DRAFT CONSENSUS GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D

Current *Step 2b* version

dated 26 July 2013

At Step 2 of the ICH Process, a consensus draft text or Guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Q3D
Document History

Current *Step 2a* version

Code	History	Date
Q3D	Approval by the Steering Committee under *Step 2a*.	6 June 2013

Current *Step 2b* version

Code	History	Date
Q3D	Approval by the Steering Committee under *Step 2b* and release for public consultation.	6 June 2013
Q3D	Post sign-off corrigendum in: • Table 4.1 W and Al were removed from the list of included elemental impurities in Class 2B and 3 respectively. • Table A.2.1 the Class for Ni was changed to read 3 instead of 2.	14 June 2013
Q3D	Post sign-off minor editorial corrections including: removal of references to Appendix 5 (pgs i & 13); deletion of redundant text (pg 4); change of Option 2 to Option 2a (pg 10); insertion of omitted text under Safety Limiting Toxicity (pg 35); removal of duplicated redundant text (pg 41); replacing references to “metals” in text and “metal” in Table A.4.7 title with “elementals” and “elements” (pg 73); and deletion of header Table A.4.10 (pg 75).	26 July 2013
Q3D	Addition of line numbers to facilitate the provision of comments by stakeholders.	30 September 2013

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Released for Consultation on 26 July 2013, at *Step 2b* of the ICH Process

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1. INTRODUCTION

Elemental impurities in drug products may arise from several sources; they may be added intentionally in synthesis, or may be present as contaminants (e.g., through interactions with processing equipment or by being present in components of the drug product) and are consequently detectable in the drug product. Since elemental impurities do not provide any therapeutic benefit to the patient, element impurity levels should be controlled within acceptable limits in the drug product. There are three components of this guideline: the evaluation of the toxicity data for potential elemental impurities, the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern, and development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE. It is not expected that an applicant tightens the limits based on process capability provided that the elemental impurities in drug products are held at or below the PDE. The PDEs established in this guideline are considered to be protective of public health for all patient populations, including pediatric patients. In some cases, lower levels of elemental impurities may be needed when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, in the case of high PDEs, other limits may have to be considered from a pharmaceutical quality perspective; other guidelines should be consulted.

Developing a strategy to limit elemental impurities in the drug product is consistent with risk management processes identified in ICH Q9. The process is described in this guideline as a four step process to assess and control elemental impurities in the drug product: identify, analyse, evaluate, and control.

The PDE of the elements may change if new safety data become available. The guideline may be updated to include other elemental impurities or other routes of administration as new data become available. Any interested party can make a request and submit the relevant safety data to be considered.

2. SCOPE

The PDEs in this guideline have been established based on acceptable safety limits of potentially toxic elemental impurities. The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products employing existing drug substances. The drug products containing: proteins and polypeptides (produced from recombinant or non-recombinant cell-culture expression systems), their derivatives, and products of which they are components (e.g., conjugates) are in the scope of this guideline. In addition, drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides are within scope of this guideline.

This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, crude products of animal or plant origin, dialysate solutions not intended for systemic circulation or drug products containing elements that are intentionally included for therapeutic benefit.

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