Establishing Impurity Specifications for Antibiotics

Guidance for Industry

DRAFT GUIDANCE

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

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Pharmaceutical Quality/CMC

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Establishing Impurity Specifications for Antibiotics Draft Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to industry for establishing specifications for **impurities**[2] in antibiotics manufactured by fermentation and **semi-synthesis.**[3] These recommendations can be used to establish consistent standards for impurity testing and ensure that batches of antibiotic drug products[4] meet appropriate impurity specifications.[5] This guidance applies to antibiotic drugs, including:

- Antibiotic drugs subject to approval under new drug applications (NDAs) and abbreviated new drug applications (ANDAs) submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and associated type II drug substance[6] drug master files (DMFs) referenced in NDAs and ANDAs for antibiotic products

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] The Glossary defines specific terms used in this guidance. Words or phrases found in the Glossary appear in **bold** at first mention.

[3] See the ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See 21 CFR 314.3(b) for the definition of *drug product.*

[5] See 21 CFR 211.165(d).

[6] See 21 CFR 314.3(b) and 210.3(b)(7) (defining *drug substance* and *active ingredient*). See also the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) (defining *active pharmaceutical ingredient* (*API*)). The terms *drug substance, active ingredient, and API* are used interchangeably in this guidance.

- Nonprescription antibiotic drugs marketed under section 505G of the FD&C Act,[7] often referred to as over-the-counter (OTC) monograph drugs[8]

Investigational new drug applications (INDs) for antibiotic drugs submitted under 21 CFR part 312 should follow the general principles outlined in this guidance.

The recommendations in this guidance are not intended to be applied retrospectively to antibiotic drugs submitted in applications or their supplements, or to antibiotic drugs marketed before finalization of this guidance. This is to prevent potential manufacturing discontinuances or interruptions of marketed antibiotic drugs that could lead to supply chain disruptions. However, applicants and manufacturers of marketed antibiotic drugs should consider updating impurity specifications in accordance with this guidance when making major changes, such as replacing a source of active ingredient(s), and to ensure the drugs are manufactured in compliance with Current Good Manufacturing Practice (CGMP) requirements.

The following types of impurities are not covered in this guidance:

- Extraneous contaminants that should not occur in drug substances and drug products[9]
- Microbiological controls (e.g., endotoxin limits, microbial limits)[10]
- Cell substrate-derived impurities due to fermentation (e.g., residual host cell proteins, residual host cell DNA)
- Residual solvents and elemental impurities
- Leachables from container closure systems or manufacturing equipment

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.

[7] 21 U.S.C. 355h.

[8] See section 744L(5) of the FD&C Act (21 U.S.C. 379j-71(5)).

[9] See, e.g., 21 CFR 211.56 and 211.65.

[10] See, e.g., 21 CFR 211.113 and 211.165(b).

II. BACKGROUND

Under section 501(a)(2)(B) of the FD&C Act,[11] drugs that are not manufactured in accordance with CGMP requirements shall be deemed to be adulterated. The minimum CGMP requirements for drug production are contained in 21 CFR parts 210 and 211.[12] Applicants and manufacturers of drug products must establish suitable impurity specifications to ensure drug product quality.[13] Likewise, manufacturers of active pharmaceutical ingredients (APIs)[14] should establish impurity specifications to comply with CGMP.[15]

Impurities, including **degradation products**, are compounds that differ from the chemical entity defined as the drug substance. These compounds may be present in drug substances or drug products due to manufacturing processes, drug degradation, or interactions among components during storage. Controlling and monitoring impurities in drug substances and degradation products in drug products[16] are important for ensuring the safety, efficacy, and quality of medications. The ICH guidances for industry *Q3A(R) Impurities in New Drug Substance*s (June 2008) (ICH Q3A(R)) and *Q3B(R2) Impurities in New Drug Products* (August 2006) (ICH Q3B(R2)) provide recommendations on thresholds for the identification, reporting, and qualification of impurities in drug substances and degradation products in drug products using drug substances that are produced by chemical synthesis. Relatedly, the ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023) provides a framework for the identification, categorization, qualification, and control of mutagenic impurities to limit potential carcinogenic risk.

