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1000 Atlantic Ave., Ste. 110
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April 1, 2020

Re: Docket No. FDA-2020-P-0042

Dear Dr. Najafi:

This letter responds to your citizen petition (Petition) submitted on behalf of Emery Pharma (Emery) received on January 2, 2020. According to the Petition, Emery's preliminary study indicates that the ranitidine[1] molecule may not be heat stable, and under elevated temperatures, it generates significant amounts of N-nitrosodimethylamine (NDMA), a probable human carcinogen (Petition at 1).[2] Based on this preliminary study, Emery requests that the Food and Drug Administration (FDA or the Agency) take the following actions:

1) Request a recall and suspend sale of all lots of all products containing ranitidine;

2) Conduct examinations and investigations under [s]ection 702(a) of the [FD&C Act (21 U.S.C. 372(a))] regarding ranitidine products, specifically stability assessment and manufacturer submissions made for FDA approval under [section] 704(a) of the [FD&C Act (21 U.S.C. 374(a))];

3) Provide information to the public regarding the high temperature instability of ranitidine products under [s]ection 705(b) of the [FD&C Act (21 U.S.C. 375(b))];

4) In addition to the instructions for disposal and/or return [of ranitidine] in the recall notices, issue additional guidance to the public for the safe disposal of ranitidine, given the recognized potential that the drug may degrade to form the probable

[1] Ranitidine hydrochloride is available in many dosage forms, including tablets, capsules, injections, and syrups, and it is available under the brand name Zantac and under the name of the active ingredient, ranitidine hydrochloride. We limit this response to ranitidine, although the substance of this may also apply to other drug products such as nizatidine, which is mentioned in passing in the Petition.

[2] We have reviewed the information on the Petitioner's preliminary study and will look for its final publication after peer review. See Petition at 6; see also sections II and III of this response, where we discuss recent Agency action regarding ranitidine and the basis for these actions.

carcinogen NDMA in municipal wastewater treatment plants and impact the public drinking water supply as was cited in the September 9 citizen petition;[3]

5) Issue a directive to the manufacturers of ranitidine products to conduct a thorough stability assessment of [ranitidine in the] formation of NDMA, both in drug substance and drug product forms;

6) Issue a directive to the manufacturers and distributors to ship ranitidine products in temperature-controlled vehicles;

7) Issue a directive to manufacturers to clearly label ranitidine products with a warning, such as: "by-products that are probable carcinogens can be generated if exposed to heat;" and

8) In the interest of public safety, require that ranitidine-containing products be moved behind the counter and dispensed by "prescription only" and ideally tested for NDMA or otherwise assessed for heat exposure (as with a temperature-indicator label) at the dispensing pharmacy and not just at the manufacturing site.[4]

We have carefully considered your Petition and other information available to the Agency. For the reasons stated below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Ranitidine

Ranitidine, is an acid reducer that is available as prescription and over-the-counter (OTC) drug products. It is an H2 (histamine-2) blocker, which decreases the amount of acid created by the stomach. OTC ranitidine products are approved to prevent and relieve heartburn associated with acid indigestion and sour stomach. Prescription ranitidine products are approved for multiple indications, including treatment and prevention of ulcers of the stomach and intestines and treatment of gastroesophageal reflux disease. The first ranitidine product, which had the brand name Zantac, was approved in 1985 and has been marketed in the United States since that time.

B. N-Nitrosodimethylamine

[3] The Valisure citizen petition, FDA-2019-P-4281 (Valisure Petition), is dated September 9, 2019, and was received by FDA on September 13, 2019. It requested that FDA recall ranitidine drug products because of NDMA impurities, among other things.

[4] Petition at 3-4.

