Final Concept Paper
Q3D: Impurities: Guideline for Elemental Impurities
Dated 17 July 2009
Endorsed by the Steering Committee on 29 October 2009

Type of Harmonisation Action Proposed

It is proposed that a new harmonised tripartite guideline be developed to provide a global policy for limiting metal impurities qualitatively and quantitatively in drug products and ingredients.

Statement of the Perceived Problem

The existing ICH Q3A Guideline classifies impurities as organic, inorganic, and residual solvents. The Q3A and Q3B Guidelines effectively address the requirements for organic impurities. An additional Guideline Q3C was developed to provide clarification of the requirements for residual solvents. The proposed new Guideline Q3D would provide similar clarification of the requirements for metals, which are included in the ICH inorganic impurities classification.

A harmonised approach for control of metal impurities, including the list of specific metals to be limited and the appropriate limits for these metals, would be beneficial to help avoid the uncertainty and duplication of work for industry to meet requirements that may otherwise differ between the ICH regions. Some regulatory guidance on specification limits for residues of metal catalysts and reagents was recently provided by EMA, but similar regulatory guidance has not yet been provided from the US or Japan for public review. An ICH Guideline will ensure that new requirements have the necessary input of the regional regulatory authorities, to the benefit of regulators, industry, and public health.

An ICH Guideline for metal impurities would emphasize control of supply chains and risk assessment, as was done with Q3C. Such an approach would be outside the usual scope of pharmacopoeias and would require significant input from regulatory authorities. Also consistent with the existing Q3C Guideline, a new Q3D Guideline would focus on the establishment of appropriate limits for specific metals, without necessarily providing details on the analytical procedures to be used. In support of the Q3D Guideline, harmonised analytical procedures should be established by the pharmacopoeias for determining levels of metal impurities, with allowance for use of any appropriate validated procedure for a particular application. It is preferable that interested parties participate in the effort to achieve initial agreement on metal impurities, rather than the regulators and the pharmacopoeias reaching independent decisions which would necessitate subsequent harmonisation. Ultimately, a harmonised guideline would provide appropriate safety-based limits for the control of metal impurities, along with consistent expectations for test requirements and regulatory filings.

Issues to be Resolved

In order to provide benefit to public health, it is envisioned that a safety-based approach would be taken for the control of metal impurities. It is especially important to establish appropriate controls for those metals with clearly established toxicological concerns. These metal impurities may arise from the drug substances, excipients, or manufacturing processes used for drug products, and may include catalysts, reagents, ligands, heavy metals or other residual metals, such as those due to the material source (e.g., Pb, Hg, As, Cd). With a focus on safety of the finished

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dosage form provided to the patient, a new ICH Guideline would assure appropriate control for the specific metals that are likely to be present in particular drug products and ingredients.

Background to the Proposal

Current control of metal impurities is primarily based on pharmacopoeial requirements for Heavy Metals, which have been widely used for routine screening of pharmaceutical ingredients since the early 20th century. The commonly used methodology was mainly intended to control metals which form a sulphide precipitate, such as lead, copper and other metals which were potential contaminants from water pipes, manufacturing equipment, processes, and other common sources. Although the risk factors for metal contamination have changed dramatically, the standards for their control have changed little for more than 50 years, and most Heavy Metals limits have little basis in toxicology.

At the ICH Meeting in Brussels in November 2008, there was some preliminary discussion of the potential need and benefit of a harmonised guideline for metal impurities. Previously, the Expert Working Group on Quality developed the Q3A, Q3B, and Q3C Guidelines in order to provide a harmonised approach to limiting impurities. Toxicologists also provided input on the subject of impurities, particularly with regard toxicity of process-related impurities and residual solvents. The existing ICH Guidelines have generally been incorporated into the pharmacopoeial standards dealing with impurities. Extending this approach to provide a similar harmonised outcome for addressing metal impurities would avoid different limits being considered among the regulatory agencies and the pharmacopoeias.

Type of Expert Working Group

It is recommended to form an EWG composed of chemists (with backgrounds in QA and R&D) along with toxicologists to develop the appropriate guideline for control of metal impurities. The ability to start with the EMA guideline on metal impurities, which was structured in a manner similar to the ICH Q3C Guideline for residual solvents, should make it feasible to develop the proposed guideline within one to two years of initiation of the work.