

September 9, 2019

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

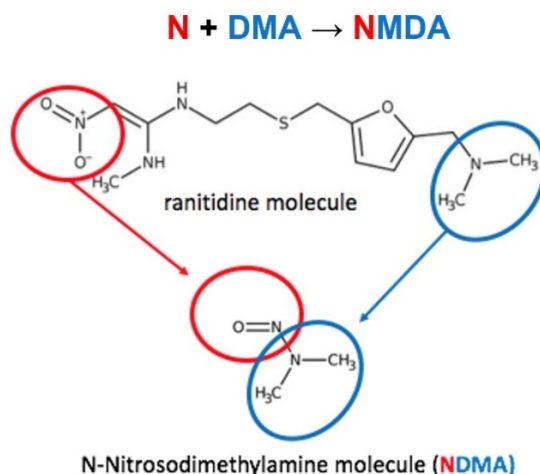
Re: Valisure Citizen Petition on Ranitidine

Dear Sir or Madam:

The undersigned, on behalf of Valisure LLC and ValisureRX LLC (collectively, “Valisure” or “Petitioner”), submits this Citizen Petition (“Petition”) pursuant to Sections 301(21 U.S.C. § 331), 501 (21 U.S.C. § 351), 502 (21 U.S.C. § 352), 505 (21 U.S.C. § 355), 702 (21 U.S.C. § 372), 704 (21 U.S.C. § 374), and 705 (21 U.S.C. § 375) of the Federal Food, Drug and Cosmetic Act (the “FDCA”), in accordance with 21 C.F.R. 10.20 and 10.30, to request the Commissioner of Food and Drugs (“Commissioner”) to issue a regulation, revise industry guidance, and request a recall and suspend sales of ranitidine from the US market and take such other actions set forth below.

#### **A. Action Requested**

The drug ranitidine, commonly sold under the brand Zantac, is an antacid, specifically an H<sub>2</sub> receptor blocker (“H<sub>2</sub> blocker”), which, due to a very high perception of safety, is heavily prescribed to adults and infants and sold over-the-counter. Valisure tests all batches of all its medications for quality and consistency issues and through such tests detected extremely high levels of N-Nitrosodimethylamine (“NDMA”), a probable human carcinogen, in every lot tested, across multiple manufacturers and dosage forms of the drug ranitidine. The Food and Drug Administration (“FDA”) has established a permissible daily intake limit for the probable human carcinogen, NDMA, of 96 ng. Valisure has detected NDMA in excess of 3,000,000 ng per tablet when analyzing ranitidine products, likely due to an inherent instability of the ranitidine molecule. The ranitidine molecule contains both a nitrite and a dimethylamine (“DMA”) group which are well known to combine to form NDMA. See illustration in Figure 1 below.



**Figure 1. The disposition of ranitidine to form NDMA.**

The ranitidine molecular structure contains both the nitrite group (circled in red) and dimethylamine (circled in blue) reactive groups that produce NDMA, a probable human carcinogen.

Valisure's tests suggest ranitidine can react with itself in standard analysis conditions (e.g. GC/MS oven temperature of 130 °C) at high efficiency to produce NDMA at levels well in excess of the permissible daily intake limit for this probable carcinogen. However, this level is not high enough for acute toxicity. Accordingly, the ability to produce NDMA at excessive levels has not been detected through the FDA's standard adverse event reporting mechanism. Combined with other data from Valisure and the scientific works of Stanford University and others, the evidence presented shows this instability and the resulting NDMA occurs in the conditions representative of those in the human body and builds a compelling case for ranitidine being a likely human carcinogen.

This Petition requests that the Commissioner take the following actions:

- 1) request a recall and suspend sale of all lots of all products containing ranitidine. Given the drug's propensity to form the probable carcinogen NDMA, the drug is misbranded under Section 502 of the FDCA (21 U.S.C. § 352);
- 2) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a));
- 3) provide information to the public regarding these products under Section 705(b) of the FDCA (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.

Background on Petitioner

Valisure is an online pharmacy currently licensed in 38 states and an analytical laboratory that is ISO 17025 accredited by the International Organization for Standardization ("ISO"). Valisure is registered with the Drug Enforcement Administration (Pharmacy: FV7431137, Laboratory: RV0484814) and the FDA (FEI #: 3012063246). Valisure's mission is to help ensure the safety, quality and consistency of medications and supplements in the market. In response to rising concerns about counterfeit medications, generics, and overseas manufacturing, Valisure developed proprietary analytical

technologies that it uses in addition to FDA standard assays to test every batch of every medication it dispenses.

In an August 7, 2018, inspection of Valisure's facilities by the FDA, it was determined that since Valisure's unique testing facility is not a part of the pharmaceutical manufacturing system and does not perform release testing, stability testing or any related services for pharmaceutical manufacturers, Valisure did not require FDA registration. However, Valisure has elected to maintain voluntary registration status with the FDA. Valisure also received guidance from the FDA that since it operates outside of the manufacturing industry using the appropriate ISO guidelines as opposed to GMPs, any product failures or concerns that Valisure identifies should be reported back to the pharmaceutical industry. Valisure has complied with this guidance and regularly provides reports to applicable parties in the pharmaceutical industry.

Valisure discovered the link between ranitidine and NDMA formation during its routine analysis of drug products in its pharmacy. Due to this discovery, Valisure's pharmacy will no longer sell any of the ranitidine products it has acquired, nor does it expect to be able to obtain a refund for these products in light of the fact that ranitidine's carcinogenicity has not been fully vetted by the FDA.

As discussed below, given the substantial risk to public safety and the high concern of medical practitioners, Valisure seeks to utilize this Citizen Petition to bring these concerns directly to the attention of the Commissioner and the FDA, and request that they take expeditious action.