NDMA is a semivolatile organic chemical that forms in both industrial and natural processes.[5] Currently, it is not produced or commercially used in the United States but may be inadvertently produced in and released from industrial sources through chemical reactions, such as those that involve alkylamines with nitrogen oxides, nitrous acid, or nitrate salts.[6] It can also be unintentionally formed in air, water, and soil from reactions to alkylamines, which are found widely distributed throughout the environment.[7]

NDMA exposure may occur through ingesting foods that contain nitrosamines[8] such as smoked or cured meats and fish; ingesting food that contains alkylamines, which can cause NDMA to form in the stomach; drinking contaminated water; drinking malt beverages (such as beer and whiskey) that may contain low levels of nitrosamines formed during processing; using toilet and cosmetic products such as shampoos and cleansers that contain NDMA; and breathing or inhaling cigarette smoke.[9] The oral route, in consumption of contaminated food and water, is the primary human exposure pathway for NDMA.[10]

NDMA has been classified as a probable carcinogen by the International Agency for Research on Cancer (IARC).[11] Based on its review, IARC concluded that there was sufficient evidence of a carcinogenic effect of NDMA in many experimental animals, and that despite the lack of epidemiological data, NDMA should be regarded for practical purposes as if it were carcinogenic

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[5] EPA Technical Fact Sheet NDMA (November 2017) (EPA Fact Sheet), https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf.

[6] Id.

[7] Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for N-Nitrosodimethylamine (Dec. 1989) at 1.

[8] In general, the term *nitrosamine* is used to describe the chemical class of organic compounds that have a certain chemical structure and are expected to react in predictable and similar ways when other chemical compounds come in contact with them. Nitrosamines, as opposed to the individual NDMA impurity, became important in FDA's evaluation of angiotensin II receptor blockers (ARBs), because more than one impurity was discovered in some of those medications. This has not been the case with ranitidine. See footnotes 36 and 38 for additional information on ARBs.

[9] EPA Fact Sheet at 3.

[10] Id., citing ATSDR Toxicological Profile.

[11] See original IARC review, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemical to Man, vol 1 (1972) NDMA at 95; IARC Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs vols 1-42; Supp 7, NDMA (1987) at 67; and see generally IARC Monographs on the Identification of Carcinogenic Hazards to Humans, Amended Preamble, January 2019.

to humans.[12] The 1987 IARC update for carcinogenic classification identifies NDMA as "Group 2A: Probably carcinogenic to humans."[13]

C. Legal Framework for Recalls, Market Withdrawals, Investigations, and Disclosure of Information to the Public

Drug applicants must ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of a drug are adequate to assure and preserve its identity, strength, quality, and purity.[14] FDA continues to review the quality of drug products throughout their life cycles, and may take regulatory action to facilitate the voluntary recall of a drug product when the Agency determines that a product in the market violates provisions of the FD&C Act or presents a danger to health.[15] The introduction or delivery for interstate of any

[12] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, *Some N-Nitro Compounds*, vol. 17 (1978) at 152.

[13] IARC Monographs, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Vols. 1 to 42 (1987) at 42. This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of *limited evidence* of carcinogenicity in humans or of *sufficient evidence* of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data. Id. at 31.

[14] See section 505(e) of the FD&C Act (21 U.S.C. 355(e)); section 505(j)(4)(A) of the FD&C Act, 21 U.S.C. 355(j)(4)(A).

[15] See 21 CFR 7.40(a) see also FDA draft guidance for industry and FDA staff *Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C* (April 2019) at 9.FDA is committed to working cooperatively with a recalling firm whenever possible to facilitate the orderly and prompt removal of, or correction to, a violative product in the marketplace, particularly when the product presents a danger to health. When final, this guidance will represent FDA's current thinking on this topic. 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.

drug that is adulterated[16] or misbranded[17] is a violation of section 301(a) of the FD&C Act (21 U.S.C. 331(a)).

A recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers.[18] It is an effective method of removing or correcting defective FDA-regulated products that have been distributed commercially, particularly when those products present a danger to health.[19] It is generally a voluntary action by manufacturers and distributors to protect the public health from products that present a risk of injury.[20] A recall may be undertaken voluntarily at any time by manufacturers and distributors, or initiated at the request of FDA when there is an urgent situation.[21] FDA generally directs a recall request to the firm that has primary responsibility for the manufacture and marketing of the product.[22] A recall is generally more appropriate and affords better protection for consumers than seizure, which

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[16] Section 501(a)(2)(B) of the FD&C Act establishes that a drug is deemed to be adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" (21 U.S.C. 351(a)(2)(B)). Under section 501 of the FD&C Act, current good manufacturing practice (CGMP) includes the implementation of oversight and controls over the manufacture of drugs to ensure quality (including managing the risk and establishing the safety of raw materials) materials used in the manufacturing of drugs and finished drug products (21 U.S.C. 351). The Agency has issued regulations at 21 CFR parts 210 and 211 concerning CGMP requirements for drugs. A drug that does not satisfy the requirements of the FD&C Act or the Agency's CGMP regulations is deemed to be adulterated. Section 501(a)(2(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(b).