Applicants and manufacturers of antibiotics produced entirely by chemical synthesis should follow the principles described in the above guidances for controlling impurities and degradation products. However, many antibiotics are derived through fermentation processes or semi-synthetic methods rather than chemical synthesis. The complex processes involved in fermentation and semi-synthetic methods can introduce a wider variety of potential impurities compared to chemical synthesis. Despite the use of these methods to produce antibiotics, available guidances do not provide recommendations for the control of impurities and degradation products in drugs produced by fermentation or semi-synthetic processes, including certain antibiotics. To address this gap, this guidance outlines recommendations for identifying, qualifying, and controlling impurities and degradation products in fermentation-based and semi-

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[11] 21 U.S.C. 351(a)(2)(B).

[12] 21 CFR 210 applies to all drugs as defined in 201(g) of the FD&C Act. See also 21 CFR 211.1(a).

[13] CGMP requires that specifications be scientifically sound and appropriate to ensure drug products meet the required standards for identity, strength, quality, and purity. See 21 CFR 211.160(b).

[14] See footnote 6.

[15] See ICH Q7.

[16] Degradation products can also be present in drug substances.

synthetic antibiotics. By providing these recommendations, FDA intends to clarify effective control strategies, support the development of high-quality antibiotic drugs, and promote consistency in quality standards.

III. DISCUSSION

Antibiotics produced by fermentation or semi-synthesis typically result in more complex drug substances compared to those made solely by chemical synthesis. The complexity stems from the use of biological systems, which generate a mixture of compounds during manufacturing. Antibiotic drug substances produced by these methods can contain a mixture that includes the active ingredient and impurities. The active ingredient is generally not a single molecular entity but rather a collection of structurally related, biologically active analogs that together define the active ingredient. These mixtures should be fully characterized to identify impurities and **antibiotic-related analogs**[17] in the drug substances, as well as degradation products in the drug products.

To comply with CGMP regulations, scientifically sound and appropriate specifications[18] must be established to ensure that drug products conform to appropriate standards of identity, strength, quality, and purity.[19] This process includes setting tests and acceptance criteria for degradation products. Likewise, drug substance specifications should include tests and acceptance criteria for impurities.[20] Implementing these controls is crucial for ensuring consistent production of high-quality antibiotic drugs.

A. Listing of Impurities and Degradation Products in Specifications

The terminology for listing impurities and degradation products in ICH Q3A(R), ICH Q3B(R2), and the ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000) should be used for antibiotic drug substances and drug products. Specifications should include the following:

- Drug Product

[17] These antibiotic-related analogs are characteristic of many drug substances and drug products produced by fermentation or semi-synthesis and can have a varying degree of biological activity. Antibiotic-related analogs are comparable to the active ingredient with respect to biological activity, while impurities are not comparable with respect to biological activity.

[18] As defined in the ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000), the term specification includes analytical procedures, references, and acceptance criteria.

[19] See 21 CFR 211.160(b).

[20] See ICH Q7.

- Each **specified identified degradation product**[21]

- Each **specified unidentified degradation product**

- Any **unspecified degradation product** with an acceptance criterion that does not exceed (i.e., ≤) the identification threshold

- Total degradation products[22]

- Drug Substance

  - Each **specified identified impurity**[23]

  - Each **specified unidentified impurity**

  - Any **unspecified impurity** with an acceptance criterion that does not exceed (i.e., ≤) the identification threshold

  - Total impurities

B. Analytical Procedures

Specifications, standards, sampling plans, and testing procedures for drug products must be scientifically sound and appropriate to ensure they conform to appropriate standards.[24] Applicants and manufacturers must document: 1) a description of the analytical procedures used to test for degradation products as established in the drug product specification,[25] and 2) evidence that the analytical procedures have been validated and are suitable under actual conditions of use.[26]

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[21] Specified degradation products in drug products can be identified or unidentified. Refer to ICH Q3B(R2) for the threshold-based approach that could be used for the reporting, identification, and/or qualification of degradation products in drug products. The thresholds are determined according to the amount of drug substance administered per day, as toxicity is dependent on the dosage level.

[22] Degradation products could also arise during storage of drug substances. Degradation products should be characterized as described in ICH Q3A(R) and Q3B(R2).

