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Deputy Commissioner for Policy, Legislation, and International Affairs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–D–0108]

Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled ''Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.'' This guidance is intended to assist abbreviated new drug application (ANDA) applicants that reference a drug product intended for parenteral, ophthalmic, or otic use in seeking approval of a drug that is qualitatively (Q1) different or quantitatively (Q2) different from the reference listed drug (RLD) with respect to the pH adjuster(s). This guidance describes how FDA intends to evaluate a request for a waiver of Agency requirements for a Q1 or Q2 difference in pH adjuster, including recommendations on the type of information to provide in support of such a waiver request. This guidance finalizes the draft guidance of the same title issued on April 14, 2022.

DATES: The announcement of the guidance is published in the **Federal Register** on November 17, 2025.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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–2022–D–0108 for ''Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.'' 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.govinfo.gov/content/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 guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale 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 guidance document.

FOR FURTHER INFORMATION CONTACT: Susan Levine, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 1674, Silver Spring, MD 20993–0002, 240–402–7936, *susan.levine@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.'' The Federal Food, Drug, and Cosmetic Act (FD&C Act) does not require an ANDA to have the same inactive ingredients as the RLD.[1] Section 505(j)(4)(H) of the FD&C Act does, however, state that an ANDA shall not be approved if information submitted in the application (or other information available) shows (1) the inactive ingredients of the drug are

[1] See section 505(j)(2)(A) of the FD&C Act (setting forth the required contents of an ANDA).

unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (2) the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included is unsafe under such conditions.[2]

The regulations at 21 CFR 314.94(a)(9)(iii) and (iv), with parallel provisions in the approval regulations at § 314.127(a)(8)(ii)(B) and (C), specify that FDA will consider an inactive ingredient in, or the composition of, a generic drug product intended for parenteral, ophthalmic, or otic use to be unsafe and will refuse to approve the ANDA unless the generic drug product contains the same inactive ingredients (with certain listed exceptions) in the same concentration as the RLD. Specifically, the inactive ingredient requirements in § 314.94(a)(9)(iii) and (iv) apply to pH adjusters, which are not expressly identified as one of the listed exceptions. Under § 314.99(b), however, an applicant may ask FDA to waive any requirement that applies to the applicant under §§ 314.92 through 314.99. Thus, an ANDA applicant for a drug product intended for parenteral, ophthalmic, or otic use who seeks to use a pH adjuster(s) that is Q1 or Q2 different from the RLD may ask the Agency to waive the inactive ingredient requirements at § 314.94(a)(9)(iii) or (iv) for the pH adjuster(s). This guidance document provides recommendations on (1) the type of information that applicants should consider submitting with a § 314.99(b) waiver request when an ANDA applicant asks the Agency to waive the inactive ingredient requirements for pH adjusters and (2) the format and process for submitting such waiver requests.

This guidance finalizes the draft guidance entitled ''Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use'' issued on April 14, 2022 (87 FR 22217). FDA considered comments received on the draft guidance as the guidance was finalized. Changes from the draft to the final guidance include recommendations for ANDA applicants to seek FDA feedback on a proposed approach for justifying a § 314.99(b) waiver request for a difference in pH adjuster, as well as in instances where the applicant also seeks to utilize a certain bioequivalence approach with a formulation that contains a Q1 or Q2 difference in pH adjuster.

In addition, this guidance includes information clarifying FDA's obligations to maintain the confidentiality of trade secret and confidential commercial information when responding to questions regarding drug product formulations, and to distinguish the regulatory provisions for requesting waiver of a Q1 or Q2 difference in a pH adjuster from the provisions that support a request to waive submission of evidence of in vivo bioequivalence.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on ''Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.'' 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.

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 part 314 relating to the submission of ANDAs, including requests for waiver for a pH adjuster difference under § 314.99(b) and waivers under § 314.90, have been approved under OMB control number 0910–0001. The collections of information in 21 CFR part 320 relating to the requirements for demonstrating bioavailability and bioequivalence, including waiver of evidence of in vivo bioavailability or bioequivalence under § 320.22(b), have been approved under OMB control numbers 0910–0014 and 0910–0291. The collections of information relating to the submission of controlled correspondence related to generic drug development and FDA approval have been approved under OMB control number 0910–0727.

III. Electronic Access

Persons with access to the internet may obtain the guidance at *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.*

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[2] Section 505(j)(4)(H) of the FD&C Act.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2025–D–4051]

Quality Management System Information for Certain Premarket Submission Reviews; Draft Guidance for Industry and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of the draft guidance entitled ''Quality Management System Information for Certain Premarket Submission Reviews.'' The medical device current good manufacturing practice (CGMP) requirements, previously in the quality system regulation (QS regulation) and now the quality management system regulation (QMSR), have been amended effective February 2, 2026, to align more closely with the international consensus standard for devices by incorporating by reference an international standard specific for device quality management systems. This draft guidance document is intended to assist FDA staff and medical device manufacturers in understanding FDA expectations about preparing and maintaining a Quality Management System (QMS) and providing the information required to be included in certain marketing submissions regarding a QMS, in line with the QMSR. This draft guidance is not final nor is it for implementation at this time.

DATES: Submit either electronic or written comments on the draft guidance by January 16, 2026 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