[17] Under section 502(j) of the FD&C Act, a drug will be deemed to be misbranded "if it is dangerous to health when used in the dosage or manner[,] or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof" (21 U.S.C. 352(j)). Under section 201(n) and 502(a)(1) of the FD&C Act, a drug may be deemed to be misbranded if the labeling fails to reveal a material fact that the drug contains, or could contain, if stored under normal storage conditions, a dangerous ingredient. (21 U.S.C. 321(n) and 21 U.S.C. 352(a)(1)).

[18] 21 CFR 7.3(g).

[19] 21 CFR 7.40(a); Preamble to Final Rule, 43 FR 26202 (June 16, 1978).

[20] Id; see also the FDA draft guidance for industry and FDA staff *Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C* (April 2019) and the FDA guidance *Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C* (February 2019). With limited exceptions not applicable here, FDA does not have authority under the FD&C Act to order a firm to recall a violative drug product.

[21] 21 CFR 7.40(b), 7.45, and 7.46; see also FDA draft guidance *on Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C* (April 2019). Section 7.45(a) specifically addresses FDA-initiated recalls, and states that the Agency may request a firm to initiate a recall when the following determinations have been made: (1) that a product that has been distributed presents a risk of illness or injury or gross consumer deception, (2) that the firm has not initiated a recall of the product, and (3) that an Agency action is necessary to protect the public health and welfare.

[22] 21 CFR 7.40(b).

requires legal action and a court order, particularly when many lots of product have been widely distributed.[23] As described in guidance, firms in a product distribution chain should be "recall ready" to help minimize public exposure to products in violation of the FD&C Act and other laws administered by FDA.[24] The Agency will work with manufacturers and distributors to develop a recall strategy and to publicize information to the public. FDA will monitor the effectiveness of any recall and take additional action as appropriate.

FDA's regulations also provide a procedure for product removal, which is called *market withdrawal*, when a firm's removal or correction of a distributed product may not be immediately subject to legal action by FDA.[25, 26] Similar to a recall, FDA will request that a firm implement a request for a market withdrawal of a specific drug product. When completed, a market withdrawal will effectively remove all of an identified product from the market. Additionally, the Agency has procedures in place under which it can monitor and oversee the effectiveness of the actions taken by manufacturers and applicants to complete the market withdrawal.[27]

Under section 704(a)(4)(A) of the FD&C Act, FDA may conduct factory inspections to obtain records from an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a drug in advance or in lieu of an inspection.[28] Section 704(a)(1) of the FD&C Act broadly defines factory, warehouse, or establishment inspections to include such facilities where prescription drugs or nonprescription drugs are manufactured, processed, packed, or held, and such inspections will include records, files, papers, processes, controls, and

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[23] 21 CFR 7.40(c).

[24] See FDA draft guidance on Initiation of Voluntary Recalls at 3 (identify and train appropriate personnel, establish a recall communications plan, identify reporting requirements, use adequate product coding, and maintain distribution records). The regulations are intended to guide industry on how it should prepare for a recall and suggest that records should be retained for a period of time that exceeds the shelf life and expected use of the product and is at least the time specified in the regulations concerning records retention (21 CFR 7.59(c)). FDA's guidance provides further information to industry recommending that distribution records should include enough detail to identify the consignees that actually received the recalled product and should conform to any applicable requirements. FDA guidance also recommends that direct accounts that further distribute the product should also maintain records of their consignees that actually received the product, to ensure the recalling firm's instructions are extended to all consignees in the distribution chain (FDA draft guidance on *Initiation of Voluntary Recalls* at 5).

[25] 21 CFR 7.3(j).

[26] A market withdrawal as defined in 21 CFR 7.3(j) differs from the procedure for withdrawal of an application as described in our regulations in 21 CFR 314.150. As used in this response, the term *withdrawal* is meant to refer to market withdrawal under 21 CFR 7.3(j) and not application withdrawal under 21 CFR 314.150.

[27] See FDA Regulatory Procedures Manual, Chapter 7: Recall Procedures (version 06) at 6, 9 (Similar to a recall, a product withdrawal recommendation can be entered into FDA's data system to allow the Agency to document and monitor the market withdrawal).

