TRIPHASE®
Pharma Solutions, LLC

CASE STUDY

ICH Q3D Elemental Impurities

BACKGROUND

As of September 15, 2015, ICH Q3D "Elemental Impurities" became the official guidance governing heavy metals and catalyst impurities in drugs for the European Union, Japan, and the United States. Prior to ICH Q3D the only "official" Guidance was USP <231> which is a colorimetric test and is not specific for nor does it address catalyst metal limits.[1] Now that ICH Q3D is official it should be the first choice for the setting of specifications for metal limits in drug substance and drug product. Additionally, as our case study illustrates, ICH Q3D allows for higher levels of metals based on projected daily dose in grams of drug product than possible under ICH <231> which is fixed at 10 ppm per metal or 20 ppm total.

OVERVIEW OF ICH Q3D

Several features of ICH Q3D are notable; i) analogous to ICH Q3A Residual Solvents Metals have been classified into four classes, with Class 1 being the most toxic and Class 2, 3, and 4 lower toxicity. In this way grouping of metal toxicity is possible much like under ICH Q3C: Residual Solvents; ii) in addition to addressing limits for API (component) metal content, total metal contribution in your finished drug product from other components may be required to be calculated; iii) allowed metal limits are aligned with increasing risk of dosage route thus limits for parenteral drugs are tighter than oral or topical drugs; iv) permitted daily exposure (PDE) has been assigned to a wide range of metals and three options are provided, the latter options allowing justification of higher levels of metals in lower dose drugs so long as overall PDEs are met. This last provision has perhaps the broadest implication. Prior to this guidance no allowance for dose was possible. The different options offered with a brief description are summarized below followed by a case study example. The ICH Q3D guidance also has many additional examples for the interested reader.

Option 1: drug products with daily intakes of not more than 10 grams that meet the PDE limits

Option 1 requires the least justification and if it can be applied it should be the preferred option. Taking an oral drug and palladium as an example, the PDE in µg/day for palladium is 100 µg/day. Thus assuming 10 g day or less dose of an oral drug product the allowed limit would be 100 µg / 10 g / day = 10 µg/g = 10 ppm.

[1] For guidance on metals not addressed in USP <231> CMC regulatory scientists typically referred to either USP <232> (draft) or the EMEA guideline on the specification limits for residues of metal catalysts or metal reagents (MEA/CHMP/SWP/4446/2000).

If the route of dosage is parenteral instead of oral a PDE of 10 µg per day must be used which means 1 ppm palladium limit would apply under option 1. Thus Option 1 can always be chosen if your total dose of formulated drug product is 10 g or less per day *and* the PDE is not exceeded for the listed metal. Also to use this option palladium can not be used in any other components used to make your drug product.

Option 2: drug products with specified daily intakes of less than 10 grams

Option 2a

This option is similar to Option 1, except that the drug daily intake is not assumed to be 10 grams rather the Sponsor would specify a daily dose in grams of drug product. In such a case a calculation is required to obtain your metal limits. Following our example using palladium this means that if total dosed drug product per day is 2.5 g per day (instead of 10 g/day) then the allowed palladium in drug product would become 40 ppm instead of 10 ppm since the dose is ¼ as large. To use this option palladium can not be used in any other components used to make your drug product.

Option 2b

This option requires additional information be assembled regarding the potential for specific elemental impurities to be present in specific drug product components in addition to drug substance. This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product. For example if one of your component excipients is PEG 400 and your Certificate of Analysis for PEG 400 specifies palladium at a limit of 10 ppm your drug substance specification would need to be changed to 10 ppm (instead of 20 ppm) so that you meet the overall PDE for palladium. In this case palladium testing and specifications and an overall analysis must be provided for palladium limits in both drug substance and finished drug product.

Option 3: Finished Product Analysis

Option 3 is used when other components in your drug product besides API utilize metals in their synthesis process. In this option the concentration of each element is measured in the final drug product and a PDE equation may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity.

CASE STUDY

In this case study a clinical drug product is a topical cream and contains four component excipients in addition to drug substance and is being dosed at a daily exposure of 5 g (cream) per day. The drug substance process uses palladium as a catalyst and a specification limit had been set (pre ICH Q3D) using USP <231> at “no more than 10 ppm” for palladium. A recent cGMP campaign for drug substance was completed and the test results came back for palladium at 19 ppm thus exceeding the specification of “no more than 10 ppm”. Neither palladium nor any other metals have been used in the manufacture of the other four drug product components (excipients). The questions at hand is whether a justification be made to allow use of this drug substance batch in humans? The

analysis for this case is presented below.

1. We choose to conduct the analysis using ICH Q3D since this guidance is official and applies to US, EU, Japan, and EU member states and since the drug failed specifications under USP <231>.[2]
2. The drug is a topical route of administration thus per ICH Q3D the oral drug guidelines from ICH Q3D apply (Table footnote).
3. The dose is no more than 10 g per day so Option 1 is considered. Option 1 PDE limit for palladium is 100 µg/day or 10 ppm thus Option 1 can not be used under ICH Q3D since the palladium level is 19 ppm.
4. Option 2a is applied at our projected Drug Product Daily Dose of 5 g/day, PDE is 50 µg / day thus our limit increases from 10 ppm to 20 ppm (since dose was reduced by ½). Thus our drug substance contains an allowable level of palladium with application of ICH Q3D.

Note in the current example no excipients used palladium or any metals in their process thus no analysis for metals is required for overall finished drug product and analysis and specifications can be restricted to drug substance alone. It is also noteworthy that if the daily dose was 1 g / day then the allowable pallidum increases to 100 ppm (since dose is reduced by 1/10).

Finally it is critical to note that ICH Q3D has different PDEs depending on dosage route. Per ICH Q3D if our drug was a parenteral the PDE is 10 µg/day or 1/10th the PDE for an oral/topical. Thus assuming a dose of 1 g per day the limit for a parenteral for drug substance would become 10 ppm and a rework of the drug substance to lower palladium levels would be required. The PDE for palladium for an inhaled product is 1/100th that of oral so in a 1 g / d dose scenario the limit for palladium for an inhaled product becomes 1 ppm. This is perhaps the "bad" news of ICH Q3D such that it can place higher demands on analytical and process development skills for high dose parenteral and inhaled products, requiring proper CMC oversight and perhaps re-design of synthetic routes to avoid metals all together.

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[2] We could also elect to use USP <232> which would in fact give same results as ICH Q3D however would only apply to US studies/ marketed drugs and furthermore USP <232> remains in draft form at this time.