Elemental Impurity & Risk Assessment

An update on the retirement of USP General Chapter <231>.

Since January 1, 2018, USP General Chapter <231> Heavy Metals has been retired, and the expectation from the FDA is that firms will comply with ICH Q3D—Guideline for Elemental Impurities (ICH Q3D), USP <232> Elemental Impurities—Limits, and USP <233> Elemental Impurities—Procedures. It was widely recognized that the USP <231> colorimetric procedure was a flawed technique as it was non-specific and relied on the precipitation of heavy metal cations with thioacetamide to form the colored metallic sulfide, which is then visually compared with a standard lead solution. It assumed that heavy elements, such as lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum, react the same way and with an equivalent response as lead with thioacetamide. USP <231> was developed over 100 years ago and its strengths were its weakness. There was no need for costly instrumentation as it was a simple "wet chemical" technique; however, there was no specificity to the method and, as such, if a positive result was afforded, it was unknown for which cation. The method was prone to matrix interference, with the impact of the sample matrix on the reported result being unknown. There was also concern regarding the subjectivity of the test and, thus, reproducibility between different analysts. The technique was labor intensive and necessitated an ashing step with the possibility of losing the more volatile elements, such as Class I mercury.

USP recognized these challenges with USP <231> and, in 2008, began the process of its replacement, which resulted in the above-referenced USP/ICH guidance documents. The cornerstone of the new documents is the USP <233> requirement of instrument-specific techniques, such as ICP OES or ICP MS, which must be verified for suitability (as per USP <1226>) for the sample matrix. The instrument approach addresses the specificity and subjectivity concerns with the USP <231> wet chemical technique. Alternative instrument-specific techniques are allowed, but would require validation (as per USP <1225>) with demonstrated equivalency/superiority to the USP <233> compendial method. ICH Q3D and USP <232> specify individual limits for Elemental Impurities (EIs) within the drug product based upon a Permitted Daily Exposure (PDE), the level of which is dependent upon the route of administration of the finished product and the class of the impurity.

The natural question to ask after the implementation of USP <232> and <233> and ICH Q3D is, "Which specific elements do I need to test for?" This should be answered through the execution of an EI Risk Assessment (RA), which is referenced in ICH Q3D and USP <232>. To execute the RA, there needs to be an understanding of the drug product's manufacturing process in terms of which EIs are intentionally added to the process (e.g., catalysts), what may be introduced with incoming materials (e.g., API, excipients, water), and what could be introduced through the manufacturing and packaging process via processing equipment, purified water, container closure, etc. The key is to implement a risk-based control strategy (based upon ICH Q9 – Quality Risk Management) to limit the level of EIs in the finished product, which requires an understanding of which elements are at risk of remaining in the finished product. The outcome of the RA should define any additional controls, which may include the implementation of test-specific EI assays for releasing incoming materials, in process monitoring, and/or release testing of the finished product.

Due to their toxicity, at a minimum, it is expected that the RA includes the ICH Q3D Class I elements arsenic, cadmium, mercury, and lead, and the Class 2A elements. The Class 2B elements can be excluded from the RA unless they are intentionally added to the API, excipient, or other incoming materials' manufacturing process. The Class 3 elements have the highest PDE and can be excluded from the RA for an oral route of administration unless the element is added to the finished product's manufacturing process. For an inhalation or parenteral route of administration, the Class 3 elements should be considered. Table 2 of USP <232> specifies which elements should be considered in the RA based upon the class of the element and the route of administration.

The RA document can be based upon a fishbone model where potential EI contributions from the following are evaluated:

- Manufacturing equipment
- Water
- API
- Excipients
- Container closure

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> "The [risk assessment] should document all incoming materials and the respective specifications/controls. This also applies to the manufacturing equipment, water supply, and container closure."

ICH Q3D refers to an EI control threshold, which is 30% of the PDE. If, through the RA, the firm can demonstrate that the current manufacturing process and incoming material controls will result in a finished product with an EI content that is consistently less than 30% of the PDE, then additional controls are not required. Therefore, the RA must contain a detailed description of the EI controls along with the data to support the validity of the controls. If, through the RA, it is shown that the level of the EI is greater than the control threshold, then additional measures should be defined within the RA.

There should be focus within the RA on the incoming materials and the established vendor controls, such as vendor release specifications, change control agreements, etc. The EI controls should be a key component of the vendor's quality agreement, and there must be an understanding of the incoming materials' manufacturing process so it is known which EIs may reside within the incoming materials. The RA should document all incoming materials and the respective specifications/controls. This also applies to the manufacturing equipment, water supply, and container closure. The firm's RA procedure should be utilized where the risk for each potential source is quantitated based upon the failure effect (the element), along with the evaluation of severity, probability, and detectability. It is likely that the higher-risk potential sources are the API—as metal catalysts are routinely used during API synthesis—and those excipients/raw materials with a geological source.

When addressing the potential EI contribution from manufacturing equipment and container closure, the materials of construction must be known and considered in the RA, in which an assessment must be made of the likelihood of those EIs leaching during the finished product's manufacturing process or upon storage of the finished product within the container closure. For example, for solid dosage forms, the risk of leaching elements from the container closure is minimal and could be justified as not requiring further evaluation within the RA, versus a liquid dosage form, where the risk is greater. For the manufacturing equipment, it is the same approach; the RA would need to assess the severity of the formulation process and the probability of leaching EIs, considering temperature, use of aggressive reagents, etc.

When conducting the RA and identifying the EIs that require further evaluation, it should be recognized that risk is cumulative and that the various sources—manufacturing equipment, container closure, and incoming materials—for the same element should be considered and combined when the afforded total for that element is compared to the respective control threshold. The identification phase of the RA highlights the EIs that need to be further evaluated, along with those for which it is determined that the risk is such that further evaluation is not required. For the latter, it is critical that the scientific rationale/justification is documented, including the current, defined EI controls (as applicable) plus all associated supporting data/documentation, such as incoming material COAs, equipment/water system qualification, and container closure specifications. For EIs that are intentionally added to the finished product's manufacturing process, evaluation data must be generated to demonstrate that there are sufficient controls built into the process to ensure the EI levels in the final materials are below the control threshold. In process data should be included, along with finished product release data, to illustrate the fate of the EIs through the manufacturing process and the effectivity of the respective critical processing parameters. Literature references should be included where applicable to support the process controls.

Based upon the results of the EI evaluation, there will be a conclusion within the RA as to whether there are sufficient controls in place for each of the EIs. It should be recognized that the evaluation data presented for each identified "at risk" EI verifies the effectivity of the implemented controls, and the RA will need to address the level of elemental analytical testing that will be required for routine production monitoring to verify the ongoing effectivity of the processing controls.

ICH Q3D states that, due to expected variability of the level of the EI due to factors such as the analytical method variability, variability from different EI sources, and the actual manufacturing process, data should be presented on three representative-scale lots or six pilot-scale representative lots. The goal is to gain an understanding of the level of variability and the ability to consistently deliver product that meets the control threshold. If the cumulative EI variability is at a level that results in a risk of not meeting the control threshold, then additional measures, such as manufacturing process modification, adjustment of incoming material specifications, and/or in process testing with a reprocessing option, may be required. **CP**

References

- *ICH Q3D - Guideline for Elemental Impurities, December 2014*
- *USP<231> Heavy Metals*
- *USP<232> Elemental Impurities - Limits*
- *USP<233> Elemental Impurities - Procedures*
- *USP<1225> Validation of Compendial Methods*
- *USP<1226> Verification of Compendial Procedures*
- *Article_Contract Pharma_Elemental Impurities_051818 (50954)*