Q3D Elemental Impurities

Guidance for Industry

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2015
ICH

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TABLE OF CONTENTS

I. INTRODUCTION (1) 1
II. SCOPE (2) 2
III. SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES (3) 2
A. Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration (3.1) 2
B. Other Routes of Administration (3.2) 4
C. Justification for Elemental Impurity Levels Higher Than an Established PDE (3.3) 4
D. Parenteral Products (3.4) 5
IV. ELEMENT CLASSIFICATION (4) 5
V. RISK ASSESSMENT AND CONTROL OF ELEMENTAL IMPURITIES (5) 7
A. General Principles (5.1) 7
B. Potential Sources of Elemental Impurities (5.2) 7
C. Identification of Potential Elemental Impurities (5.3) 8
D. Recommendations for Elements to be Considered in the Risk Assessment (5.4) 10
E. Evaluation (5.5) 10
F. Summary of Risk Assessment Process (5.6) 11
G. Special Considerations for Biotechnologically Derived Products (5.7) 12
VI. CONTROL OF ELEMENTAL IMPURITIES (6) 13
VII. CONVERTING BETWEEN PDES AND CONCENTRATION LIMITES (7) 13
VIII. SPECIATION AND OTHER CONSIDERATIONS (8) 16
IX. ANALYTICAL PROCEDURES (9) 16
X. LIFECYCLE MANAGEMENT (10) 16
GLOSSARY 16
REFERENCES 18
APPENDIX 1: METHOD FOR ESTABLISHING EXPOSURE LIMITS 19
APPENDIX 2: ESTABLISHED PDES FOR ELEMENTAL IMPURITIES 22
APPENDIX 3: INDIVIDUAL SAFETY ASSESSMENTS 24
APPENDIX 4: ILLUSTRATIVE EXAMPLES 72

Contains Nonbinding Recommendations

Q3D Elemental Impurities
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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page of this guidance.

I. INTRODUCTION (1)[2]

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. There are three parts of this guidance:

- 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 application of a risk-based approach to control elemental impurities in drug products.

An applicant is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs. The PDEs established in this guidance are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted 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, for elements with high PDEs, other limits may have to be considered from a pharmaceutical quality perspective and other guidances should be consulted (e.g., ICH Q3A).

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[1] This guidance was developed within the Quality Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2014, and revised to correct several inconsistencies, December 2014. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2013.

This guidance presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE (2)

The guidance applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances. The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or nonrecombinant origins), their derivatives, and products of which they are components (e.g., conjugates) are within the scope of this guidance, as are drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides.

This guidance does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guidance does not apply to products based on genes (gene therapy), cells (cell therapy), and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products.

This guidance does not apply to drug products used during clinical research stages of development. As the commercial process is developed, the principles contained in this guidance can be useful in evaluating elemental impurities that may be present in a new drug product.

Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH.

III. SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES (3)

A. Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration (3.1)

The method used for establishing the PDE for each elemental impurity is discussed in detail in Appendix 1. Elements evaluated in this guidance were assessed by reviewing the publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports. This process follows the principles described in ICH

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