4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-D-1530]

Control of Nitrosamine Impurities in Human Drugs; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing the availability of a final guidance for industry, entitled "Control of Nitrosamine Impurities in Human Drugs." This guidance recommends steps manufacturers of active pharmaceutical ingredients and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also describes conditions that may introduce nitrosamine impurities. The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers, ranitidine, nizatidine, and metformin, has made clear the need for a risk assessment strategy to identify and minimize nitrosamines in any pharmaceutical product at risk for their presence.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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-2020-D-1530 for "Control of Nitrosamine Impurities in Human Drugs." 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 the guidance to the Office of Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor, Silver Spring, MD 20993-0002. Send two self-addressed adhesive labels to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Dongmei Lu, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 6649, Silver Spring, MD, 20993, 240-402-7966.

SUPPLEMENTARY INFORMATION:

I. Background

We are announcing the availability of a guidance for industry entitled "Control of Nitrosamine Impurities in Human Drugs." We are issuing this guidance consistent with our good guidance practices (GGP) regulation (§ 10.115 (21 CFR 10.115)). We are implementing this guidance without prior public comment because we have determined that prior public participation is not feasible or appropriate (§ 10.115(g)(2)). We made this determination because of the importance of providing timely information to manufacturers regarding risk assessments, testing, and other appropriate actions they should take to reduce and mitigate nitrosamine impurities in active pharmaceutical ingredients (APIs) and drug products. Although this

guidance document is immediately in effect, it remains subject to comment in accordance with FDA's GGP regulation (§ 10.115(g)(3)(D)).

Nitrosamines have been classified as probably carcinogenic to humans by the World Health Organization. This guidance recommends steps manufacturers of APIs and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also describes conditions that may introduce nitrosamine impurities.

The recent discovery of nitrosamine impurities in some types of drug products, including angiotensin II receptor blockers, ranitidine, nizatidine, and metformin, led FDA and other international regulators to conduct a detailed analysis of these impurities in affected APIs and drug products. Recently, preliminary results from FDA stability testing raised concerns that *N*-Nitrosodimethylamine (NDMA) levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels. Results from other tests FDA conducted suggest that the NDMA levels increase with storage time. On April 1, 2020, FDA requested that all ranitidine products be withdrawn from the U.S. market.

Based on the testing results and the Agency's current understanding of the chemistry, FDA has developed this guidance to provide API and drug product manufacturers information on the potential root causes of nitrosamine formation. It recommends ways API and drug product manufacturers can conduct risk assessments of their products, whether approved, marketed, or with pending applications. The guidance also suggests actions they should take to reduce or prevent the presence of nitrosamines in APIs and drug products.

API and drug product manufacturers should assess the risk of nitrosamine contamination or formation in their drugs. These risk assessments should be conducted in a timely manner.

Manufacturers do not need to submit risk assessment documents to the Agency, but they should retain them so that they are available if requested. FDA may request an expedited risk assessment, confirmatory testing, or other regulatory action based on information available to the Agency.

For products at the pre-submission stage, FDA recommends that applicants conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed prior to submission of an original application. However, the risk assessment and submission of any confirmatory testing or changes to the drug master file or application may be submitted in an amendment if they are not available at the time of the original submission filing. For applications that are pending with the Agency, applicants should conduct the risk assessment expeditiously and inform FDA if confirmatory testing finds nitrosamine levels above the recommended acceptable daily intake (ADI) limit. If a nitrosamine impurity is detected above the limit of quantitation but is within the ADI limit, the applicant should amend the application as appropriate. The Agency will work with the applicant to resolve issues during the review cycle or immediately after approval, and before distribution, if determined to be necessary by the Agency.

This guidance is being issued consistent with FDA's good guidance practices regulation (§ 10.115). The guidance represents the current thinking of FDA on the "Control of Nitrosamine Impurities in Human Drugs." 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

This guidance refers to previously approved FDA collections of information. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR parts 210 and 211 have been approved under OMB control number 0910-0139; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338; the collections of information for the permanent discontinuation or interruption in manufacturing of certain drug and biological products have been approved under OMB control number 0910-0759; the collections of information pertaining to the guidance for industry entitled "Controlled Correspondence Related to Generic Drug Development" have been approved under OMB control number 0910-0797.

III. Electronic Access

Persons with access to the internet may obtain the document at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm or https://www.regulations.gov. Use the FDA website listed in the previous sentence to find the most current version of the guidance.

Dated: August 28, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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