## **B. Statement of Grounds**

The World Health Organization ("WHO") and the International Agency for Research on Cancer ("IARC") have classified NDMA as a Group 2A compound thereby defining it as "probably carcinogenic to humans."<sup>1</sup> The FDA currently recognizes the danger of such compounds and, as a result, has set strict daily acceptable intake limits on NDMA in pharmaceuticals of 96 nanograms.<sup>2</sup> There have been a multitude of manufacturer recalls of angiotensin receptor blocker ("ARB") medications, such as valsartan and losartan, due to the detection of NDMA in excess of these limits.<sup>3</sup>

Valisure's analysis using an FDA-recommended protocol for the detection of NDMA reveals the ability of the ranitidine molecule to form NDMA at high efficiency. The FDA protocol uses conditions that are benign for nearly all other molecules discussed in this petition, however, it is suspected that the modest

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<sup>1</sup> IARC Monographs on the Identification of Carcinogenic Hazards to Humans (1987). *International Agency for Research on Cancer and World Health Organization*. Vol. 17, Supp. 7 (<https://monographs.iarc.fr/list-of-classifications-volumes/>) and Preamble to IARC Monographs on the Identification of Carcinogenic Hazards to Humans.(2019). *World Health Organization*. (<https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf>)

<sup>2</sup> FDA updates table of interim limits for nitrosamine impurities in ARBs (February 28, 2019). *US Food and Drug Administration*. (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan>)

<sup>3</sup> Search List of Recalled Angiotensin II Receptor Blockers (ARBs) Including Valsartan, Losartan and Irbesartan. (current as of 06/28/2019). *US Food and Drug Administration*. (<https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and>)

heating in the GC/MS of 130 °C oven incubation for 15 minutes results in this highly efficient conversion of ranitidine to NDMA. Therefore, other conditions that are designed to reflect those in the human body were also tested by Valisure and other academic groups, including Stanford University which ran a clinical study in healthy adult volunteers. These tests also reveal high NDMA levels well in excess of the FDA's current daily acceptable intake limit.

Valisure investigated further mechanisms relevant to the conditions in the human body and identified a broadly expressed enzyme, DDAH-1, which is known to cleave DMA from its substrate and release it, presenting a known risk of NDMA formation.<sup>4</sup> Valisure's computational modelling suggest this enzyme may also act on the ranitidine molecule to produce DMA. This would provide a straightforward mechanism for NDMA formation from ranitidine throughout the human body.

Furthermore, an epidemiological study has implicated ranitidine's drug class as being correlated to cancer.

Given that all drugs approved by the FDA undergo significant safety testing, Valisure also investigated the information available to it concerning ranitidine safety studies. In Valisure's opinion, these studies are insufficient to rule out potentially carcinogenic properties and, in fact, reveal weaknesses in testing methodology that likely enabled this specific issue to avoid detection.

In consideration of the above, a copy of this Petition is also being submitted to the WHO and IARC as a nomination for ranitidine to be included in the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans and classified as a human carcinogen. Expeditious response from the FDA could accelerate action from such international agencies and effect global recalls for the benefit of human health worldwide.

Petitioner urges the Commissioner and the FDA to expeditiously request recalls of all ranitidine products to protect the American public from further exposure to the potentially carcinogenic properties of ranitidine, which is not labeled for such risk and in light of such risk, would not likely be acceptable for most, if not all, its intended treatments, and to take other such actions outlined in this Petition as deemed appropriate.

#### Instability of the Ranitidine Molecule and Formation of NDMA

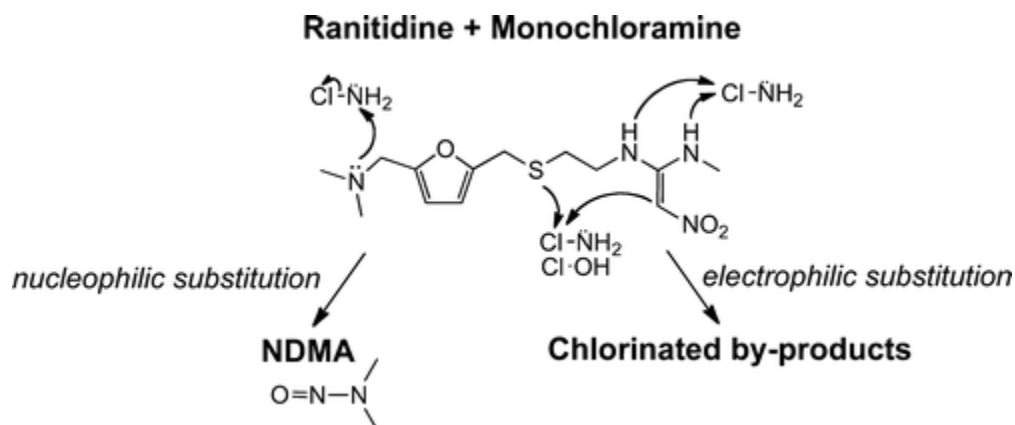
Since at least 2002, the formation of NDMA by the reaction of DMA and a nitroso source (such as nitrite) has been well characterized in the scientific literature and identified as a concern for contamination of the American water supply.<sup>5</sup> In 2003, it was further proposed that elevated levels of NDMA in drinking

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<sup>4</sup> See Ogawa, T., Kimoto, M., and Sasaoka, K. (1989). Purification and properties of a new enzyme, N<sup>G</sup>, N<sup>G</sup>-dimethylarginine dimethylaminohydrolase, from rat kidney. *The Journal of Biological Chemistry*. Vol 264, No. 17 p. 10205-10209 (<http://www.jbc.org/content/264/17/10205.full.pdf>).

<sup>5</sup> Mitch, W.A. and Sedlak, D.L. (2002). Formation of N-Nitrosodimethylamine (NDMA) from Dimethylamine during Chlorination. *Environmental Science & Technology*. Vol. 36 (4), p. 588-595 (<https://pubs.acs.org/doi/10.1021/es010684q>).

water produced by American wastewater treatment plants may be associated with the drug ranitidine.<sup>6</sup> As the high instability of the ranitidine molecule was further elucidated, scientific studies were conducted specifically investigating ranitidine as a source of NDMA in drinking water and specific mechanisms for the breakdown of ranitidine were proposed, as shown in Figure 2 below.<sup>7</sup>



**Figure 2. A proposed mechanism for the decomposition of ranitidine to NDMA.**

Multiple scientific groups have described the breakdown of ranitidine to form NDMA during wastewater treatment. This proposed mechanism is supported by experimentation and shows reaction with a chloride complex that nitrosates the ranitidine dimethylamine (from La Roux et al, 2012).

These studies underscore the instability of the DMA group on the ranitidine molecule and its ability to form NDMA in the environment of water treatment plants which supply many American cities with water.

However, these studies did not fully appreciate the full extent of NDMA formation risk from ranitidine; specifically, the added danger of this drug having not only a labile DMA group but also a readily available nitroso source in its nitrite group on the opposite terminus of the molecule. Valisure's testing reveals NDMA levels so high that the nitroso for NDMA likely comes from no other source than the ranitidine molecule itself. See statement by the experienced medicinal chemist, Wolfgang Hinz, attached to this petition as [Attachment A](#).