[28] 21 U.S.C. 374(a)(4)(A).

facilities.[29] Furthermore, FDA may request and evaluate information from applicants and manufacturers to ensure that an approved drug product continues to be safe and effective and to ensure that drug products meet applicable standards under CGMP[30] and are not adulterated.[31]

An important priority for FDA is to disclose information to the public about drugs that may harm the public health. The recall regulations specifically address the need for FDA to issue public warnings when there is a company-initiated or FDA-recommended recall of a product under 21 CFR part 7, subpart C.[32] 21 CFR 7.42(b)(2). The purpose of a public warning under this section is to alert the public that a product being recalled presents a serious health risk. FDA may issue public warnings in a variety of forms, including but not limited to press releases, emails, and web and social media postings.[33] Id. It is important that a public warning be distributed in a way that ensures that the information conveyed in the warning actually reaches the public. Although regulations and guidance on communications typically refer to recalls, it is FDA's policy to provide similar, appropriate public warning and communications regarding the market withdrawal of a product.[34]

II. SUMMARY OF FDA ACTIONS REGARDING RANITIDINE DRUG PRODUCTS

FDA issued its first public statement on ranitidine on September 13, 2019, when the Agency alerted patients and health care professionals that it had learned that some ranitidine drug products had NDMA impurities at low levels.[35] The Agency stated that it would investigate this

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[29] 21 U.S.C. 374(a)(1).

[30] 21 CFR parts 210 and 211; see e.g., 21 CFR 210.1(b) (the failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug will render such drug to be adulterated under section 501(a)(2)(B) of the FD&C Act); 21 CFR 211.80(b) (requiring manufacturers to handle and store active ingredients and other drug product components, among other things, in a manner to prevent contamination); 211.160(b) (requiring manufacturers to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that active ingredients and other drug product components, among other things, conform to appropriate standards of identity, strength, quality, and purity); 211.166 (requiring a written testing program to assess the stability characteristics of drug products, which will be used in determining appropriate storage conditions and expiration dates).

[31] See footnote 16.

[32] See FDA guidance for industry *Public Warning and Notification of Recalls Under 21CFR Part 7, Subpart C* (February 2019).

[33] Id. at 5 and 10.

[34] See footnote 27; FDA's web page FDA 101:Product Recalls, available at https://www.fda.gov/consumers/consumer-updates/fda-101-product-recalls; and FDA guidance on Product Recalls, Including Removals and Corrections (November 2003) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-recalls-including-removals-and-corrections.

[35] FDA created a website to inform the public of its investigation and recommendations, see FDA Updates and Press Announcements on NDMA in Zantac (ranitidine), available at https://www.fda.gov/drugs/drug-safety-and-

concern and would keep the public informed. Shortly thereafter, FDA announced that a manufacturer was voluntarily recalling certain lots of prescription ranitidine because NDMA was found to be above limits established by FDA. At that time, FDA scientists also published an appropriate testing protocol that could be used to detect NDMA impurities in ranitidine.[36] Subsequently, on September 26, 2019, FDA alerted patients and health care professionals on its web page that certain retailers would be voluntarily recalling OTC ranitidine products sold under their labels and produced by a certain manufacturer because the medicines may contain low levels of NDMA.[37]

Both FDA and industry reacted quickly to sampling data that indicated NDMA impurities might be present in ranitidine because of information and data collection from the ongoing investigation of nitrosamine impurities in angiotensin II receptor blockers (ARBs).[38] However, it was important to obtain NDMA impurity information on ranitidine to see how frequently it appeared and at what levels, and to research and determine the potential root causes of the impurity in these drug products. In October 2019, FDA sent information request letters to all ranitidine active drug master file (DMF)[39] and application holders asking them to assess their processes for nitrosamine formation risk and to test recent batches of drug substance and drug product for NDMA. If NDMA was found, the firms were asked to provide FDA a summary of

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availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine (Ranitidine webpage). FDA's laboratory began testing a small number of ranitidine products for the presence of NDMA. The preliminary results found all of the samples were positive for NDMA at low levels. Based on these results, the Agency began a thorough investigation of the levels of NDMA in ranitidine.