[23] Specified impurities in drug substances can be identified or unidentified. Refer to ICH Q3A(R) for the threshold-based approach that could be used for the reporting, identification, and/or qualification of impurities in drug substances. The thresholds are determined according to the amount of drug substance administered per day, as toxicity is dependent on the dosage level.

[24] See 21 CFR 211.160(b).

[25] See 21 CFR 211.160(b)(1).

[26] See 21 CFR 211.165(e) and 211.194(a)(2).

Likewise, drug substance specifications should be scientifically sound and appropriate to ensure drug substances meet established standards of quality and purity.[27] Applicants and manufacturers should document: 1) a description of the analytical procedures used to test for impurities in drug substances, and 2) evidence that the analytical procedures have been validated and are suitable under actual conditions of use. Reference standards used in the analytical procedures for control of impurities and degradation products should be evaluated and characterized according to their intended uses.[28]

The validation of analytical procedures for evaluating impurities and degradation products should be carried out in accordance with the ICH guidance for industry *Q2(R2) Validation of Analytical Procedures* (March 2024). This entails assessing various parameters such as specificity, range, accuracy, precision, and robustness. Specifically, the reportable range assessment involves establishing linearity and validating lower range limits, including detection limit and quantitation limit. Furthermore, specificity assessment should involve demonstration of stability-indicating properties using samples collected from **stress testing**,[29] if appropriate.

C. Establishing Acceptance Criteria for Impurities and Degradation Products

The establishment of acceptance criteria for impurities and degradation products should be supported by data derived from clinical trials; nonclinical studies (e.g., in silico, in vitro, and animal studies); comparative analysis of degradation products in a drug product with its respective reference listed drug (RLD), when applicable; context of use;[30] prior knowledge;[31] publicly available information;[32] and precision of analytical procedures, as appropriate.

Certain impurities, such as nitrosamine impurities, which are probable or possible human carcinogens,[33] have been identified in many drug products and could be present in drug substances. Applicants and manufacturers of antibiotic drugs should conduct a risk assessment of

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[27] See ICH Q7.

[28] See ICH Q6A.

[29] See the ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

[30] Context of use includes, but is not limited to, dosage forms, dosing regimens, route and duration of drug administration, clinical indications, and the intended patient populations.

[31] Prior knowledge can be internal knowledge from a company's proprietary development and analytical experience, external knowledge such as reference to scientific and technical publications, or established scientific principles. See the ICH guidance for industry *Q14 Analytical Procedure Development* (March 2024).

[32] Publicly available information includes, but is not limited to, scientific literature, FDA approved package inserts, and FDA research and assessment.

[33] See the guidances for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024) and *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023).

drug substances and drug products for potential impurities that fall under the "cohort of concern" category.

The principles of ICH Q3A(R), ICH Q3B(R2), and ICH M7(R2) should be applied, as applicable, to antibiotics manufactured by fermentation and semi-synthesis. Antibiotic drugs that have United States Pharmacopeia (USP) monographs must meet the requirements outlined in the respective USP monographs for the drug substance and the drug product.[34] The following sections outline FDA's recommendations regarding the establishment of acceptance criteria for antibiotic impurities and degradation products.

1. New Drug Applications under 505(b)(1) and 505(b)(2) of the FD&C Act and Associated Type II Drug Substance Drug Master Files

The acceptance criteria for impurities and degradation products should be established based on the following:

- Acceptance criteria for specified impurities in drug substances or specified degradation products in drug products that do not exceed the qualification thresholds outlined in ICH Q3A(R) or ICH Q3B(R2) are considered appropriate without additional justification. This recommendation remains applicable only if there are no toxicological concerns. If a **structural alert** for mutagenicity or a signal for carcinogenicity has been identified, follow ICH M7(R2).[35]

- To support the use of the acceptance criteria for specified impurities in drug substances or specified degradation products in drug products at levels greater than the qualification thresholds in ICH Q3A(R) or ICH Q3B(R2), applicants should submit a justification for the safety of the impurity or degradation product at the proposed limit (e.g., a repeat-dose general toxicology study using the appropriate route of administration and doses, and of 14–90 days in duration, depending on the chronicity of the indication). Applicants should also submit a risk assessment for mutagenic potential as described in ICH M7(R2).

