Leveraging of Table 5.1 and any catalyst. Must be linked to the finished product risk – each risk source must be assessed as an individual or as a package/matrix.

6. **How do you plan on documenting your risk assessment evaluations and maintaining?**
    a. Elemental Impurities will need to be managed as a complete Quality Program / System. Full documentation, change control, and lifecycle assessments.
        i. Master Plan similar to residual solvents.
    b. Historical USP General Chapter <231> Heavy Metals data can be used to support the Risk Assessment.

7. **When testing is performed in support of risk assessment what level of validation should be performed?**
    a. Screening data: Pre-digestion spikes (consistent with USP General Chapter <233> / ICH Q3D) and visual digestion assessment is acceptable.
    b. Validation to support a Control Strategy: Full TM Validation consistent with USP General Chapter <233> / ICH Q3D)

8. **How often might you envision, based on information you have already seen, that a justification may be needed for exceeding the PDE**
    a. Vague responses. Some "not a concern".
    b. If a concern – evaluate on case by case bases with regulatory bodies as needed.

Outstanding Issues / Concerns

1. Extensive discussion on a database to help establish / aid in the identification of risk associated with materials based on the sources and variability of sourcing that may be used in manufacturing the material (refer to Outstanding Issue #5 in Breakout Session I Summary).
2. Clarification from regulators is needed on what strategies are appropriate to determine the level of screening data needed to be able to perform an appropriate risk assessment
3. How much information is required to define the variability and/or "lack of variability" associated with a raw material. Example: 1 batch every year over 3 years or more in-line with processing controls concepts? Additional data would be needed when a known change occurs.
4. Meeting the 30% ICH PDE option would not exempt one from performing the drug product risk assessment. Controversy exists on how exactly to apply the 30% ICH PDE option.