<sup>6</sup> Mitch, W.A., Sharp, J.O., Trussell, R.R., Valentine, R.L., Alvarez-Cohen, L. and Sedlak, D.L. (2003). N-Nitrosodimethylamine (NDMA) as a Drinking Water Contaminant: A Review. *Environmental Engineering Science*. Vol. 20, p. 5 (<https://superfund.berkeley.edu/pdf/231.pdf>).

<sup>7</sup> Le Roux, J., Gallard, H., Croue, J., Papot, S., Deborde, M. (2012). NDMA Formation by Chloramination of Ranitidine: Kinetics and Mechanism. *Environ. Sci. Technol.* Vol. 46, p. 20 (<https://pubs.acs.org/doi/10.1021/es3023094>).

Valisure has Detected Excessive Levels of NDMA in All Ranitidine Products Tested

As set forth in the summary table below, Petitioner has detected extremely high levels of NDMA in all lots tested, across multiple manufacturers of ranitidine products and in ranitidine reference standard. Petitioner’s pharmacy acquired these medications from the manufacturers reasonably available to it through its distributors and local pharmacy chains. Valisure’s ISO 17025 accredited laboratory used FDA recommended GC/MS headspace analysis method FY19-005-DPA<sup>8</sup> for the determination of NDMA levels. As per the FDA protocol, this method was validated to a lower limit of detection of 25 ng.

**Table 1. Ranitidine samples tested for NDMA.**

All ranitidine samples tested by Valisure’s laboratory formed very high levels of NDMA. Attachment B contains detailed data from each test.

150 mg Tablets or equivalent	Lot #	NDMA per tablet (ng)	Attachment B Data Reference #
Reference Powder*	125619	2,472,531	1
Zantac, Brand OTC	18M498M	2,511,469	2
Zantac (mint), Brand OTC	18H546	2,834,798	3
Wal-Zan, Walgreens	79L800819A	2,444,046	4
Wal-Zan (mint), Walgreens	8ME2640	2,635,006	5
Ranitidine, CVS	9BE2773	2,520,311	6
Zantac (mint), CVS	9AE2864	3,267,968	7
Ranitidine, Equate	9BE2772	2,479,872	8
Ranitidine (mint), Equate	8ME2642	2,805,259	9
Ranitidine, Strides	77024060A	2,951,649	10

\* Estimated NDMA scaled to equivalent of 150 mg.

Instability of the Ranitidine Molecule in Human Conditions

Valisure’s testing of all its drug products for NDMA and other probable carcinogens originally revealed the extremely high levels of NDMA from ranitidine. The extreme nature of the results prompted Petitioner to undergo further scientific investigation to determine the origin of the NDMA. Suspecting that the modest oven heating parameter of 130 °C in the FDA recommended GC/MS protocol contributed to the high results, Valisure developed a low temperature GC/MS method that could still detect NDMA but would only subject samples to 37 °C, the average temperature of the human body. This method was validated to a lower limit of detection of 100 ng and used for a variety of biologically relevant conditions of the human body discussed below.

Using this method, Valisure tested ranitidine tablets by themselves and in conditions simulating the human stomach. Industry standard “Simulated Gastric Fluid” (“SGF” 50 mM potassium chloride, 85 mM hydrochloric acid adjusted to pH 1.2 with 1.25 g pepsin per liter) and “Simulated Intestinal Fluid” (“SIF” 50 mM potassium chloride, 50 mM potassium phosphate monobasic adjusted to pH 6.8 with hydrochloric acid and sodium hydroxide) was used alone and in combination with various

<sup>8</sup> US Food and Drug Administration. (updated 01/25/2019). Combined N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay, FY19-005-DPA-S (<https://www.fda.gov/media/117843/download>).

concentrations of nitrite, which is commonly ingested in foods like processed meats and is elevated in the stomach by antacid drugs. These more biologically relevant tests were done in 100mL reaction volumes with one 150 mg tablet of ranitidine for each test that was allowed to react for one hour. 1mL of solution from each experiment was analyzed using the low temperature GC/MS method.

The results of Valisure’s tests on ranitidine tablets in biologically relevant conditions demonstrate significant NDMA formation under simulated gastric conditions with nitrite present (see Table 2).

**Table 2. Biologically relevant tests for NDMA formation.**

Conditions tested in Valisure’s laboratory produced high levels of NDMA from ranitidine. NDMA was detected in conditions of simulated gastric fluid with sodium nitrite, which is found in certain foods and produced by bacteria in the stomach.

Ranitidine Tablet Studies Lot# 77024060A	NDMA (ng/mL)	NDMA per tablet (ng)	Attachment B Data Reference #
Tablet without Solvent	Not Detected	Not Detected	11
Tablet	Not Detected	Not Detected	12
Simulated Gastric Fluid (“SGF”)	Not Detected	Not Detected	13
Simulated Intestinal Fluid	Not Detected	Not Detected	14
SGF with 10 mM Sodium Nitrite	Not Detected	Not Detected	15
SGF with 25 mM Sodium Nitrite	236	23,600	16
SGF with 50 mM Sodium Nitrite	3,045	304,500	17

Antacid drugs, like those outlined toward the end of this petition in Table 3, are known to increase stomach pH and thereby increase the growth of nitrate-reducing bacteria which further elevate levels of nitrite. This fact is well known and even present in the warning labels of antacids like Prevacid<sup>9</sup> (lansoprazole) and was specifically studied with ranitidine in the original approval of the drug:<sup>10</sup>

“Total gastric bacterial counts were increased at the end of the treatment [with ranitidine]. Three hours after the final dose, 9 of 11 subjects had an increase in the total count from a median of  $4.7 \times 10^2$  pre-treatment to  $2.5 \times 10^7$ ; 8 of the 11 subjects had an increase in total count at 12 hours amounting to  $1.1 \times 10^7$ . The bacterial content was closely related to the pH.”

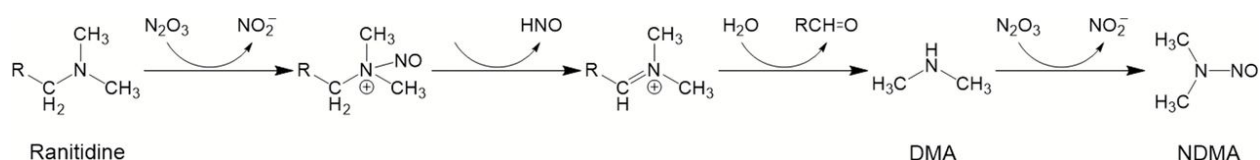
One third of all the bacterial strains isolated from the gastric juice reduced nitrate to nitrite. The median total number of nitrate reducing organisms increased from 9 in the pre-treatment samples to  $6 \times 10^5$  after 12 hours and  $3 \times 10^6$  after 4 hours.”

