David Light
Kaury Kucera, PhD
Valisure, LLC
5 Science Park
New Haven, CT 06511

April 1, 2020

Re: Docket No. FDA-2019-P-4281

Dear Mr. Light and Dr. Kucera:

This letter responds to your citizen petition submitted on behalf of Valisure LLC and ValisureRX, LLC (collectively referred to as Valisure), received on September 13, 2019 (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency) take the following actions based on Valisure's testing and detection of high levels of N-Nitrosodimethylamine (NDMA) in specific lots of ranitidine hydrochloride (ranitidine), sold under the brand name Zantac:[1]

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

(2) Conduct examinations and investigation under section 702(a) of the FD&C Act (21 U.S.C. 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for approval under section 704(a) of the FD&C Act (21 U.S.C. 374(a));

(3) Provide information to the public regarding these products under section 705(b) of the FD&C Act (21 U.S.C. 375(b));

(4) In addition to the instructions for disposal and/or return 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 carcinogen NDMA in municipal wastewater treatment plants and impact the public water supply; and

(5) Promulgate regulations requiring robust independent chemical testing and verification of pharmaceuticals and, while these regulations are pending, issue guidance requesting such testing and verification.

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

Petition at 2.

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 in prescription and over-the-counter (OTC) drug products. It is a histamine-2 (H2) 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

NDMA is a semivolatile organic chemical that forms in both industrial and natural processes.[2] It is not currently produced or commercially used in the United States, but may be unintentionally produced in and released from industrial sources through chemical reactions, such as those that involve alkylamines with nitrogen oxides, nitrous acid, or nitrate salts.[3] It can also be inadvertently formed in air, water, and soil from reactions to alkylamines, which are found widely distributed throughout the environment.[4]

NDMA exposure may occur through ingesting foods that contain nitrosamines,[5] 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

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[2] See the United States Environmental Protection Agency's (EPA) November 2017 "Technical Fact Sheet—NDMA" (EPA Fact Sheet), available at https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf.

[3] Id.

[4] See the *Toxicological Profile for N-Nitrosodimethylamine* at 1, (December 1989), available through the Agency for Toxic Substances and Disease Registry's (ATSDR) web page, "Toxic Substances Portal - N-nitrosodimethylamine" at https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=884&tid=173.

[5] 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.

cosmetic products such as shampoos and cleansers that contain NDMA, and breathing or inhaling cigarette smoke.[6] The oral route, in consumption of contaminated food and water, is the primary human exposure pathway for NDMA.[7]

NDMA has been classified as a probable carcinogen by the International Agency for Research on Cancer (IARC).[8] 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 to humans.[9] The 1987 IARC update for carcinogenic classification identifies NDMA as "Group 2A: Probably carcinogenic to humans."[10]

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 drugs are adequate to assure and preserve identity, strength, quality, and purity.[11] FDA continues to review the quality of drug products throughout the life cycle of the products, 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.[12] The introduction or delivery for introduction into

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[6] EPA Fact Sheet at 3.

[7] Id., citing ATSDR toxicological profile for NDMA.

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

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

[10] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 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.

[11] 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).

[12] See 21 CFR 7.40(a); see also the 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

interstate commerce of any drug that is adulterated[13] or misbranded[14] 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.[15] 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.[16] It is generally a voluntary action by manufacturers and distributors to protect the public health from products that present a risk of injury.[17] 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.[18] FDA generally directs a recall request to the firm that has primary responsibility for the manufacture and marketing of the product.[19] A recall is generally more appropriate and affords better protection for consumers than seizure, which

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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/RegulatoryInformation/Guidances/default.htm.

[13] 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 of 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 promulgated 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).

[14] Under 502(j) of the FD&C Act, a drug shall be deemed to be misbranded "[i]f 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)).

[15] 21 CFR 7.3(g).

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

[17] Id.; see also FDA draft guidance *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.

[18] 21 CFR 7.40(b), 21 CFR 7.45, 21 CFR 7.46; see also FDA draft guidance *Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C* (April 2019). Section 7.45(a) specifically addresses FDA requested 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.

[19] 21 CFR 7.40(b).

requires legal action and a court order, particularly when many lots of product have been widely distributed.[20] 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.[21] 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 a *market withdrawal*, when a firm's removal or correction of a distributed product may not be immediately subject to legal action by FDA.[22,23] 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.[24]

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.[25] 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 include inspection of records, files, papers processes, controls and facilities.[26] Further, FDA may request and evaluate information from applicants and

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[20] 21 CFR 7.40(c).

