May 28, 2020

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

Re: Docket No. FDA-2020-P-0978

Dear Mr. Light, Dr. Kucera, and Dr. Wu:

This letter responds to your citizen petition submitted on behalf of Valisure, LLC, and ValisureRX, LLC (collectively referred to as Valisure), received on March 2, 2020 (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 metformin drug products:

(1) Request a recall of identified batches of metformin

(2) Conduct examinations and investigation under section 702(a) of the Federal Food, Drug &Cosmetic Act (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)), and effect labeling revisions as needed

(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) Update and revise FDA guidance document FY20-058-DPA-S to include the analytical methodology outlined in the Petition and in Attachment A for improved quantitation of NDMA in metformin and to avoid underestimation of NDMA levels

(5) Promulgate regulations requiring robust independent chemical batch-level testing and verification of the chemical content of batches of pharmaceuticals and, while these regulations are pending, issue guidance requesting such testing and verification

Petition at 2.

We have carefully considered your Petition, comments to the docket, and other information available to the Agency. The presence of NDMA above acceptable intake limits as described in the recall request presents a safety concern that must be addressed immediately; however, FDA will need additional time to evaluate and respond to the remaining requests in this Petition.

Therefore, this is a partial response to your Petition. With respect to your request for a recall, we grant it in part and deny it in part. FDA intends to respond to your other requests at a later date.

I. BACKGROUND

A. Metformin Hydrochloride

Metformin hydrochloride (metformin) is an oral antihyperglycemic drug approved for the management of type 2 diabetes. Metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The maximum recommended daily dose of metformin hydrochloride extended-release (ER) tablets is 2000 milligrams (mg) in adults, and the maximum recommended daily dose of metformin immediate-release (IR) is 2550 mg. Metformin is available in oral tablet, oral ER tablet, suspension, and solution formulations. The drug is also available in combination with other medications.[1]

B. N-Nitrosodimethylamine

NDMA is a semi-volatile 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] NDMA 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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[1] See FDA's *Approved Drug Products With Therapeutic Equivalence* Evaluations (the Orange Book) (available at https://www.accessdata.fda.gov/scripts/cder/ob/) for a full listing of approved metformin drug products.

[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.

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]

NDMA is one compound included in a class of compounds referred to as nitrosamines. The International Council for Harmonisation (ICH) addressed the need for control of nitrosamines in pharmaceuticals in the guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018) (ICH M7).[11] A chemical that is a probable carcinogen may increase the risk of cancer in humans, and this guidance explains how to calculate an *acceptable intake* for NDMA that would be considered reasonably safe for human ingestion.[12] An acceptable intake for NDMA has been calculated as 96 nanograms (ng) per day.[13] The maximum daily dose of metformin is

[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] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] ICH M7 at 128 defines an *acceptable intake* as an intake level that poses negligible cancer risk, or for serious/life threatening indications where risk and benefit are appropriately balanced.

[13] It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. For the nitrosamine NDMA, that limit is 96 ng/day for a single drug product. The conversion of acceptable intake (AI) limit into parts per million (ppm) varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

2000 mg for ER and 2550 mg for IR. The acceptable intake for NDMA in metformin ER is therefore 0.048 parts per million (ppm), and for metformin IR, is 0.038 ppm.

C. Legal Framework for the Recall of Drug Products

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.[14] 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.[15] The introduction or delivery for introduction into interstate commerce of any drug that is adulterated[16] or misbranded[17] is a violation of section 301(a) of the FD&C Act (21 U.S.C. 331(a)).

A recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers.[18] Recalls are an effective method of removing or correcting defective FDA-regulated products that have been distributed commercially, particularly when those products present a danger to health.[19] They are generally a voluntary action by manufacturers and distributors to protect the public health from products that present a risk of injury.[20] A recall may be undertaken voluntarily at any time by manufacturers and distributors,

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

[15] 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) (draft guidance on *Initiation of Voluntary Recalls)* at 9. FDA is committed to working cooperatively with a recalling firm whenever possible to facilitate the orderly and prompt removal of, or correction to, a violative product in the marketplace, particularly when the product presents a danger to health. When final, this guidance will represent FDA's current thinking on this topic.

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

[17] Under section 502(j) of the FD&C Act, a drug will 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 sections 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 352(a)(1)).

[18] 21 CFR 7.3(g).

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

[20] Id.; see also the FDA draft guidance on *Initiation of Voluntary Recalls* and the FDA guidance *Public Warning*

or initiated at the request of FDA when there is an urgent situation.[21] FDA generally directs a recall request to the firm that has primary responsibility for the manufacture and marketing of the product.[22] A recall is generally more appropriate and affords better protection for consumers than seizure, which requires legal action and a court order, particularly when many lots of product have been widely distributed.[23] As described in guidance, firms in a product distribution chain should be "recall ready" to help minimize public exposure to products in violation of the FD&C Act and other laws administered by FDA.[24] The Agency will work with manufacturers and distributors to develop a recall strategy and to publicize information to the public. FDA will monitor the effectiveness of any recall and take additional action as appropriate.