[36] The test method identified and posted on FDA's Ranitidine web page is appropriate for testing nitrosamines, the class of chemical compounds to which NDMA belongs. FDA decided to publish this appropriate test method, and subsequently published an alternative test method because it found that some types of test methods themselves created the impurity that was being tested. Specifically, the test method FDA had previously posted for testing angiotensin II receptor blockers (ARBs) for nitrosamines was not appropriate for use in testing NDMA in ranitidine. See FDA 10/2/2019 update; FDA 10/23/2019 update includes second test method.

[37] See Ranitidine web page identified in footnote 35. FDA conducted a health hazard evaluation (HHE) as required under section 7.41 of the recall regulations (21 CFR 7.41). Based on the HHE, FDA determined that the recall would be assigned to a classification of II, which is defined as "a product that might cause a temporary health problem, or pose a slight threat of a serious nature." See FDA's web page FDA 101:Product Recalls discussing recall classifications, available at https://www.fda.gov/consumers/consumer-updates/fda-101-product-recalls.

[38] See FDA's web page FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB), (Valsartan, Losartan, and Irbesartan), available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan..

[39] A DMF contains information that FDA may use to permit the holder to incorporate the information by reference when the holder submits an application, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person (21 CFR 314.420(a)). A DMF may include information about the drug substance, drug substance intermediate, and materials used in their preparation, or drug product; packaging materials; excipient, colorant, flavor, essence, or materials used in their preparation (21 CFR 314.420(a)(2), (3) and (4)).

their root cause analysis. FDA also asked specific companies to send samples of ranitidine drug product and drug substance to FDA to be tested by our scientists.

During October 2019, some application holders initiated additional voluntary recalls that were included on FDA's ranitidine web page. By the end of the month, FDA concluded it had sufficient information to recommend to manufacturers that they voluntarily recall ranitidine if either their testing, or FDA's testing of their products, indicated that the NDMA level was above an acceptable daily intake (ADI) concentration of 0.32 parts per million (ppm) or 96 nanograms (ng)/day.[40] FDA sent additional information requests to inform application holders and DMF holders that a limit had been set for this impurity and to ask for additional information.

A summary of this information was published on the FDA Ranitidine web page on November 1, 2019. It informed the public that FDA was asking companies to continue to test their products, and the Agency was continuing to work with manufacturers to understand the root cause of the low levels of NDMA in these drug products. The Agency published a second document that contained a summary of the results FDA had obtained on NDMA testing in ranitidine products.[41] Since September 2019, overall, the Office of Testing and Research in FDA's Office of Pharmaceutical Quality has tested approximately 180 ranitidine samples, including prescription and OTC products.[42] Samples were purchased from the marketplace, collected by FDA inspectors, or received in response to information requests. The dosage forms tested included tablets (75-150 milligrams (mg)), injectables (50 mg dose), and liquid syrups (75 mg dose).

Test results from industry and from samples obtained and tested by FDA showed that NDMA was consistently detected in ranitidine, and in many instances, NDMA was detected above the ADI. On December 4, 2019, FDA announced to the public that the Agency had asked manufacturers to expand testing for NDMA to include all lots of the medication before releasing them for consumer use. The announcement reiterated that if test results for any lots showed NDMA above the level previously identified as the ADI, the manufacturer should recall the product if distributed, or not release the product to consumers and inform FDA. The Agency also communicated that it needed to further investigate how ranitidine behaves in the body, and that it had found some evidence of a link between the presence of nitrites and the formation of

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[40] This level had previously been calculated as an interim acceptable limit for NDMA in ARBs. It is based on a calculated acceptable intake for NDMA in drugs based on methods described in the International Council for Harmonisation (ICH) guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018). See footnote 38 for more information on ARBs.

[41] See Ranitidine web page identified in footnote 35, FDA update for November 1, 2019.

[42] The range of NDMA observed in ranitidine was 0.013 ppm to 2.97 ppm. FDA test results further showed that 46 samples from 12 DMF or abbreviated new drug application (ANDA) holders had NDMA levels above the acceptable daily intake of 0.32 ppm based on a 300-milligram daily dose of ranitidine (which corresponds to the 96 ng acceptable daily limit). Ranitidine manufacturers reported similar values for NDMA levels in their products as those observed by FDA.

