ICH Q3D: Elemental Impurities

Frequently Asked Questions

Purpose: To provide answers to questions that have been frequently asked of members of the ICH Q3D Expert Working Group.

General FAQs

1. Why is Q3D necessary?

   Q3D is the culmination of several initiatives intended to modernize the control of elemental impurities in pharmaceutical products. The U.S. Pharmacopeia had been discussing the modernization of its heavy metals monograph for several years prior to the initiation of the Q3D Expert Working Group. The European Medicines Agency, after many years of discussion, had implemented a safety and risk-based approach to control of residual catalysts in pharmaceutical products approved to be marketed in the EU. Q3D arose out of a need to develop a globally harmonized guideline, which built upon these efforts as well as the efforts of other pharmacopeias and regulatory authorities.

   Q3D comprises safety-based permitted daily exposures for 24 elementals and recommendations for a risk-based and science-based approach to control of those elements in pharmaceutical products.

2. How can Q3D be implemented?

   The Q3D Implementation Working Group has provided 10 training modules to assist with implementation. When appropriate, the modules include examples of the application of certain principles recommended in Q3D. The modules are available on the ICH website. See Module 0 for a summary of the module content. (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html)

3. Why are herbal products excluded from Q3D?

   Herbal products are subject to regulations that differ between ICH regions. Regional regulations take precedence over harmonized guidances. Application of Q3D to herbal products will be addressed by regional regulatory authorities.

4. Are sunscreens within the scope of Q3D?

   Sunscreens are treated differently by regulatory authorities in different ICH regions. Application of Q3D to sunscreens will be addressed by regional regulatory authorities.

FAQs Related to Pharmacopeial Considerations

5. What is the relationship between ICH Q3D and pharmacopoeia specifications?

   Q3D applies to new finished drug products and new drug products containing existing drug substances. Application to existing products is not expected prior to 36 months after publication on the ICH website.

Pharmacopoeias establish and maintain legally binding quality standards. Pharmacopoeial standards include not only specifications but also general texts and general methods, for existing substances for pharmaceutical use (i.e. drug substances, excipients and other components of drug products), dosage forms and drug products.

Q3D has been developed as a harmonised guideline under the aegis of ICH. Q3D does not deal with testing methods, however it stipulates in chapter 9 that "*pharmacopoeial procedures or suitable alternative procedures for determining levels of elemental impurities should be used*". The pharmacopoeias of the three ICH regions (JP, Ph. Eur. and USP) participated in the development of Q3D as observers to help ensure prospective alignment according to respective legislations. A concrete example of this alignment is the Ph. Eur., which will reproduce verbatim the content of the Guideline in its chapter 5.20. and cross-reference to the general monograph on Pharmaceutical preparations, thereby making it legally binding in Europe.

The three pharmacopoeias are in the process of elaborating texts on elemental impurities testing. See the respective websites for more information.

FAQs Related to Safety

6. What elements were included in the guideline? What elements were excluded?

   Elements included in the guideline were based on evaluation of toxicity, previous regional guidelines, and industry survey. After safety evaluation, some elements were dropped from inclusion due to lack of safety concern in the Step 4 guideline (e.g., B).

   Elements of low risk (Fe, B, W, Zn, K, Ca, Na, Zr, Mn, and Mg) were not considered by the EWG to require route specific PDEs. Individual safety monographs were not prepared for these elements. These elements do not need to be included in a risk assessment, unless required by regional regulations. The rationale for not providing a PDE is discussed in Section 4 of Q3D under "Other elements".

   For Al, the EWG recognized there are regional regulations regarding the acceptable levels in parenteral drug products that take precedence over ICH guidance. This is discussed under "Other elements" in Section 4 of Q3D.

7. Why is Cr (III) used in the chromium monograph rather than Cr (VI)?
   Because Cr (VI) is reactive, the EWG did not consider it likely that this form would appear in pharmaceuticals. As noted in the monograph, if this form is used as a catalyst, than the assessment should incorporate this form.
8. Please provide a scientific explanation why the inhalation PDE for mercury shall be lower than the parenteral PDE.

   The rationale for derivation of PDEs is discussed in Section 3.1 of Q3D and in the individual monograph. The parenteral and inhalation PDEs for mercury are in the same order of magnitude (3 and 1 µg/day). There is little data for inorganic mercury by the parenteral route and the inhalation PDE is based on occupational data.

