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

Breakout Session #: 1

Update on Recent US/EU/JP Regulatory Guidance and Further ICH EI Initiatives

Facilitators: Priscilla Zawislak
Denise McClenathan
Tim McGovern

PQRI
Product Quality Research Institute

usp™

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1. Are there any areas in current guidelines that need further clarification?
   a. If EIs in the drug product are <PDEs based on the risk assessment or testing, what will you do if an individual ingredient monograph has specifications for individual elements?
   b. How should other routes of administration be handled, e.g. dermal, hair/scalp, broken skin vs. normal?

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Question 1 Notes:

- For non-ICH elements there is no threshold or PDEs (e.g. Al). Are specifications needed, and if so, how should limits be set?
- What is the Agency's expectation for non-compendial materials?
- What is the Agency's expectation for IND filings (stage I, II and III)? Is the information in Q3D applicable at Stage III?
- Are there acceptable templates for risk assessment?
- There are still questions about timing even though dates are published in the USP.
- There is still misunderstanding as to what companies can/should expect from suppliers.
- What documentation is expected in an Annual Report to demonstrate compliance?

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Question 1 Notes continued:

- There are questions about how detailed the narrative should be that is provided to the Agency.
- Are there different expectations for a reassessment vs the initial assessment in a Risk Management Summary?
- How should information on proprietary materials be handled?
- Need clarification from the Agency on the meaning of “verification”.
- How much is sufficient data for a new drug product vs existing drug product.
- Concerns expressed with inconsistency among reviewers with regard to what is sufficient information.
- PDEs for solvents are not available.
- Difficult to characterize what the “dose” is for dermal applications (e.g. Questions regarding what is surface area? How many times per day? How much is applied? For what duration?)

2. Global status of EI/heavy metals requirements outside US/EU

a. How are companies planning to manage existing HM/USP <231> requirements in countries that have not planned to implement ICH Q3D and methods (e.g. USP <233>)?

b. For countries that do not permit skip lot testing, will companies test every lot even if there is sufficient EI data to confirm compliance to the HM limit specs/test?

c. How do companies plan to address requirements in countries where they have adopted lower limits for specific elements (e.g. India – Hg) than listed or may not be aligned with ICH Q3D?

d. The same product may be regulated as a drug in one country and a cosmetic in another. How do companies plan to manage this relative to EIs?

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Question 2 Notes:

- There are concerns about ICH Q3D implementation timing in other countries and continued use of <231> type requirements.
- How do we conduct and document the testing when the specs are no longer in the monograph and the methods and chapter no longer exists?
- Some companies will no longer refer to <231> as USP but will keep the method.
- Compendia and industry need to influence further adoption of ICH Q3D.
- Some countries use it for cosmetics.
- Some countries do not want to implement or harmonize on this guideline.
- One company reported submitting an ICP method where this chapter is not applied and it was rejected.

3. What happens after Day 1?
   a. What plans does your company have for reviewing risk assessments or conducting on-going monitoring? At what frequency?
   b. Are pharmaceutical companies 'owning' this process?
      i. Did you receive the necessary information from suppliers?
      ii. Are you putting pressure on suppliers to provide information now/on-going?
      iii. How are you handling contract manufacturers?
      iv. Have you included exchange of EI information in quality agreements?

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Question 3 Notes:

- It is very difficult to get information from supplier so some companies separate raw materials into high, medium and low risk.
  - If it is high risk – then do internal testing of the raw material and for others sometimes just do product testing
- Not just depending on vendors. Some companies taking the drug product approach screen commercial batches and gather as much info from vendors as possible, then develop some type of combined approach.
- Companies request risk assessments from CROs.
- Drug product approach is working well.
- At ICH, it was recognized that things change. Annual product review is the key time to review the status. Some changes may occur in reassessments.
- What is the expectation for timing of re-evaluation? It depends on the material, its source, its impact and level of use in the formulation. Must be determined case by case based on your knowledge and experience.

4. What challenges have you encountered for veterinary drugs or in using ingredients that come from food/cosmetic/industrial suppliers?
   a. Have you had an particular challenges in collecting the information or doing risk assessments related to animal drugs?
   b. Have you had challenges with suppliers who do not often sell into the veterinary or pharmaceutical market, e.g. food, cosmetic or industrial grade products
      i. Are they familiar with ICH Q3D?
      ii. Are you getting information from them?

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Question 4 Notes:

- Getting information from these types of suppliers has been a significant challenge.
- Since FDA CVM has no guidance, it is a major challenge to know what is impacted and what the strategy will be.
- Getting information to support <2232> for dietary supplements is challenging.

5. New drug submissions – have any specific regulatory agency questions or concerns been raised during the review process?
   a. Are there differences in how specific countries (e.g. US, EU, others) are implementing ICH Q3D?
   b. Are there issues that need further clarity or guidance (e.g. FDA's final guidance has not been published yet)?

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Question 5 Notes:

- Submitted 6-7 applications and received no comments - good news.
- Question for the Agency – what is the trend of good vs bad submissions, i.e. in terms of numbers?