<sup>9</sup> Takeda Pharmaceuticals America, Inc. (Revised September 2012). PREVACID (lansoprazole) Delayed-Release Capsules. Highlights of Prescribing Information ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020406s078-021428s0251bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020406s078-021428s0251bl.pdf)).

<sup>10</sup> Frank, LLP provided Petitioner with hard copies of Glaxo and FDA documents concerning NDA 18-703 from the FDA that it obtained pursuant to the Freedom of Information Act, 5 U.S.C. § 552 *et seq.*



NDMA formation in the stomach has been a concern for many years and specifically ranitidine has been implicated as a cause of NDMA formation by multiple research groups including those at Stanford University. A detailed chemical reaction mechanism for the formation of NDMA from ranitidine in gastric conditions is proposed below from a Stanford University paper published in 2016:<sup>11</sup>



**Figure 3. A Proposed mechanism for the formation of NDMA from ranitidine.**

This proposed reaction mechanism describes how ranitidine could generate NDMA in the chemical environment of the human stomach (Zeng and Mitch, 2016). Results from tests by Valisure and others support this mechanism.

In addition to the gastric fluid mechanisms investigated in the scientific literature, Valisure identified a possible enzymatic mechanism via dimethylarginine dimethylaminohydrolase (“DDAH”) for the liberation of ranitidine’s DMA group which can occur in other tissues and organs separate from the stomach. Liberated DMA could lead to the formation of NDMA when exposed to nitrite present on the ranitidine molecule, nitrite freely circulating in the body,<sup>12</sup> or other potential pathways particularly in weak acidic conditions<sup>13</sup> such as that in the kidney or bladder. The original scientific paper detailing the discovery of the DDAH enzyme in 1989 specifically comments on the propensity of DMA to form NDMA.<sup>14</sup>

“This report also provides a useful knowledge for an understanding of the endogenous source of dimethylamine as a precursor of a potent carcinogen, dimethylnitrosoamine [NDMA].”

<sup>11</sup> Zeng, T. and Mitch, W.A. (2016). Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. *Carcinogenesis*. Vol. 37, p. 625-634 (<https://www.ncbi.nlm.nih.gov/pubmed/26992900>).

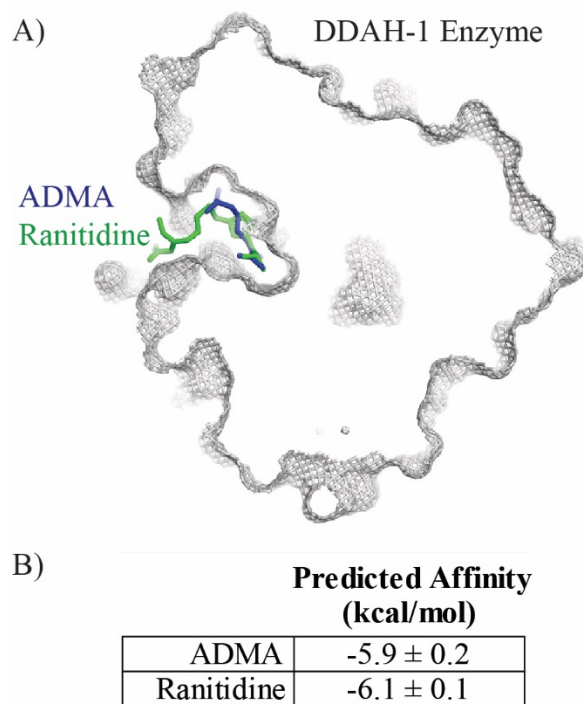
<sup>12</sup> Rassaf, T., Ferdinandy, P., and Schulz, R. (2013). Nitrite in organ protection. *British Journal of Pharmacology*. Vol. 171, 1, p. 1-11 (<https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.12291>).

<sup>13</sup> Showing metabocard for Dimethylamine. ID HMDB0000087. *The Human Metabolome Database*. (<http://www.hmdb.ca/metabolites/HMDB0000087>)

<sup>14</sup> Ogawa, T., Kimoto, M., and Sasaoka, K. (1989). Purification and properties of a new enzyme, N<sup>G</sup>, N<sup>G</sup>-dimethylarginine dimethylaminohydrolase, from rat kidney. *The Journal of Biological Chemistry*. Vol. 264, No. 17 p. 10205-10209 (<http://www.jbc.org/content/264/17/10205.full.pdf>).



The possibility that DMA could be liberated from ranitidine enzymatically is supported by computational modeling<sup>15</sup> using the chemical structure of DDAH-1.<sup>16</sup> Two isoforms of the DDAH gene exist, DDAH-1 and DDAH-2. Valisure was able to acquire a chemical structure only for DDAH-1 and therefore focused efforts on the DDAH-1 isoform. Results from computational modeling of DDAH-1 with ranitidine support binding of ranitidine within the catalytic active site of DDAH-1 in a similar fashion to that of its natural substrate asymmetric dimethylarginine (ADMA), see Figure 4 below.