9. What about other routes of administration that are not covered in the Guideline or the training material? What starting point should I use?

   In brief, Q3D recommends using the PDE developed for the oral route as the starting point for a risk assessment. Details for developing a PDE for a risk assessment for routes other than oral, parenteral and inhalation are discussed in Section 3.2 of Q3D and Module 1of the IWG training material.

FAQs Related to CMC

10. What information regarding the risk assessment should be held at the manufacturing site?

    The detailed risk assessment should be documented in the manufacturer's pharmaceutical quality system. Regional regulatory authorities may provide additional guidance on how these recommendations may be satisfied.

11. What information on the risk assessment should be presented in a regulatory submission?

    Training Modules 5, 6 and 8 (case studies) provide some suggestions regarding the content of the risk assessment and the summary that should be included in the new drug application dossier. However, currently there is no universal agreement on where a risk assessment should be located in the CTD. Regulatory authorities may provide additional guidance as experience with Q3D increases.

12. Until recently, the control of residual catalysts and heavy metal impurities has been addressed separately through the EMA residual catalyst guideline and compendial heavy metals monographs, respectively. Why was it considered necessary to address a wider range of elemental impurities in a single guideline?

    It has been recognized for several years that certain metals can be introduced into a drug product from impurities in raw materials or from processing equipment, which are not satisfactorily controlled by a test for heavy metals. From a scientific point of view, the characteristic that is relevant to patient safety is the total daily mass of an elemental impurity delivered to the patient because the toxicological risk depends only on the total exposure. Thus a science-based approach should consider all elemental impurities in the same way, regardless of their source.

    Q3D emphasizes a holistic, risk-based approach to control of elemental impurities, and provides a rational assessment mechanism that is appropriate for all elemental impurities. The risk assessment provides an opportunity to identify those elemental impurities that have the potential to pose a safety risk to the patient, whether or not they are intentionally added. Within the risk assessment, it is prudent to consider the most toxic elements that may be introduced as impurities in raw materials, including the Class 1 and Class 2A elements. These elements would only require routine testing in drug products or components of drug products if the risk assessment provides evidence that there is a risk that these elements could exceed the permitted daily exposures.

13. Can periodic testing be applied to elemental impurities?
    Under certain circumstances, periodic testing may be applied to elemental impurities with suitable justification. Periodic testing is subject to different regulations in different ICH regions.

Regulatory authorities may provide additional guidance on regional considerations for periodic testing. (Refer to Training Module 6)

14. Is one calculation option presented in Section 7 preferred over the others?
    No. As noted in Q3D Section 7, the choice of calculation option is at the discretion of the drug product manufacturer.

15. What evidence is needed to demonstrate that primary container/closure systems do not contribute elemental impurities to drug products?

    Scientific evidence (e.g., from published literature or suppliers) may support a determination of lack of elemental impurities (e.g., no elements used in manufacture of packaging). Extractable and leachable studies and risk assessment for specific dosage forms may also contribute evidence.

16. When will testing be required for catalysts used in synthesis of drug substance?
    When catalysts are demonstrated to be consistently below 30% of the PDE, no further controls are required. Catalysts that are used in the last synthetic step may require testing even when they are below the control threshold, but periodic testing may be justified in some cases.

17. If data for 3 commercial batches (or 6 pilot batches) of drug product, demonstrate that the levels of Class 1 are negligible, is this sufficient to justify no further testing for these elements?

    This information alone would not be adequate to justify no further testing. Scientific justification and a suitable risk assessment, along with good manufacturing practices for acceptance of materials for use in pharmaceutical products should be among the points to consider when evaluating the need for routine testing of Class 1 elements.

18. If changes are made to a product during the lifecycle e.g. changes to a synthetic route or excipient supplier, what does an applicant need to do to ensure compliance with Q3D?

    Product and/or process changes across the product lifecycle have the potential to impact (positively or negatively) the elemental impurity content of the drug product. The impact of such changes on the original risk assessment should be evaluated, and implications for the control strategy should be considered. The regulatory implications of any modifications to the risk assessment and control strategy should be considered, and appropriate variations submitted according to specific regional requirements. (Refer to Training Module 6)