NDMA in the body if ranitidine was present. Since December, additional manufacturers have announced voluntary recalls of their products, which have been posted on the FDA ranitidine web page.

Today, April 1, 2020, FDA is sending letters to each firm marketing ranitidine requesting that they immediately initiate a voluntary withdrawal of all ranitidine drug product batches from the U.S. market.[43] Firms are also asked to cease further distribution. Firms should not resume marketing of ranitidine finished drug products unless and until FDA approves a supplemental application that demonstrates adequate control over NDMA.[44] Applicants are instructed to send market withdrawal plans, including a product withdrawal timeline, to the designated division recall coordinator in the FDA Office of Regulatory Affairs, Division of Pharmaceutical Quality Operations (I-IV).

Additionally, FDA is announcing to consumers that they should stop taking over-the-counter ranitidine products, dispose of them properly, and not purchase any more. Patients who are taking prescription ranitidine products should talk to their health care professional about other treatment options.

III. DISCUSSION

Your Petition specifically requests that FDA take eight actions based on the results of your preliminary testing and one action based on statements made in the Valisure Petition. We are granting your petition with respect to the following requests: 1 (recall), 2 (investigate), 3 (inform the public) and 5 (require manufacturers to conduct stability assessment). We are denying request 4 (provide instructions for disposal of ranitidine) because our web page on drug disposal adequately addresses this concern. We are denying the following requests: 6 (change shipment methods), 7 (change labeling) and 8 (prescription only status) in light of the actions taken today that request the removal of all ranitidine drug products from the market. These decisions are discussed further below.

A. Recall, Investigate, Inform the Public and Require Ranitidine Manufacturers to Conduct Thorough Stability Testing To Assess NDMA in Ranitidine

[43] FDA sent Information Requests (IR) to applicants and pending applicants that market all dosage forms and strengths of ranitidine requesting a market withdrawal.

[44] The IR explains the data applicants must generate to demonstrate to the Agency that their ranitidine drug product meets applicable drug quality standards, specifically to ensure that adequate controls are in place to eliminate or limit NDMA levels in drug products. Companies that want to resume distribution of a ranitidine finished drug product in the U.S. market should provide acceptable stability data, including in-use conditions as described in the IR, through labeled shelf life. FDA also recommends that applicants evaluate the cause or causes and extent of NDMA (and any other nitrosamine, if present as an impurity) formation over time, and optimize formulation and manufacturing controls and/or container/closure design to avert the formation of NDMA.

FDA's thinking on how to address NDMA impurities in ranitidine has evolved since it began its investigation in the summer 2019 to its decision today to request a market withdrawal of the drug products. FDA initially provided information that ranitidine drug products contained NDMA above acceptable limits to the public and manufacturers and distributors. The Agency supported applicants and manufacturers who voluntarily recalled ranitidine, and after obtaining sufficient scientific information on the levels of NDMA in ranitidine, FDA requested that manufacturers and distributors test their products and recall all ranitidine containing the impurity above acceptable levels.

FDA's investigation into NDMA impurities in ranitidine is ongoing. Recently, preliminary findings from stability testing raised concerns that NDMA levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels, although in other products smaller changes were observed.[45] FDA's preliminary stability testing, using standard accelerated stability conditions, demonstrated that elevated levels of NDMA were measured in all products after 2 weeks. Other testing conducted by FDA suggests that there is a correlation between NDMA levels and expiration date. Based on the data from NDMA testing in ranitidine drug products and drug substances, the preliminary results from FDA's stability testing, and other information available to the Agency, FDA is no longer confident that any ranitidine product will remain stable through its labeled expiration date.

Because of the recent data developed through the Agency's stability testing, and the continued availability of ranitidine, FDA is requesting the market withdrawal of all ranitidine products, whether or not confirmatory testing has been conducted to demonstrate the presence of the NDMA impurity. FDA will continue to monitor the effectiveness of this market withdrawal and will take further action as appropriate.

FDA also agrees on the appropriateness of conducting examinations and investigations into the existence of NDMA impurities in ranitidine products. This information has been discussed above and published on the Agency's Ranitidine web page. In the second request, the Petition specifically identifies review of stability assessments as part of its request for investigations. We agree that it is appropriate to ask manufacturers to demonstrate their product has acceptable levels of NDMA and that they have implemented adequate controls to ensure that any ranitidine drug product will remain stable through its labeled expiration date. FDA's action today specifically notifies applicants that if they want to return ranitidine drug products to the market, they should provide new stability data as described in the IR and discussed above.