**Figure 4. Computation modelling of ranitidine binding to DDAH-1 enzyme by Valisure.**

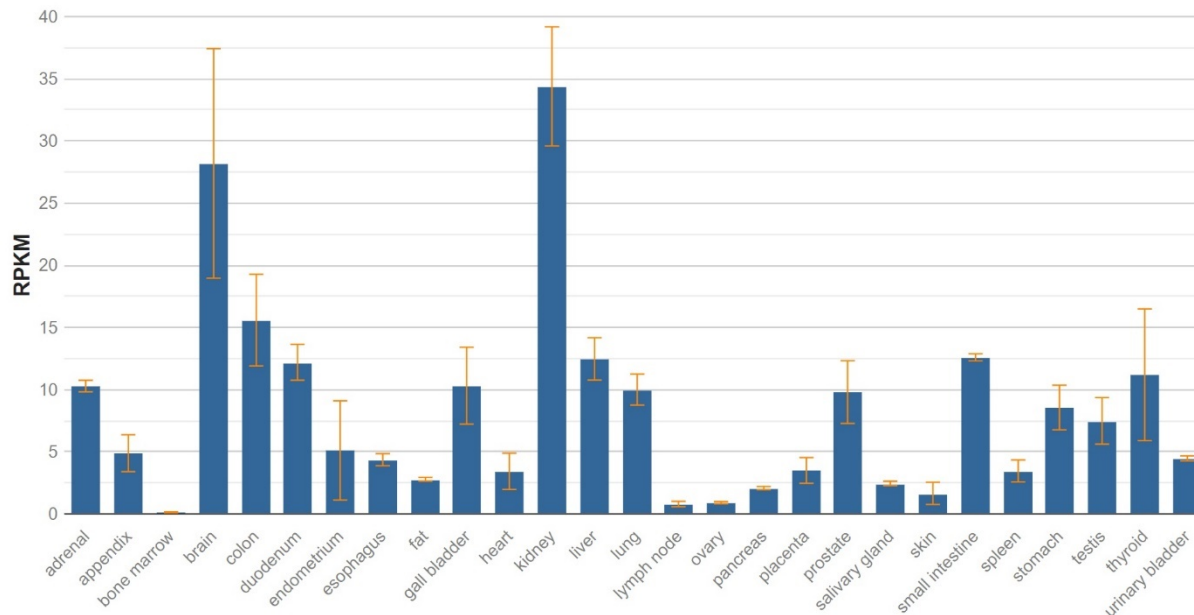
A) Molecular modelling predicts reasonable placement of the ranitidine molecule (shown in green) in the active site of DDAH-1 enzyme (shown as a cross-section in grey) when compared to asymmetric dimethylarginine (ADMA, shown in blue), the natural substrate of DDAH-1. B) The predicted affinity of ranitidine is similar to that of ADMA using the same modelling parameters

These results suggest that the enzyme DDAH-1 may increase formation of NDMA in the human body when ranitidine is present; therefore, the expression of the DDAH-1 gene is useful for identifying organs

<sup>15</sup> Trott, O., Olson, A.J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *Journal of Computational Chemistry*. Vol. 31, p. 455-461 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041641/>)

<sup>16</sup> Wang, Y., Monzingo, A.F., Hu, S., Schaller, T.H., Robertus, J.D., Fast, W. (2009). Developing dual and specific inhibitors of dimethylarginine dimethylaminohydrolase-1 and nitric oxide synthase: toward a targeted polypharmacology to control nitric oxide. *Biochemistry*. Vol. 48: 8624-8635 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746464/>)

most susceptible to this action. The chart below from the National Center for Biotechnology Information<sup>17</sup> illustrates the expression of the DDAH-1 gene in various tissues in the human body:



**Figure 5. Expression levels of DDAH-1 enzyme.**

Expression levels across many human tissue types suggests that the DDAH-1 enzyme is functionally expressed throughout the human body. RPKM are reads per kilobase of transcript, per million mapped reads of the DDAH-1 gene (NCBI, 2019)

DDAH-1 is most strongly expressed in the kidneys but also broadly distributed throughout the body. This offers both a general mechanism for NDMA formation in the human body from ranitidine and specifically raises concern for the kidneys.

#### In Vivo Studies Strongly Suggest Ranitidine’s Formation of NDMA and Carcinogenicity

In addition to the aforementioned *in vitro* studies that suggest a strong connection between ranitidine and NDMA formation, *in vivo* clinical studies in living animals add further weight to concern over this action and overall potential carcinogenicity. A study published in the journal *Carcinogenesis* in 1983 titled “Genotoxic effects in rodents given high oral doses of ranitidine and sodium nitrite” specifically suspected the carcinogenic nature of ranitidine in combination with nitrite<sup>18</sup> (only two years after the drug entered the market in 1981). Despite rat gastric physiology being different than human, the authors of this study concluded:

<sup>17</sup> DDAH1 dimethylarginine dimethylaminohydrolase. (updated 07/08/2019). *National Center for Biotechnology Information* (<https://www.ncbi.nlm.nih.gov/gene/23576>).

<sup>18</sup> Brambilla, G. et al. (1983). Genotoxic effects in rodents given high oral doses of ranitidine and sodium nitrite. *Carcinogenesis*. Vol. 4, 10, p. 1281-1285 (<https://academic.oup.com/carcin/article-abstract/4/10/1281/2391364>).

“Our experimental findings have shown that simultaneous oral administration in rats of high doses of ranitidine and NaNO<sub>2</sub> [nitrite] can produce DNA fragmentation either in liver or in gastric mucosa.”

Arguably most important of all *in vivo* studies are those conducted in humans. One such study was completed and published in 2016 by Professor William Mitch and his team at Stanford University.<sup>19</sup> The study showed that healthy individuals, both male and female, that took Zantac 150 mg tablets produced roughly 400 times elevated amounts of NDMA in their urine (over 40,000 nanograms) in the proceeding 24 hours after ingestion. These results alone are extremely alarming, given NDMA has been implicated as an etiological agent for bladder cancer,<sup>20</sup> however, the implications could be significantly worse given that NDMA is known to be heavily absorbed by the body instead of being excreted into urine.<sup>21</sup> Relevant excerpts from this study are shown below:

Summary findings of study:

“Following ranitidine intake, the urinary NDMA excreted over 24 h increased 400-folds from 110 to 47,600 ng, while total N-nitrosamines increased 5-folds. NDMA excretion rates after ranitidine intake equaled or exceeded those observed previously in patients with schistosomiasis, a disease wherein N-nitrosamines are implicated as the etiological agents for bladder cancer.”

Regarding urinary NDMA likely being a small fraction of total NDMA exposure in the body:

“While urinary N-nitrosamine concentrations may more directly reflect systemic exposure, it is important to note that such estimates are conservative. Actual systemic NDMA exposure is likely much higher than that eliminated in urine, as previous studies have indicated a high metabolic conversion rate of NDMA (i.e. >99.9%) and therefore its low renal clearance (i.e. only ~0.05% excreted in urine)”

#### Epidemiological Link of Ranitidine to Cancer in Humans and Physician Concern

Likely due to the perceived high safety profile of ranitidine, very few epidemiological studies have been conducted on this drug. In fact, Petitioner was unable to find any epidemiological studies on only ranitidine in the U.S., though at least one exists on its class of H<sub>2</sub> blockers that began in 1986 during a time when only two H<sub>2</sub> blocker drugs were available, ranitidine and cimetidine. This 2004 study published by the National Cancer Institute<sup>22</sup> investigated 414 cases of peptic ulcer disease reported in 1986 and then followed for 14 years. One of the variables investigated by the authors was if the

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<sup>19</sup> Zeng, T. and Mitch, W.A. (2016). Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. *Carcinogenesis*. Vol. 37, p. 625-634 (<https://www.ncbi.nlm.nih.gov/pubmed/26992900>).

