PQRI/USP Workshop on ICH Q3D Elemental Impurities Requirements – Recent Experience and Plans for Full Implementation in 2018

Breakout Session III: Acceptable Risk Assessment Strategies & Outstanding Analytical Challenges

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Acceptable Risk Assessment Strategies & Outstanding Analytical Challenges

1. What questions have sponsors received from regulators regarding their risk assessment strategies?

Question 1 Notes:

- **Exceeding PDE – regulators ask for control study in place or may be good to look for other supplier if there are any concern.**

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- **Question 1 Notes continued:**

- For drug product mainly
  - One comment: Used component approach, not drug product for Commercial product
  - Another one: assess excipeints first, then assess the commercial product
  - A few companies perform tests in-house
  - Focus on what is on the market already
  - Biological product – cell culture, also did risk assessment; recombinant protein products
  - Sometimes, rely on internal inforamtion, hard to get outside

A. Risk assessment reports. A case with agency requesting more data. LOQ with option 1 was not enough.
B. New submissions with existing approvals-no feedback received form agency.
C. CEP-concerns on training and inconsistency in same product different concentration. Concerns on different people
D. What is expected vs reported. Submissions could include raw data? Or just a summary?
E. One case audited by different FDA auditors. Different approaches what they were looking for, and different reactions to the same document (e.g., checkbox vs review)

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- **Question 1 Notes continued:**
- In a family of several formulations- 6 to 12 batches. Ex Cherry flavor for cough and cold. – time of use verification as they are well below the level.
- 7 for orals and 3 for parentals?
- One manufacturer is doing 26 –all of them. Mainly concerned that they are not getting enough information from supplier. Others response -Used literature data to guide which ones are going to be included.
- If it not intentionally added, can be remove them from the list?
- Intentionally added – Ex. a catalyst is not intentionally added but it is part of the process. However, if there is a mineral in one of the component that was not intentionally added and they are Type 2B, there is no need to be worry about.

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- **Question 1 Notes continued:**
  - One comment: Paper excise first, with analytical data, compile the Risk Assessment report
  - Discuss Equipment, utility (water quality), drug substance, excipeints, etc.
  - Response from agency
  - One comment – not yet;
  - Others may have
  - Some may not hear it before, but in this workshop.
  - Additional information
  - Could it be extended to containers&closures?
  - Interested in contributing to it, if possible
  - Some sponsors are compiling internal database
  - Sometimes, data may be different from the database compared to internal product data
  - Sample Matrix impact is critical , eg. excipients
  - Regarding excipients, does 30% threshold trigger the testing?
  - Initially 3 lots. Depending on data, more lots possible
  - Excipients database may provide some rationale for testing later on?

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2. If testing performed, what was done?

Question 2 Notes:

- **Specificity - Typically do multiple isotopes, combinations to check interferences.**
- **No great isotope interference for specificity for lead.**
- **What is the definition of J. In <233> J talks about instrument and not PDE – clarity will be helpful.**
- **Difficult elements – Hg – causes problems with Arsenic. Very small amount of fluorine seem to make it stable.**

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- Question 2 Notes continued:

- All mentioned use of ICP –MS
- Level of validation- full validation of <233>.
  - Alternative methods? -
  - All validated methods are used
  - Basically based on ICH guideline. May have exception for excipients?
  - Specificity , Accuracy/Recovery performed as per guideline or <1225>. How about Robustness?
  - What acceptance criteria for Accuracy/recovery? --- 70-150%. by design, may be due to matrix effect. Not in guidance, but based on practice
  - Robustness – such as solution stability, changing parameters in the testing conditions, end components, different nebulizers
  - Based on <232>
  - Precision at LOQ level – requirements: not defined

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- **Question 2 Notes continued:**
- Question is almost impossible to answer because it depends on the particular situation
- Not full validation for screening (creative validation?). Verification parameters in the general protocol with proper justification.
- What should be done in order to support the data?
  - Same principles as per validation. Different levels, concentrations on the same concentration are not different values
- Once case of Laser Ablation-ICP MS is being limited used for confirmation for a few excipients. For qualitative purposes information they used it.
- Quadrupole is barely used for certain applications (as starting point)
- Special case for Silver testing. “Regular” screening but now for 24 elements likely to be present in drug product.
- One case using full validation with a specific method for the matrix being used. First choice is generic, if it is not applicable, then a specific protocol.
- Testing 24 EI to cover both intended and unintended added.
- Testing 7 plus intentionally added

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3. Does risk assessment strategy leverage the ICH Q3D 30% threshold?

- **Question 3 Notes:**
- **It is too early to tell. We are not quite there yet**
- **In some cases, there are natural materials that need to be considered.**
- **30% is an arbitrary number but it is a good number to consider as safe for control strategy. Something to use as a baseline value.**
- **It depends on how many lots you are talking about to understand the variability.**
- **For existing product – there is already a limit and still using it.**
- **For two component product – the individual component is below 30% but when you sum the two components then it is tricky**

- **Question 3 Notes continued:**
- YES!
- Voluntarily performing it for risk assessment strategy purposely. It reduces routine testing in control strategy
- It helps when knowing the sources
- It could be all the way to complete PDE
- If you do not have the information, it is not appropriate. You need data to be confident.
- When you submit your LOQ not less than 2, you may get questions. One case was asked to provide a table with ICH values (adjusted)
- Excipients typically have LOQ higher. Sometimes >10g is a better option
- What is the cut off for traces?
  - -> Risk assessment (LOQ as the worst case)
- What is my LOQ = 30%?
  - Summation is a good approach for these cases

4. What analytical challenges have been encountered?

Question 4 Notes:

- DP with full digestion – with HF and nitric acid – the final concentration of HF was low enough that it did not pose any safety risk.
- Sample digestion – no sample that we could not dissolve was found.
- Tricky element is vanadium when nitric acid was used in the matrix for digestion.
- If there are any technical issues that were noticed/understood by someone, is there a way to report that so that other industry people can benefit from – a valuable information shared via publication or database will have a tremendous value.
- Regulatory will also support to provide literature or other data to understand the technical details.

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- **Question 4 Notes continued:**
- In situ vs other approaches? It depends on the nature of the sample
- HF for certain sample preps and not all over the place
- One case with a organic sample with 75% nitric acid digesting (e.g., not digesting silicates)
- Diluted acid is safer and easier to work with (e.g., training, safety)
- No one simple method work for many excipients. Not even 4 or 5 “good methods”. One case with 57 different methods for excipients. Internal database which works for what.
- To start: One has to get as much information as possible in advance first. Then several digestion/extraction, then multiple spiked samples to try
- Specificity is challenging for this application: Correction factors, reaction gases, different equations. You need to investigate for an acceptable range.

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5. Are there remaining concerns regarding risk assessment strategies or analytical challenges?

Question 5 Notes:

If anyone has thought about how often you are going back monitoring the mine (?) material for DP below 30% threshold after January 1, 2017?

Life cycle management documents

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- **Question 5 notes continued:**
- How to know how excipients are contributing to the summation?
- Diverse criteria in inspectors from audit to audit (what is correct/acceptable for one is not the same for another)
- Different amount of info requested by the agency
- Revision to ICH Q3D has been mentioned to clarify expectations
- Transferring of analytical systems is challenging (from pilots)
- Concerns on compliance after January 1, 2018 (not on the analytics). Risk assessments and risks identified. What does that mean to compliance and market? As we approach the deadline, how to fill the gaps and how they will impact the market/public health/compliance? More guidance from the authorities is needed