In the Petition, you request that FDA provide information to the public regarding the high temperature instability of ranitidine products. We are granting that request. Today, FDA is announcing that the Agency's laboratory tests indicate that temperature and time contribute to an increase in NDMA levels in some ranitidine products. Our preliminary stability tests under

[45] For example, the Agency observed through its own laboratory testing that NDMA increased in the same batch of ranitidine over a period of 5 months at room temperature. The increase appears to be dependent on the formulation and how close the batch was to expiry.

accelerated conditions, one of which was conducted at 40ºC/75% humidity, indicate that elevated temperatures can lead to the presence of NDMA in the drug product. It is important to communicate this information to the public and to share the reasoning behind the Agency's actions.

As mentioned above, FDA's investigation into the root cause of NDMA impurities in ranitidine is on-going. The Agency will continue to review the information provided by applicants to understand the mechanism by which ranitidine becomes contaminated with NDMA. The Agency also continues to conduct stability testing of ranitidine and will continue to communicate information to the public as it becomes available.

In the fifth request, the Petition asks FDA to require manufacturers of ranitidine products to conduct a thorough stability assessment of the ranitidine and the formation of NDMA in both drug substance and drug product. FDA is granting that request by asking manufacturers to withdraw ranitidine products from the market and to conduct specific stability assessments for FDA to review and approve before their ranitidine products can return to the market. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies over time under the influence of a variety of environmental factors such as temperature, humidity, and light.[46] Stability testing is also used to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.[47] Stress testing of the drug substance can help identify the likely degradation products that the drug substance forms as it breaks down. Knowing what these degradation products are can help scientists understand how ranitidine degrades and can help to confirm that the analytical procedures used to measure its stability were appropriate. The nature of the stress testing will depend on the drug substance and the type of drug product involved. The protocol provided to applicants today was designed to elicit appropriate information on the stability of ranitidine.

B. Current Instructions on Appropriate Disposal of Ranitidine Are Sufficient

The Petition requests that in addition to the instructions for disposal and/or return of ranitidine in the recall notices, that FDA should issue additional guidance to the public for the safe disposal of ranitidine, given its recognized potential to form NDMA in municipal treatment plants and its possible effects on public drinking water.

FDA does not agree that new provisions for the safe disposal of ranitidine need to be developed for the removal of ranitidine from the market given the potential for ranitidine to contain NDMA. FDA's web page on Disposal of Unused Medicine describes how to properly dispose of old,

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[46] ICH guidance for industry *Q1A(R2) on Stability Testing of New Drug Substances and Products* (November 2003, Revision 2).

[47] Id.

unused, unwanted or expired medicine.[48] We recently updated the drug disposal recommendations to highlight that the best way to dispose of most types of medicines (both prescription and over-the-counter) is to use a drug take-back site location or program immediately after the drug is no longer used. Additionally, FDA provides information to consumers on proper disposal of prescription and OTC medicines when take-back programs are not available. This information is also being provided to consumers in the Agency's public statements on the removal of ranitidine from the market.

C. Changes to Transportation, Labeling, and OTC Status

The remaining requests ask FDA to direct manufacturers to modify procedures for the transportation and storage of ranitidine, to add language to labeling that ranitidine may contain a carcinogen, and to move OTC ranitidine products to prescription use only.[49] In light of the Agency's regulatory actions taken today that instruct applicants to remove all ranitidine products from the market and to submit new data on the stability of their ranitidine drug products before returning these products to the market, FDA declines to take these actions at this time. FDA is continuing to evaluate the safety of ranitidine and will take regulatory action as appropriate.

IV. CONCLUSION

For the foregoing reasons, your Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

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[48] FDA offers resources consumers can use to learn about the Agency's recommendation for proper disposal of unused medications: Disposal of Unused Medicines: What You Should Know, available at www.fda.gov/drugdisposal; Where and How to Dispose of Unused Medicines, https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines; Drug Disposal: Flush Potentially Dangerous Medicine, https://www.fda.gov/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-flush-potentially-dangerous-medicine#FlushList.

[49] Petition at 4.