<sup>20</sup> See *id.*

<sup>21</sup> Spiegelhalter, B., Eisenbrand, G., Preussmann, R. (1982). Urinary excretion of N-nitrosamines in rats and humans. *IARC Sci Publ.* Vol. 41 p. 443-449 (<https://www.ncbi.nlm.nih.gov/pubmed/7141551>).

<sup>22</sup> Michaud, D.S., Mysliwiec, P.A., Aldoori, W., Willett, W.C., Giovannucci, E. (2004). Peptic ulcer disease and the risk of bladder cancer in a prospective study of male health professionals. *Cancer Epidemiol Biomarkers Prev.* Vol. 13, 2, p. 250-254 (<https://www.ncbi.nlm.nih.gov/pubmed/14973090>).

patients had been taking a prescription antacid, either Tagamet (cimetidine) or Zantac (ranitidine). The study did not differentiate between which drug was taken, just that the patient was on a prescription antacid. Despite the data being confounded with the two drugs, the study concluded:

"Recent use of ulcer treatment medication (Tagamet and Zantac) was also related to the risk of bladder cancer, and this association was independent of the elevated risk observed with gastric ulcers."

The authors also note that:

"N-Nitrosamines are known carcinogens, and nitrate ingestion has been related to bladder cancer risk."

NDMA is among the most common of the "N-Nitrosamines."

In considering this study published by the National Cancer Institute, it should be noted that a 1982 clinical study in rats compared ranitidine and cimetidine exposure in combination with nitrite.<sup>23</sup> When investigating DNA fragmentation in the rats' livers, no effect was observed for cimetidine administered with nitrite but ranitidine administered with nitrite resulted in a "significant DNA fragmentation."

Investigators at Memorial Sloan Kettering Cancer Center are actively studying ranitidine to evaluate the extent of the public health implications of these findings. Regarding ranitidine, one of the investigators commented to Valisure:

"A potential link between NDMA and ranitidine is concerning, particularly considering the widespread use of this medication. Given the known carcinogenic potential of NDMA, this finding may have significant public health implications,"<sup>24</sup>

To further underscore the concern from medical professionals, a statement from Dr. Jon Ernstoff, a gastroenterologist practicing for 41 years, is appended to this petition as Attachment C. An excerpt from this attachment is below:

"Had I known of the NDMA risk associated with Zantac, I would have strongly considered prescribing alternative medications for the indicated conditions, such as another histamine blocker or a PPI. For the indicated conditions, there were always alternative treatments available with acceptable safety, cost, and efficacy profiles."

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<sup>23</sup> Brambilla G., Cavanna M., De Flora S. (1982). Genotoxic Effects of Drugs: Experimental Findings Concerning Some Chemical Families of Therapeutic Relevance. In: Nicolini C. (eds) Chemical Carcinogenesis. NATO Advanced Study Institutes Series (Series A: Life Sciences), Vol 52. Springer, Boston, MA ([https://link.springer.com/chapter/10.1007/978-1-4684-4334-9\\_11](https://link.springer.com/chapter/10.1007/978-1-4684-4334-9_11)).

<sup>24</sup> Email from Dr. Lior Z. Braunstein, a physician and cancer research scientist at Memorial Sloan Kettering Cancer Center, New York City.

### Weaknesses of Existing Safety Data on Ranitidine

Petitioner recognizes that while extensive safety data is produced for any new drug approval, cancer risks can be difficult to determine in studies that are inherently short and conducted primarily in animals. Valisure has identified key studies that investigated ranitidine safety but contained important weaknesses in the studies' investigations. It is important to emphasize that these studies do not negate the data presented in this petition and instead illustrate how evidence of the potentially carcinogenic nature of ranitidine could have gone largely unreported to the FDA for 38 years.

In a 1981 study published by Glaxo Group Research Ltd., the originator of the ranitidine molecule, the metabolites of ranitidine in urine were studied using industry standard detection technology of high-performance liquid chromatography.<sup>25</sup> Many metabolites were listed, though there is no indication that NDMA was looked for, and it was not till the 2016 Stanford University study that NDMA was specifically identified in large quantity in human urine from individuals ingesting ranitidine.

By 1987, after numerous studies raised concerns over ranitidine and cancerous nitroso compounds,<sup>26 27</sup> <sup>28 29</sup> Glaxo Group Research Ltd. published a clinical study specifically investigating gastric contents in human patients and N-nitroso compounds.<sup>30</sup> The study concluded:

“During treatment with ranitidine median 24 hour intragastric pH, nitrate concentration, and counts of total and nitrate reducing bacteria increased significantly regardless of dietary nitrate content; there was no significant increase in the median day time concentration of N-nitroso compounds.”

However, Petitioner notes that this study, which likely built confidence in the medical community that ranitidine was not associated with N-nitrosamines like NDMA, had a few significant weaknesses that prevented the detection of NDMA formation from ranitidine. Importantly, this study used an analytical system called a “nitrogen oxide assay” for the determination of N-nitrosamines, which was developed

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<sup>25</sup> Carey, P.F., Martin, L.E., Owen, P.E. (1981). Determination of ranitidine and its metabolites in human urine by reversed-phase ion-pair high-performance liquid chromatography. *Journal of Chromatography B: Biomedical Sciences and Applications*. Vol. 225, 1, p. 161-168

(<https://www.sciencedirect.com/science/article/pii/S0378434700802558>).

<sup>26</sup> Brambilla, G. et al. (1983). Genotoxic effects in rodents given high oral doses of ranitidine and sodium nitrite. *Carcinogenesis*. Vol. 4, 10, p. 1281-1285 (<https://academic.oup.com/carcin/article-abstract/4/10/1281/2391364>).

<sup>27</sup> Martelli, A., Fugassa, E., Voci, A., Brambilla, G. (1983). Unscheduled DNA synthesis induced by nitrosated ranitidine in primary cultures of rat hepatocytes. *Mutation Research Letters*. Vol. 122, 3-4, p. 373-376 (<https://www.sciencedirect.com/science/article/pii/0165799283900222>).

<sup>28</sup> Maura, A. et al. (1983) DNA damage induced by nitrosated ranitidine in cultured mammalian cells. *Toxicology Letters*. Vol. 18, 1-2, p. 97-102 (<https://www.sciencedirect.com/science/article/pii/0378427483900772>).