- For 505(b)(2) applications, applicants should use any of the following approaches:

  – The acceptance criteria for specified impurities in drug substances and specified degradation products in drug products in a relevant USP monograph or, if there is no

[34] See sections 501(b), 502(e)(3)(B) and (g), and 201(j) of the FD&C Act (21 U.S.C. 351(b), 352(e)(3)(B) and (g), respectively). To avoid being deemed adulterated under 501(b), a drug which bears the name which is recognized in the USP-NF must comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs from compendial standards.

[35] See also the ICH guidance for industry *M7(R2)* A*ssessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Questions and Answers* (July 2023).

USP monograph, a relevant alternative compendial monograph,[36] are considered appropriate if there are no toxicological concerns.[37]

– Acceptance criteria for specified impurities in drug substances and specified degradation products in drug products can be informed by a side-by-side comparative analysis between the proposed drug product and the listed drug, using the same validated analytical method that has been shown to be suitable for its intended purpose. The comparative analysis should be conducted on multiple batches of the proposed drug product and the listed drug.

- The acceptance criteria for total impurities in drug substances or total degradation products in drug products should not exceed the sum of the acceptance criteria for individual specified (identified and unidentified) and unspecified impurities in drug substances or degradation products in drug products.

Before application submission, applicants should contact the Agency (such as in a pre-NDA or an end-of-phase 2 meeting)[38] to discuss the nature and level of impurities and antibiotic-related analogs and receive specific recommendations.

2. Abbreviated New Drug Applications under 505(j) of the FD&C Act and Associated Type II Drug Substance Drug Master Files

The acceptance criteria for impurities and degradation products should be established based on the following:

- Applicants can use any of the following three approaches:

  – The acceptance criteria for specified impurities in drug substances and specified degradation products in drug products in a relevant USP monograph or, if there is no USP monograph, a relevant alternative compendial monograph,[39] are considered appropriate if there are no toxicological concerns.[40]

  – The acceptance criteria for specified impurities in drug substances and specified degradation products in drug products can be informed by a side-by-side comparative analysis between the proposed drug product and the RLD using the same validated analytical procedure that has been shown to be suitable for its intended purpose. The

[36] See MAPP 5310.7 Rev. 1 *Acceptability of Standards from Alternative Compendia*.

[37] See ICH M7(R2).

[38] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[39] See MAPP 5310.7 Rev. 1.

[40] See ICH M7(R2).

comparative analysis should be conducted on multiple batches of the proposed drug product and the RLD.[41]

– If the acceptance criteria for specified impurities in drug substances or specified degradation products in drug products do not exceed the qualification thresholds in ICH Q3A(R) or ICH Q3B(R2), no additional justification is needed. This recommendation remains applicable only if there are no toxicological concerns.[42] Proposals for higher acceptance criteria using a risk-based approach can be provided and will be evaluated based on the totality of evidence.

- To support proposed acceptance criteria for new impurities in drug substances or for new degradation products in drug products that exceed the qualification thresholds in ICH Q3A(R) or ICH Q3B(R2), or impurity levels higher than those of the RLD, applicants should submit a justification for the safety of the impurity at the proposed limit (e.g., a repeat-dose general toxicology study using the appropriate route of administration and doses, and of 14–90 days in duration, depending on the chronicity of the indication). If a structural alert for mutagenicity or a signal for carcinogenicity is identified for a new impurity or degradation product not identified in the RLD, follow the recommendations in ICH M7(R2). Applicants should also submit a risk assessment for mutagenic potential as described in ICH M7(R2).

- The acceptance criteria for total impurities in drug substances or total degradation products in drug products should not exceed the sum of the acceptance criteria for individual specified (identified and unidentified) and unspecified impurities in drug substances or degradation products in drug products.

ANDA applicants can submit a controlled correspondence[43] to receive specific recommendations regarding impurities and antibiotic-related analogs.