[21] See the FDA draft guidance *Initiation of Voluntary Recalls* (April 2019) 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 suggests 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. It 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 (see the draft guidance *Initiation of Voluntary Recalls* at 5).

[22] 21 CFR 7.3(j).

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

[24] See FDA Regulatory Procedures Manual, Chapter 7: Recall Procedures (Version 6) at 6 and 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).

[25] 21 U.S.C. 374(a)(4)(A).

[26] 21 U.S.C. 374(a)(1).

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[27] and are not adulterated.[28]

An important priority for FDA is to disclose information to the public on 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.[29] 21 C.F.R. 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 release, emails, and web and social media postings.[30] 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. While regulations and guidance on communications typically refer to recalls, it is FDA's policy to provide similar, appropriate public warnings and communications regarding the market withdrawal of a product.[31]

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 healthcare professionals that it had learned that some ranitidine drug products had NDMA impurities at low levels.[32] The Agency stated that it would investigate this

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[27] 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 shall 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).

[28] See footnote 13.

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

[30] Id. at 5 and 10.

[31] See footnote 24; 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.

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

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.[33] Subsequently, on September 26, 2019, FDA alerted patients and healthcare professionals on its webpage 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.[34]

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 on-going investigation of nitrosamine impurities in angiotensin II receptor blockers (ARBs).[35] 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)[36] 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 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.

Also during October 2019, some application holders initiated additional voluntary recalls that were included on FDA's Ranitidine webpage. By the end of the month, FDA concluded it had

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[33] 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's 10/2/2019 update; FDA's 10/23/2019 update includes second test method).

[34] See Ranitidine web page identified in footnote 32. 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.

[35] See FDA's web page FDA Updates and Press Announcements on angiotensin II receptor blockers (ARBs), (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.

[36] A drug master file (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)).

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.[37] 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.[38] Since September 2019, overall, the Office of Testing and Research (OTR) in FDA's Office of Pharmaceutical Quality has tested approximately 180 ranitidine samples, including prescription and OTC products.[39] 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, it 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 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 webpage.

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.[40] Firms are also asked to cease further distribution. Firms should not resume

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[37] 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 35 for more information on ARBs.

[38] See footnote 32, FDA update for November 1, 2019.

[39] 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 ANDA holders had NDMA levels above the ADI of 0.32 ppm based on a 300 mg daily dose of ranitidine (which corresponds to the 96 ng ADI). Ranitidine manufacturers reported similar values for NDMA levels in their products as those observed by FDA.

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

marketing of ranitidine finished drug products unless and until FDA approves a supplemental application that demonstrates adequate control over NDMA.[41] 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 (ORA) 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 five actions based on testing conducted by Valisure. We are granting your Petition with respect to requests 1 (recall), 2 (investigate), and 3 (inform the public). We are denying requests 4 (additional instructions on waste disposal), and 5 (promulgate regulations and/or guidance). These decisions are discussed further below.

A. Recall, Investigate and Inform the Public

FDA's thinking on how to address NDMA impurities in ranitidine has evolved since it began the investigation in the summer 2019 to its decision today to request a market withdrawal of the drug product. 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, we 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.[42] FDA's preliminary stability testing, using standard

[41] 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(s) 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.

[42] 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 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 continuing 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. Additionally, as noted above, FDA has been providing information to the public on a regular basis about the recalls and our investigation into NDMA impurities in ranitidine.

Although we are granting your Petition with respect to requesting manufacturers to remove all ranitidine products from the market, we did not rely on Valisure's testing results as presented in the Petition to reach this conclusion. We found that the test method you used in sampling ranitidine for NDMA was inappropriate and contributed to or caused the levels of NDMA to be artificially high.[43] In general, scientists ensure quality standards by testing a defined characteristic of a specific drug substance or specific drug product against established acceptance criteria for that characteristic.[44] To be considered an appropriate analytical test, FDA recommends that the tester provide data to demonstrate that a test procedure meets proper standards of accuracy, sensitivity, specificity and reproducibility, and is suitable for its intended purpose.[45] FDA also recommends that a quantitative analytical method be validated for its intended use through the demonstration of certain characteristics that are applicable for all types of tests. Typical validation characteristics are: specificity, linearity, accuracy, precision (repeatability, intermediate precision and reproducibility), range, and quantitation and detection limits.[46] Developing and validating a method requires the selection of appropriate analytical

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[43] The Petition indicates that Valisure used FDA's GC-MS headspace analysis method FY19-005-DPA for the determination of NDMA levels in ranitidine or other products. Even though this test method is appropriate for ARBs, this method is not suitable for ranitidine. This method utilizes a heat source, which leads to degradation of ranitidine and produces these artificially high levels of NDMA.