<sup>29</sup> Brambilla G., Cavanna M., De Flora S. (1982). Genotoxic Effects of Drugs: Experimental Findings Concerning Some Chemical Families of Therapeutic Relevance. In: Nicolini C. (eds) *Chemical Carcinogenesis*. NATO Advanced Study Institutes Series (Series A: Life Sciences), Vol 52. Springer, Boston, MA ([https://link.springer.com/chapter/10.1007/978-1-4684-4334-9\\_11](https://link.springer.com/chapter/10.1007/978-1-4684-4334-9_11)).

<sup>30</sup> Thomas, J.M., et al. (1987). Effects of one year's treatment with ranitidine and of truncal vagotomy on gastric contents. *Gut*. Vol. 28, 6, p. 726-738 (<https://www.ncbi.nlm.nih.gov/pubmed/3623220>).

for analysis of food<sup>31</sup> and is a detection method that indirectly and non-specifically measures N-nitrosamines.

In addition to being a less accurate and less specific detection method than industry standard chromatography, this method necessitated discarding all gastric samples that contained ranitidine. Thus, without ranitidine being present in any samples taken, the degradation products of ranitidine, like NDMA, could not reasonably be detected. Relevant excerpts are below:

“When sufficient gastric juice was present, samples for estimation of N-nitroso compound were collected hourly between 1200 and 2100 h in studies R1, R3, R4, and R5 and after vagotomy. In all samples studied ranitidine was undetectable by radioimmunoassay with a lower limit of detection at 20 ng of ranitidine/ml.

N-nitroso compounds were assayed by measurement of nitrogen oxide evolved under special conditions. The assays were restricted to ranitidine free samples because the presence of ranitidine in gastric juice may result in falsely high concentrations of N-nitroso compounds being recorded.”

...

“Because of the overriding need to be certain that ranitidine present in gastric juice would not be assayed as if it were a N-nitroso compound, aspirates of juice were only used for N-nitroso compound analysis at times when ranitidine was absent. Results for N-nitroso compounds are consequently based on assay of approximately one third of the samples that were analysed for pH, bacterial counts and nitrite concentration; conclusions must be correspondingly less certain, especially as no night-time samples were studied. N-nitroso compounds were not measured at all during study R2 but no increase in day time median values was found during (R3 and R4) or after (R5) maintenance treatment, an observation in agreement with other 24 hour studies.”

The “other 24 hour studies” referenced contained only one full study and this study had patients that were treated with cimetidine only, a different H2 blocker. It should also be noted that the referenced cimetidine study took samples through the entire 24 hour period<sup>32</sup> and used analytical methods specifically designed for gastric juice<sup>33</sup> as opposed to food.

The 1987 safety study does not negate the current findings in this petition since this new data simply fills in areas that were not fully investigated.

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<sup>31</sup> Walters, C.L., Downes, M.J., Edwards, M.W., Smith, P.L. (1978). Determination of a non-volatile N-nitrosamine on a food matrix. *Analyst*. Vol. 103, 1232, p. 1127-1133 (<https://www.ncbi.nlm.nih.gov/pubmed/736263>).

<sup>32</sup> Milton-Thompson, G.J. et al. (1982). Intra-gastric acidity, bacteria, nitrite, and N-nitroso compounds before, during, and after cimetidine treatment. *The Lancet*. Vol. 319, 8281, p. 1091-1095 (<https://www.sciencedirect.com/science/article/pii/S0140673682922772>).


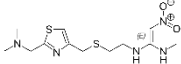
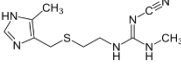
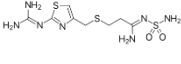
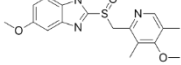
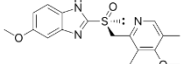
<sup>33</sup> Bavin, P.M., Darkin, D.W., Viney, N.J. (1982). Total nitroso compounds in gastric juice. *IARC Scientific Publications*. Vol. 41, p. 337-344 (<http://europepmc.org/abstract/med/7141541>).

### Instability of Ranitidine is Unique Within Its Drug Class; Availability of Alternatives

Petitioner recognizes that ranitidine is a very commonly used over-the-counter and prescription drug for both adults and infants and is in the top 50 most prescribed drugs in the United States with over 15 million prescriptions in 2016.<sup>34</sup> However, the antacid drug class that ranitidine belongs to, H2 Blockers, and the related antacid class of proton-pump inhibitors (“PPIs”), were analyzed by Valisure and many alternatives were identified which should minimize any disturbances to patients currently being treated by ranitidine if the drug were recalled. Of the ten drugs tested, eight formed no detectable amounts of NDMA and only ranitidine formed millions of nanograms of NDMA. The drug nizatidine formed tens of thousands of nanograms of NDMA and should also be investigated. Petitioner notes that nizatidine, like ranitidine, also contains both a nitrite and DMA group on terminal ends of the molecule and may be sensitive to the same degradation mechanism shown in Figure 1. However, eight drugs remain in these drug categories that do not possess this ability to easily form NDMA.

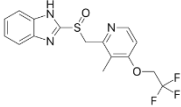
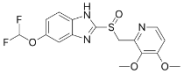
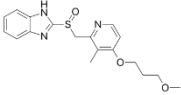
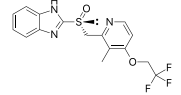
**Table 3. Analysis of NDMA levels across common antacid medications.**

Valisure’s laboratory detected NDMA in ranitidine and nizatidine tablets. Ranitidine, however, formed about 70 times more NDMA per mg compared to nizatidine.

Scientific Name (Tablets tested)	Brand (Lot#)	Structure	NDMA per tablet (ng)	Attachment B Data Reference #
Ranitidine (1x 150 mg tablet)	Zantac (7702406A)		2,978,551	18
Nizatidine (1x 150 mg capsule)	Axid (1290625A)		41,693	19
Cimetidine (1X 200 mg tablet)	Tagamet (9AE2576)		Not Detected	20
Famotidine (2x 40 mg tablets)	Pepcid (1805012732)		Not Detected	21
Omeprazole (2x 40 mg capsule)	Prilosec (19182878)		Not Detected	22
Esomeprazole (2x 40 mg capsule)	Nexium (C806922)		Not Detected	23

<sup>34</sup> ClinCalc DrugStats Database. (2006-2016). The Top 200 of 2019. *Agency for Healthcare Research and Quality (AHRQ)*, Rockville, MD. Version 19.1 (<https://clincalc.com/DrugStats/Top200Drugs.aspx>).