3. Over-the-Counter Monograph Drugs under 505G of the FD&C Act

The acceptance criteria for impurities and degradation products should be established based on the following:

- The acceptance criteria for specified impurities in drug substances and specified degradation products in drug products in a relevant USP monograph or if a USP monograph is not available, a relevant alternative compendial monograph[44] are generally

[41] See the guidances for industry *ANDAs: Impurities in Drug Substances* (July 2009) and *ANDAs: Impurities in Drug Products* (November 2010).

[42] See ICH M7(R2).

[43] See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024).

[44] See MAPP 5310.7 Rev. 1.

considered appropriate. If a USP monograph or an alternative compendial monograph does not list acceptance criteria for specified impurities in drug substances or specified degradation products in drug products, the acceptance criteria for the specified impurities in drug substances and the specified degradation products in drug products should follow the principles of USP<476> *Control of Organic Impurities in Drug Substances and Drug Products*, USP<466> *Ordinary Impurities*, and USP<1086> *Impurities in Drug Substances and Drug Products*, as applicable. These recommendations remain applicable only if there are no toxicological concerns.[45] If there are toxicological concerns, the proposed acceptance criteria for the specified impurities in drug substances and the specified degradation products in drug products should not exceed the threshold of toxicological concern. If any potential risks are identified regarding the proposed acceptance criteria for specified impurities in drug substances or for specified degradation products in drug products, the manufacturer should conduct and document a justification for the safety of the impurity at the proposed limit (e.g., a repeat-dose general toxicology study using the appropriate route of administration and doses, and of 14–90 days in duration, depending on the chronicity of the indication). Manufacturers should also conduct and document a risk assessment for mutagenic potential as described in ICH M7(R2).

- The acceptance criteria for total impurities in drug substances or total degradation products in drug products should not exceed the sum of the acceptance criteria for individual specified (identified and unidentified) and unspecified impurities in drug substances or degradation products in drug products.[46]

[45] See ICH M7(R2).

[46] Records related to the establishment of specifications must be maintained (e.g., 21 CFR 211.160(a) and 211.180(c)) and may be reviewed during an inspection or requested by FDA pursuant to section 704(a)(4) of the FD&C Act.

GLOSSARY

For purposes of this guidance,[1] key terms are defined as follows:

Antibiotic-Related Analog: A molecular variant of the active ingredient formed during the manufacture of antibiotics. This variant has biological activity and does not have deleterious effects on the safety and efficacy of the drug product. These variants possess properties comparable to the active ingredient with respect to biological activity.

Degradation Product: An impurity resulting from a chemical change of the drug substance brought about during manufacture and/or storage of the drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system. (ICH Q3B(R2))

Identified Degradation Product: A degradation product for which a structural characterization has been achieved. (ICH Q3B(R2))

Identified Impurity: An impurity for which a structural characterization has been achieved. (ICH Q3A(R), ICH Q6A)

Impurity: Any compound of the drug substance that is not the chemical entity defined as the drug substance or an excipient in the drug product. (ICH Q3A(R), ICH Q3B(R2), ICH Q6A) An impurity does not have comparable biological activity to the active ingredient, nor is it an antibiotic-related analog.

Semi-Synthesis: A process that introduces structural constituents to substances through a combination of chemical synthesis and elements of biological origin, such as those obtained from fermentation or extracted from botanical material.

Specified Degradation Product: A degradation product that is individually listed and limited with a specific acceptance criterion in the drug product specification. A specified degradation product can be either identified or unidentified. (ICH Q3B(R2))

Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the drug substance specification. A specified impurity can be either identified or unidentified. (ICH Q3A(R))

Stress Testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products). (ICH Q1A(R2))

Stress Testing (drug substance): Studies undertaken to elucidate the intrinsic stability of the

[1] The definitions provided here are intended solely for purposes of this guidance. The same terms may have different meanings in other contexts.

drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing. (ICH Q1A(R2))

Structural Alert: A chemical grouping or molecular (sub)structure that is associated with mutagenicity and has been identified following ICH M7(R2) and according to principles in the ICH M7(R2) Q&As.

Unidentified Degradation Product: A degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time). (ICH Q3B(R2))

Unidentified Impurity: An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time). (ICH Q3A(R))

Unspecified Degradation Product: A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the drug product specification. (ICH Q3B(R2))

Unspecified Impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the drug substance specification. (ICH Q3A(R))