[44] See FDA guidance *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015) (guidance on Analytical Procedures) at 3.

[45] See Id. at 2-3. Applicants must submit appropriate analytical methods in their new or abbreviated drug application (21 CFR 314.50(d)(1); 314.94(a)(9)(i)).

[46] See guidance on Analytical Procedures at 7; see also ICH guidance for industry *Q2A on Text Validation of Analytical Procedures* (March 1995) and ICH guidance for industry *Q2B on Validation of Analytical Procedures: Methodology* (November 1996).

techniques, optimization of operation conditions, designing strategies for sample and standard preparations, and evaluating their stabilities. A method developed and validated for certain types of drugs or formulations is not appropriate for use on other drugs or formulations without separate validation.

To ensure that appropriate NDMA testing was used on all ranitidine products, FDA's Office of Testing and Research developed and validated two alternative liquid chromatography coupled with mass spectrometry (LC-MS) methods and posted them on the Agency's website.[47,48] Neither has the potential for "method-based" NDMA formation.[49] These two methods were validated for ranitidine drug substance and certain types of ranitidine drug products and have a limit of quantitation of 0.033 ppm of NDMA in drug products and a limit of detection of 0.011 ppm of NDMA. FDA's testing using these two orthogonal test methods (LC-HRMS and LC-MS/MS with multiple reaction monitoring), which are validated fit for purpose methods, have repeatedly indicated the presence of much lower levels of NDMA in ranitidine medicines than reported by Valisure.

The Petition makes several other arguments in support of its assertion that ranitidine drug products contain excessive levels of NDMA: the ranitidine molecule itself is unstable; ranitidine is unstable in humans, specifically in the stomach and intestines; the existence of a broadly expressed enzyme in the human body (DDAH-1) that facilitates NDMA formation; and an epidemiological study that implicated the drug class that includes ranitidine as being correlated to cancer. Because we have granted the Petition with respect to our market withdrawal action based on sufficient testing demonstrating NDMA in ranitidine and the lack of confidence that ranitidine will remain stable through expiration, FDA will not address these additional arguments regarding causation.

B. Current Instructions on Appropriate Disposal of Ranitidine are Sufficient

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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[47] One method, FY19-177-DPA-S utilizes high resolution mass spectrometry (LC-HRMS). See the FDA web page available at: https://www.fda.gov/media/130801/download.

[48] Another method, FY20-006-DPA-S, uses triple quadrupole mass spectrometry (LC-MS/MS), for the determination of NDMA in active pharmaceutical ingredients (API) and drug product. See FDA web page available at: https://www.fda.gov/media/131868/download. FDA released the second liquid chromatography-mass spectrometry (LC-MS) method to detect and quantify NDMA in ranitidine that uses a more widely available technology as an alternative. International regulators using similar LC-MS testing methods have also shown the presence of low levels of NDMA in ranitidine samples.

[49] In these two methods, NDMA is chromatographically separated from ranitidine API prior to ionization and detection by mass spectrometer, thus eliminating the risk of false NDMA results from ranitidine thermo-degradation. NDMA is selectively detected by its accurate mass or signature fragments in combination with LC retention time.

unused, unwanted or expired medicine.[50] 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 utilize 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. We note that this information is also being provided to consumers in the Agency's public statements on the removal of ranitidine from the market.

With respect to commercial disposal of unused or recalled ranitidine products, we expect that manufacturers and pharmacies will use appropriate disposal methods as identified by applicable federal, state or local jurisdictions. The Petition cites literature that shows a propensity for ranitidine to degrade to NDMA in conditions present in wastewater treatment facilities.[51] However, other literature indicates that the formation cannot be directly related to the decomposition of ranitidine and that there are many other conditions needed to form NDMA.[52] Based on the limited information provided in the Petition, it is not necessary for FDA to provide additional information or guidance on disposal of ranitidine drug products at this time.