Lansoprazole (3x 30 mg capsule)	Prevacid (C807365)		Not Detected	24
Pantoprazole (2x 40 mg tablets)	Protonix (PAN18101)		Not Detected	25
Rabeprazole (4x 20 mg capsules)	AcipHex (BY33E009)		Not Detected	26
Dexlansoprazole (2x 60 mg capsule)	Dexilant (A27540)		Not Detected	27

Recall Request and Other Actions

This Petition seeks to have the Commissioner and FDA request recalls and suspend sales for all products containing the API ranitidine, consistent with FDA’s mandate to ensure the safety of prescription and over the counter the drugs in the United States.

Such recalls are extremely important for public safety. The elimination of ranitidine from the market is not expected to create a significant impact to the U.S. healthcare system or patients currently taking the drug due to the fact that many alternatives exist in the same drug class and similar drug classes. As Table 3 shows, nearly all other treatments for gastroesophageal reflux disease (“GERD”) and similar diseases in the drug categories of PPIs and H2 Blockers did not generate NDMA in Valisure’s tests. The only notable exception is nizatidine, which, like ranitidine, also has a nitrite and a DMA group on the terminal ends of the molecule. Valisure also recommends the investigation of this product, though the detected NDMA levels are roughly 70X lower.

Petitioner notes that there is precedent for recalling widely used medications due to concern over carcinogenic properties. In 1979 the FDA and industry jointly announced a recall due to the suspected carcinogenic properties of methapyrilene, an “antihistamine that for years has been the active ingredient of such nonprescription [i.e. over-the-counter] sleeping pills as Somnex, Excedrin P.M. and Compoz.”<sup>35</sup> According to the announcement, the recall followed a conclusion by the National Cancer Institute (“NCI”) two months earlier, that methapyrilene causes liver cancer in rats and mice and should be presumed to do so in humans; after evaluating the NCI’s data, the FDA reached the same conclusion.<sup>36</sup> Similar to ranitidine, methapyrilene’s link to cancer was widely believed to be associated

<sup>35</sup> U.S., Industry Recall Sleep Aids Containing Cancer-Causing Agent (June 9, 1979). *The New York Times*, New York, NY. (<https://www.nytimes.com/1979/06/09/archives/us-industry-recall-sleep-aids-containing-cancer-causing-agent.html>)

<sup>36</sup> *Id.*

with the same probable human carcinogen, NDMA, formed by an unstable DMA group on the molecule.<sup>37 38</sup>

In addition, for the reasons stated above, FDA should conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed. Further, FDA should provide information to the public regarding these medications under Section 705(b) of the FDCA (21 U.S.C. § 375(b)).

#### Safe Disposal of Ranitidine for Avoidance of Increased NDMA in American Water Supply

Petitioner notes that, as illustrated in this Petition, nearly two decades of research has shown a strong propensity for ranitidine to degrade into NDMA in the conditions present in wastewater treatment facilities throughout the United States. In several areas of the United States, treated municipal wastewater is used as a drinking water supply (i.e., potable reuse).<sup>39</sup> The treatment techniques employed to further purify the wastewater for this purpose frequently incorporate treatment with inorganic chloramines. The reaction of ranitidine with inorganic chloramines produces NDMA with high efficiency.<sup>40</sup> Increasing the amount of ranitidine in municipal wastewaters will likely increase the amount of NDMA in drinking waters where potable reuse is practiced.

In addition, disposal of ranitidine in landfills could increase the drug's levels in the leachate runoff. "Chemical methods" are commonly used for treatment of landfill leachate,<sup>41</sup> and the instability of ranitidine could cause it to degrade into NDMA during this treatment. Therefore, public disposal of ranitidine either directly into municipal wastewater (e.g. dumping in a sink or toilet) or indirectly dumping into landfills (e.g. dumping in standard trash), should be explicitly avoided. Pharmacies and others in the industry should be instructed to quarantine ranitidine products and utilize disposal methods that do not risk ranitidine exposure to wastewater treatment plants, and the public should be urged to take similar actions.

In addition to the language regarding return or disposal in the recall notices, Valisure urges the FDA to issue additional guidance and instructions to the public regarding appropriate disposal of ranitidine, to avoid the potential for significant increases in exposure of the general population to the probable human carcinogen NDMA via municipal water supplies.

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<sup>37</sup> Lijinsky, W. (1974). Reaction of drugs with nitrous acid as a source of carcinogenic nitrosamines. *Cancer Research*. Vol. 34, p. 255-258 (<https://cancerres.aacrjournals.org/content/34/1/255>)

<sup>38</sup> Mergens, WJ. et. al. (1979) In vitro nitrosation of methapyrilene. *Journal of Pharmaceutical Sciences*. Vol. 68, p. 827-832. (<https://www.ncbi.nlm.nih.gov/pubmed/458597>)

<sup>39</sup> National Research Council(2012). Water reuse: Expanding the nation's water supply through reuse of municipal wastewater. The National Academies Press, Washington, D.C. (<https://www.nap.edu/catalog/13303/water-reuse-potential-for-expanding-the-nations-water-supply-through>)

<sup>40</sup> Roux, J. L., Gallard, H., Croué, J.-P.; Papot, S., Deborde, M. (2012). NDMA formation by chloramination of ranitidine: Kinetics and mechanism. *Environ. Sci. Technol.* 2012, 46 (20), 11095–11103 (<https://www.ncbi.nlm.nih.gov/pubmed/22967139>)

<sup>41</sup> S. Renou et al. (2007). Landfill leachate treatment: Review and opportunity. *Journal of Hazardous Materials*. Vol. 150, Issue 3, Pages 468-493 (<https://www.sciencedirect.com/science/article/pii/S0304389407013593>).

### Independent Testing and Verification of Drug Products in the United States

Petitioner is also requesting that the FDA promulgate regulations requiring robust independent chemical testing and verification of medications. In the interim, while these regulations are pending, FDA should issue formal guidance recommending such testing and verification.

This is necessary in order to serve public health and help protect Americans from adulterated and poor-quality drug products, an issue of growing concern. Grounds for this request are also rooted in strong support from the medical community, as evidenced by a recent resolution from the American College of Cardiology (“ACC”), calling for the American Medical Association to advocate for legislation requiring independent testing and verification of the chemical content of batches of pharmaceuticals. The resolution is at Attachment D.

#### **C. Environmental Impact**

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.30, and believes that this Petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement.

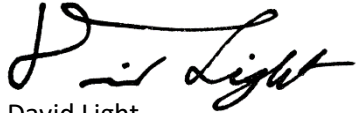
#### **D. Economic Impact**

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted by the Petitioner only upon request of the Commissioner following review of this Petition.

#### **E. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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