Guidance for Industry

Q3B(R) Impurities in New Drug Products

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)

November 2003
ICH

Revision 1

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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1.0)[2]

This guidance provides recommendations for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state. This guidance revises the ICH guidance of the same title, which was issued in May 1997. The revised guidance clarifies the 1997 guidance and makes some changes.[3] The revision also provides consistency with more recently published ICH guidances (e.g., *Q3A(R) Impurities in New Drug Substances*, *Q3C Impurities: Residual Solvents*, and *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*). This guidance complements the ICH Q3A(R) guidance, which should be consulted for basic principles along with ICH Q3C when appropriate.

This guidance addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as *degradation products* in this guidance). Generally, impurities present in a new drug substance need not be monitored or

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[1] This guidance was developed within the Q3B(R) 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 was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 5, 2003. 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 in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

[3] For example, addressing reporting, identification, and qualification thresholds; listing impurities in specifications and making a clear distinction between ICH Q3B (listing impurities) and Q6A (setting specifications); and deleting the exception to conventional rounding practice (i.e., the provision recommending no rounding up to 0.1 percent for values between 0.05 and 0.09 percent).

specified in new drug product unless they are also degradation products (see ICH Q6A guidance on specifications).

Impurities arising from excipients present in a new drug product or extracted or leached from the container closure system are not covered by this guidance. This guidance also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guidance:

- Biological/biotechnological products
- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Fermentation products and semi-synthetic products derived therefrom
- Herbal products
- Crude products of animal or plant origin

Also excluded from this document are (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

FDA's guidance documents, including this guidance, 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. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS (2.0)

The applicant should summarize the degradation products observed during manufacture and/or stability studies of a new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product. This summary also should include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients). The impurity profiles of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development, and any differences should be discussed.

Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is infeasible, a

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