2017 PQRI/USP Workshop on ICH Q3D Elemental Impurities Requirements – Recent Experience and Plans for Full Implementation in 2018

Breakout Session II:

Industry Experience with Previous Submissions on New Drugs and Concerns about Implementation for Existing Drugs

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November 2017

Industry Experience with Previous Submissions on New Drugs and Concerns about Implementation for Existing Drugs

1. **What questions have sponsors received from regulators on current submissions containing EI information?**
   - If yes, have you received comments regarding the risk assessment submitted? Analytical method used?
   - Have regulators requested setting of EI specification limits on drug products? Components (e.g. drug substance, excipients)?
   - Is regulatory feedback consistent from region to region?

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Question 1 Notes: **questions from regulators on current submissions**

- General questions from FDA on plans to move from heavy metals to Q3D for existing drug products
- An innovator company filed submission following ICH Case 1A model
- Several workshop attendees have submitted applications; however, limited feedback thus far. Some still waiting for response from regulators.
- Based on warning letters, FDA is focusing on data.
- Comment that only ~ 25% of FDA currently trained on ICH Q3D. More training/education needed.
- Comment that Guidance with Q&A would be useful, including Guidance for process validation.

QUESTIONS FROM WORKSHOP ATTENDEES

- Can information from existing product be used to support new product submissions. (generic companies may have many products to file)?
- Can regulators share how many new applications have been filed since June 2016? How many deficiencies were issued? Can they share examples? Type of data/info needed?

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Question 1 Notes: **questions from regulators on risk assessments/summaries**

- Query from regulators for more risk assessment details.
- Request information for validation batches/data to support/justify risk assessment strategy.
- According to FDA, if EI limits are above threshold and below PDE, it may be necessary to include validation data in the submission.
- Risk assessment should be based on quality of data obtained (from suppliers, other data bases, etc.)
- Info from closure/packaging systems sometimes requested when a risk has been identified. Need to include data for extractables/leachables.
- For a parenteral product, the Agency requested info for EIs not listed in Q3D (toxicity too high). Risk assessment more than Q3D may be needed. "nutrient" purpose may be in conflict

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Question 1 Notes: **questions from regulators on analytical method(s) used**

- Several noted that they did not receive requests from regulators for analytical methods (<233> provides methods).
- Questioned reliance of screening method, data and whether the sensitivity to determine LOQ is reliable. Need data to confirm validity.

Question 1 Notes: **questions from regulators on setting EI specification limits**

- For mineral API, regulator asked to put specs in for both API and DP
- For inorganic excipients, regulators request setting specification limits
- Data showed EIs were below threshold; however, needed to further lower specs. To support risk assessment.
- Deficiencies on threshold control have been claimed. If vendors provide info, there should be no reason for further evaluation

Question 1 Notes: **regulators feedback consistent region to region?**

- region-to-region feedback too early to comment on.

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2. What have sponsors included in filings? At what level of detail?

- Summary of EI Risk Assessment?
- Supporting EI data (summary?)?
  - Has 3rd party data/data bases been used in control strategy decisions? If not, would you consider referencing them in the future?
- Summary of supplier provided information?
- Assessment of variability/justification for predictability?
- Change control strategy(ies)?
- Highlights of potential risks and mitigation strategies?
- Statement of compliance?
- What information is being provided by vendors?
- Is each batch being tested?

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Question 2 Notes: **what and level of detail included in application?**

- Narrative on what was done including approach based on guideline from USP and ICH
- Information on injectable products- biologics
- Drug substance and excipients info but no extractables information
- 3 lots of drug product data in some cases
- RMS for Biologics, inhalation products, etc. --supplemented with data to tell a full story and draw a conclusion
- Brief summary (limited details)

Question 2 Notes: **what and level of detail included in RMS?**

- Not sure, so included detailed assessment
- Submission of RMA with summary tables (e.g.. ICH Table 5) and justification for excluding some EIs
- Supporting screening and risk assessment summaries. What is suitable? Full process validation?
- Full risk assessment and control strategies for new applications
- Question if regulators will require full risk assessment in first annual report and if so what all to include.

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Question 2 Notes: **will industry/regulators accept reference data from 3rd party?**

- Some workshop attendees already referencing Lhasa database as part of control strategy
- Neither FDA or EMA have seen reference to the Lhasa database in application. They do not know how it is going to evolve in the future
- Some companies reviewing data in Lhasa vs their own data and using to support risk strategy/summary.
- Other companies using internal understanding, but not referencing in submissions.
- The database contains blinded information on drug components (no traceability back to component manufacturer).

Question 2 Notes: **assessment for variability/justification for predictability?**

- Assessment of equipment, vendor change, manufacturing site changes --- predict the variability and make justifications
- Include assessment in the Quality standard system

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Question 2 Notes: **change control strategy?**

- Include snapshot of possible change assessments and provide justifications for future product manufacturing in Annual Report

Question 2 Notes: **information provided by vendors?**

- Questionnaires sent; however, value of feedback received often questionable and more details needed, including: “what method was used?”
- Need better one-on-one supplier communication to get the information. Most suppliers will provide information **if the right question is asked**!!
- Data shared with assurance the source and data are valid.
- Sometimes industrial data (food grade) may have tighter specification than excipients

Question 2 Notes: **miscellaneous**

- Some attendees concerned that the 30% threshold could become an upper limit, but believe that variability should be considered. For example, it should be acceptable to have 50% PDE if tight control ensure EI won’t exceed PDE.
- One example of EI due to contamination demonstrated importance of experience and knowledge

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3. What supporting information do sponsors have available on-site?

