



## Current Position on Pharmaceutical Company Requests for Metal Impurity Levels in Excipients

March 28, 2012

IPEC Federation member companies who manufacture excipients have been receiving questions from their customers regarding elemental (metal) impurities. **The IPEC Federation believes that it is pre-mature for pharmaceutical companies to be requesting this type of information at this time and recommends that all excipient suppliers respond to these requests by referring their customers to this document.**

The USP chapters have been proposed in PF 37 but are not yet finalized or official. The current version of the ICH Q3D Guideline is only a draft and has not been finalized or made public. Since the draft ICH Q3D guideline is still in early draft form, and not public, the IPEC Federation does not feel it is appropriate for pharmaceutical companies to begin requesting compliance related information to the metal impurity limits listed in this draft at this time.

Many excipient companies will only begin to develop information on what trace levels of metal impurities exist in their excipients after the final limits are agreed to by all ICH parties and the limits are known. Only then can appropriate data and information be developed to answer the questions that pharmaceutical companies will need to know.

The purpose of the ICH Q3D guideline is to establish appropriate controls for the final dosage form of the drug for those elements with clearly established toxicological concerns. The scope of the ICH guideline is limited to the criteria and limits, with the limits based on published safety and toxicology data. Test methods will be addressed in the compendia in the future, however, testing is not the only way to determine the metal impurities and levels which may be important. Levels of metal impurities can be established by means other than testing.

The Permitted Daily Exposure (PDE) being established in the ICH Q3D guideline applies to the drug product, not the individual components. It is important to note that if the risk assessment indicates that there is no potential for an element to be present, there is no need to establish a quantitative result for that element.

Excipient suppliers will need to provide some information to customers with respect to the metal impurities which may be present in the excipient and expected levels of these metal impurities based on what they may know. **However, note that because it is the overall dosage form that must meet the PDE limits, the excipient is not required to comply with the limits in the ICH Q3D guideline. The only limits that the excipient must comply with, from a regulatory perspective, are the existing limits in the pharmacopeial monographs or other specific regulatory references which may apply directly to the excipient such as 21 CFR, etc.** The information provided by the excipient supplier will be incorporated into the drug manufacturer's control strategy to meet the PDEs for the final drug product. It should not be expected that most excipient suppliers will be performing routine testing for all these metals.

At this time, excipient suppliers are in the process of evaluating the individual metal impurities that may be present in their excipient products and the typical levels present. Many companies have been using USP <231> in the past which is a limit test and is not specific to individual elements. Therefore, this data is not typically relevant to discussions about metal impurities down to the types of levels being discussed by the ICH Q3D EWG. Assessment of individual metal impurities in excipients is underway by many companies, however, final assessment and presentation of the data will, in many cases, be dependent on the final version of the ICH Q3D guideline. Until the ICH Q3D guideline is finalized, the industry does not know what the final PDEs will be which will also drive other parameters such as the limit of detection needed for any analytical testing that they may choose to perform.

Until the ICH Q3D guideline reaches Step 2 and is sent out for public consultation, the IPEC Federation believes that exchange of preliminary metal impurity information between supplier and users may simply lead to more confusion rather than help to address the issue.