C. Promulgation of Regulations and/or Guidance Requiring Independent Chemical Testing and Verification of Pharmaceuticals is Not Necessary at this Time

In the Petition, Valisure requests that FDA require independent chemical testing and verification of pharmaceuticals through regulation. We disagree that a regulation requiring or a guidance recommending independent testing is necessary. Applicants and manufacturers are required to ensure that their products meet all applicable standards for identity, strength, quality, purity and potency throughout the lifecycle of their drug products. See e.g. section 501 of the FD&C Act (21 U.S.C. 351). Existing regulations and guidance provide sufficient information for applicants and manufacturers, and FDA conducts sufficient oversight to ensure that quality drug products are released into the market.

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[50] 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.

[51] Petition at 17.

[52] See Le Roux, J, et al, *NDMA Formation by Chloramination of Ranitidine: Kinetics and Mechanism*, 2012, Environ Sci Technol, Vol 46, 11095-11103; Chen, Z, and Valentine, RL, 2007, *Formation of N-nitrosodimethylamine (NDMA) from humic substances in natural water*, Environ Sci Technol, 41(17), 6059-6065; Krasner, SW, Mitch, W, et al., 2013, *Formation, precursors, control, and occurrence of nitrosamines in drinking water: A Review*, Water Research, 47:4433-4450.

FDA's CGMP regulations set minimum requirements for drug product manufacturers to use in adequately controlling their manufacturing operations.[53] This formal system of controls helps to prevent instances of contamination, mix-ups, deviations, failures, and errors and assures that drug products meet the quality standards identified in regulations. FDA guidance recommends that similar controls be exercised by active ingredient manufacturers before they release a batch of active ingredient for use by drug product manufacturers.[54] In addition, every establishment that is registered to engage in the manufacture, preparation, propagation, compounding or processing of a drug is subject to an inspection under section 704 of the FD&C Act. 21 U.S.C. 374) FDA's inspection programs provide additional oversight of manufacturing.[55]

FDA guidance provides recommendations to industry on how to assure quality standards are met by active ingredient manufacturers and drug product manufacturers.[56] If a new risk is identified, it is expected that the manufacturer will assess that risk and, as appropriate, take steps to address it, for example by updating control strategies. Manufacturers are the most familiar with their own processes, facilities and supply chains, and are therefore best placed to assess a risk. FDA evaluates data generated from any risk assessment and proposed changes by industry to address risk in accordance with the requirements in the statute and Agency regulations. While manufacturers may choose to use an independent third-party to perform certain tests if they have reason to be concerned about the reliability of their own results or to access sophisticated methods or equipment that may not otherwise be available to them, independent testing does not provide unique insight into risks and is therefore generally not warranted.

Similarly, FDA does not agree that guidance recommending independent chemical batch-level testing and verification of the chemical content of all pharmaceuticals is necessary. Because FDA does not agree that regulations should be implemented to require third-party independent testing of all pharmaceuticals, we also do not agree that a guidance on this topic should be

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[53] See generally 21 CFR parts 210 and 211. These regulations include requirements to establish strong quality management systems, obtaining appropriate quality components (ingredients), establishing robust laboratory controls and operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. Specifically, manufacturers must evaluate incoming component quality, test and/or examine the quality of in-process material, and test statistically representative samples of the drug product before each batch is released for consumer use.

[54] ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016 (Revision 1)); ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and Answers* (April 2018).

[55] Section 510(h), 21 U.S.C. 360(h); see FDA Manual of Policies and Procedures 5014.1 "Understanding CDER's Risk-Based Site Selection Model" at 3 (September 26, 2018) (Goals of the surveillance inspection program are to ensure that sites consistently manufacture drug products of acceptable quality and minimize consumers' exposure to adulterated products).

[56] See e.g., ICH guidance for industry *Q8 (R2) Pharmaceutical Development* (November 2009, Rev. 2); ICH guidance for industry *Quality Risk Management* (June 2006) and ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

developed in the interim. We also note that implementation of such a system would be difficult. As a general principle, the degree of regulatory scrutiny over batch-level testing should be commensurate with the degree of risk, and an independent tester cannot evaluate the risk without sufficient knowledge of all manufacturing processes. Additionally, testing methods can only be developed with a target analyte in mind; testing of all possible chemical impurities or contaminants is not feasible. Beyond the problem of the volume of potential impurities to test, an independent third-party would need information concerning the formulation and manufacturing of a product to determine which chemical tests are appropriate, and to develop suitable methods for detection of impurities.

Because we do not agree that independent chemical testing and verification of pharmaceuticals are necessary, we deny this request. The Agency will reevaluate and update our policy as appropriate.

IV. CONCLUSION

For the foregoing reasons, FDA grants the Petition in part and denies the Petition in part.

Sincerely,

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research