- Risk assessment reports?
- Documented procedures?
- Screening data, scan/digital copies of information?
- Full documentation, method validation, risk assessment, data on how samples where tested, any data given by a third party, references to resources used for your risk assessment?

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Question 3 Notes: **supporting information available on-site?**

- Test data for water quality, even if it meets USP or EP water, testing may be required to support risk assessment strategy.
- Question whether annual testing will be required. Dependent on level of details provided and completeness / effectiveness of documented strategy to control risk?
- Comment that hard to test all products (too many). Will 3 lots be sufficient?
- Analytical report, risk assessments documents (diagrams, tables).
- Secondary documents such as validation and recovery values may be required for raw materials to support control strategy and documented changes. Specifications.
- Detailed control strategies required for everything? Is bridging based on site/product family acceptable?
- Risk assessment are living documents. Change control needs to reflect when change can impact product EIs. Include assessment for ICH Q3D in annual reports as part of the CQA.
- Conduct risk assessments only based on drug product data (due to high product volume).
- Some only collect and use existing data and complement with lab work.
- Some try to divide the responsibilities for testing with both good and bad experiences.
- Case study justification based on calculation of what could be leached into the drug product. PDE is critical. Many times, the data quality is not verified
- The worst-case scenario is not always appropriate for some EI (e.g., As). More research on leachables justification should be considered.

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4. **Where is information being provided in filings? Is filing location consistent for all regions?**
   - **Cover page** (statement that RA summary included)**?**
   - **P.2.2 QOS?**
   - **3.2.P.2 Pharma development** (summary)**?**
   - **3.2.P.3.3 Manufacturing process and process controls** (control strategy)**?**
   - **3.2.P.4 Excipients?**
   - **3.2.P.5 Control of Drug product?**

When provided in multiple section, are hyperlinks included?

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Question 4 Notes: **where to put information in applications?**

- Health Canada suggested P2, EU suggests P5.5 and P5.6
- Some workshop attendees suggested putting the story in P2. P5.5, P5.6
- It is currently acceptable to put in any of the above sections.
- Consider including hyperlinks to data included elsewhere.
- Link to toxicology specification may be needed.
- Sponsor should submit in the same location/format for all regions.
- Location of control strategy and risk assessment is not critical, the complete story (narrative) and supporting data are the critical elements.
- Would be nice to harmonize location of control strategy and risk assessment, globally.
- Some attach a summary of their global strategy and risk assessments. Justification includes compliance statements.
- One attendee only provides a short summary, another submits over 20 pages.
- Most commercial products are low risk of exceeding 30% of an EI PDE; therefore, screening 3 batches of commercial product should be acceptable and consistent with several attendees global strategies.
- There may be no need for full evaluation.
- Global justification for common products. Minimal testing in each location along with general information of the product.
- Flavor is an example of augmentation of certain EI. Very different strategies could be needed

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5. What concerns are there for implementation of existing drugs?

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Open Ended – solicit discussion

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Question 5 Notes: **what concerns for implementing Q3D for existing drugs?**

- Other than existing product risk assessment, what is needed? – prior approval supplement…
- Regulator response – for most product there should not be an issue. If the manufacturer realize during changing control strategy, file 999 (not sure??) report or supplement – include cover letter.
- Concern with how suppliers/users should handle non-compendial materials having specifications to USP <231>, when <231> is deleted.
- US FDA and Health Canada currently allow reporting of changes in requirements from HM to EI in Annual reports; however, what about EU?
- Can suppliers simply justify that HM is not needed and move forward without testing?
- EMA response: Type IA is acceptable for drugs, but not sure if it would be acceptable for biologics.
- If you are working on risk assessment and not completed by Jan 1, 2018 – what will be the regulators response – is there a training for inspectors /reviewers on handling the situation.
- Regulator response – no formal training or thinking in this aspect.
- Recommended regulators consider issuing guidelines on how to handle removal of <231> from non compendial materials. Another thought was for industry to document recommendation in a publication.
- For DMF filings, regulatory filing is forcing them to include heavy metals – companies have the information but did not include based on new guideline.

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Question 5 Notes: **what concerns for implementing Q3D for existing drugs? CONTINUED**

- Concern about adding RMS requirement in the guidelines about PDE for the specific sensitive populations
- One attendee performs it when doing a reformulation
- Calculation and validation at low levels, is the supplier going to make this excipient available with consistent data from different sources/concentrations?
- Has anyone had push back from Agencies to large volume parenterals (MDD more than 2 L) about the calculation of the risk? ICH makes references to the bioaccessability (BA) factors. Not aware about what standards can be used by the available status? Someone could challenge the calculations for BA. Should be handled away from these studies for now until more experience in implementing ICH Q3D. Oral products are easier to manage. Gaps to be filled.
- What about cosmetics or inactive ingredients for topical applications, for example?