



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2025-D-6130]

Establishing Impurity Specifications for Antibiotics; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a draft guidance for industry entitled “Establishing Impurity Specifications for Antibiotics.” The draft guidance provides recommendations regarding the establishment of specifications for organic impurities in antibiotics manufactured by fermentation and semi-synthesis. This draft guidance applies to antibiotic drugs subject to approval under new drug applications (NDAs) and abbreviated new drug applications (ANDAs) and associated type II drug substance drug master files (DMFs) referenced in antibiotic NDAs and ANDAs. This guidance also applies to nonprescription antibiotic drugs, often referred to as over-the-counter (OTC) monograph drugs. By providing these recommendations, FDA intends to clarify effective control strategies, support the development of high-quality antibiotic products, and promote consistency in quality standards.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions".

Instructions: All submissions received must include the Docket No. FDA-2025-D-6130 for "Establishing Impurity Specifications for Antibiotics." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillendale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the

SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Ashley Boam, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4192, Silver Spring, MD 20993-0002, 240-402-6341.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Establishing Impurity Specifications for Antibiotics.” This draft guidance provides recommendations for establishing specifications for organic impurities in antibiotics manufactured by fermentation and semi-synthesis. These recommendations can be used to establish consistent standards for impurity testing and ensure that batches of antibiotic drug products meet appropriate impurity specifications.

This draft guidance applies to antibiotic drugs subject to approval under NDAs and ANDAs submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355), associated type II drug substance DMFs referenced in antibiotic NDAs and ANDAs, and nonprescription antibiotic drugs marketed pursuant to section 505G of the FD&C Act (21 U.S.C. 355h) (often referred to as OTC monograph drugs). INDs submitted under 21 CFR part 312 should follow the general principles outlined in the draft guidance.

The recommendations in the draft guidance are not intended to be applied retroactively (i.e., to antibiotic drugs submitted in applications or their supplements, or 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 draft 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 ICH guidances for industry *Q3A(R) Impurities in New Drug Substances* (June 2008) and *Q3B(R2) Impurities in New Drug Products* (August 2006) provide recommendations on thresholds for the identification, reporting, and qualification of impurities and degradation products in new drug substances and drug products using drug substances that are produced by chemical synthesis. However, current guidances do not provide recommendations for the control of impurities and degradation products in fermentation and semi-synthetic products, including certain antibiotics manufactured from these processes. Antibiotics manufactured by fermentation or semi-synthesis are typically more complex than those produced solely by chemical synthesis, often containing a mixture of 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. To address this gap, the draft guidance provides recommendations on the identification, qualification, and control of impurities and degradation products in fermentation-based and semi-synthetic antibiotics. The principles described in ICH Q3A(R), ICH Q3B(R2), and ICH M7(R2) should apply 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 (section 501(b) of the FD&C Act).

The draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Establishing Impurity Specifications for Antibiotics." 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.

As we develop final guidance on this topic, FDA will consider comments on costs or cost savings the guidance may generate, relevant for Executive Order 14192.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in 21 CFR parts 210 and 211 pertaining to CGMP requirements have been approved under OMB control number 0910-0139. The collections of information in 21 CFR parts 312 and 314 have been approved under OMB control numbers 0910-0014 and 0910-0001, respectively. The collections of information pertaining to 21 CFR part 201 Subpart C pertaining to over-the-counter drug product labeling have been approved under OMB control number 0910-0340.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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