II. FDA ANALYSIS OF NDMA IN METFORMIN

In the summer of 2018, FDA recognized that the active pharmaceutical ingredient (API) in valsartan, an angiotensin II receptor blocker (ARB) used to treat high blood pressure and heart failure, contained NDMA at levels that were unacceptable. This unexpected finding led to an investigation during which FDA found this impurity, and other nitrosamines, in APIs from multiple API producers of valsartan and in other drugs in the ARB class; however, not all drugs in the ARB class contained nitrosamine impurities. Based on information from its own investigation and investigations being conducted by applicants, FDA announced the recall of drug products containing these nitrosamine impurities above the acceptable intake limit.[25]

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and Notification of Recalls Under 21 CFR Part 7, Subpart C (February 2019). With limited exceptions not applicable here, FDA does not have authority under the FD&C Act to order a firm to recall a violative drug product.

[21] §§ 7.40(b), 7.45, and 7.46; see also the FDA draft guidance on *Initiation of Voluntary Recalls*. 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.

[22] § 7.40(b).

[23] § 7.40(c).

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

[25] For further discussion, see FDA webpage on voluntary recall of several medicines containing valsartan following detection of an impurity, available at https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.

Subsequently, FDA investigated a concern about NDMA impurities in ranitidine, a heartburn medication, which resulted in a number of product recalls, and ultimately a recommendation by FDA that manufacturers implement a market withdrawal of all ranitidine drug products.[26]

In light of that background, FDA evaluated information from international regulators that some regulators had observed low levels of NDMA in certain lots of metformin. FDA promptly notified the public of this information, issuing a statement on December 5, 2019.[27] Based on the information available at that time, the levels seen outside of the United States were within the range of NDMA naturally occurring in some food and water. No products in the United States had NDMA levels above what the Agency considered acceptable. However, based on the initial information from international regulators, FDA began to purchase metformin drug products to conduct its own testing for NDMA.

On February 3, 2020, FDA posted 10 test results on the FDA Metformin web page that showed either no detectable levels of NDMA, or low levels of NDMA that were below the acceptable intake for NDMA. These samples had been tested by FDA's Office of Testing and Research (OTR) using a laboratory test method developed and verified for NDMA in metformin.[28] The test methodology was also published on the web page.[29] FDA will update this web page with information about the request to recall identified lots of metformin ER.

III. DISCUSSION

Your Petition requests five actions based on testing conducted by Valisure. We are limiting this response to your first request, which asks FDA to request the recall of 16 identified lots of metformin that, based on Valisure test results, exceed the acceptable intake limit for NDMA. We are granting that request in part and denying it in part.

According to the Petition, Valisure acquired 38 lots of metformin, both ER and IR formulations, sold by 22 different companies, from its pharmacy suppliers, and tested these metformin products for NDMA (Petition at 4).[30] You state that 16 of these lots of metformin drug products

[26] For further information on the voluntary recall and market withdrawal of ranitidine see https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine.

[27] See FDA webpage on NDMA in Metformin, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin (FDA Metformin webpage).

[28] See FDA Metformin webpage available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-metformin.

[29] The FDA testing results were generated using the Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Metformin Drug Substance and Drug Product that was presented by FDA on the FDA Metformin webpage and is available at https://www.fda.gov/media/134914/download. The limit of detection is 1.0 ng/mL or 0.01 ppm. The limit of quantitation is 3.0 ng/mL, or 0.03 ppm. The range is 3.0-10 ng/mL, or 0.03-0.1 ppm.

[30] The Petition apparently counts Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York, LLC

from 11 different companies exceeded the FDA acceptable intake limit for NDMA (Petition at 11-12). You further state that the level of NDMA in these 16 lots ranged from 30 ng/tablet to 529 ng/tablet (Petition at 8-11).[31] You also note that Valisure modified the methodology of the FDA LC-HRMS Metformin test protocol to achieve a lower limit of detection, a lower limit of quantitation and a wider reportable range (the Valisure NDMA test method).[32] The test results presented in the Petition were all obtained by using the Valisure NDMA test method.

After receiving your Petition, FDA accelerated its investigation into the possibility that metformin drug products in the United States contained NDMA, and focused on the identified lots of metformin with NDMA above the acceptable intake as discussed in the Petition. To obtain specific applicant information, on March 31, 2020, FDA sent information requests to the companies holding applications for the metformin drug products that you identified in your Petition as containing NDMA above the acceptable intake. These information requests informed the companies that we received a citizen petition in which their product was identified as having NDMA above the acceptable intake limit, requested that companies verify their drug product does not contain NDMA in amounts above the acceptable intake, requested that companies provide test results, including testing methodology, and requested that companies provide samples of metformin drug products to FDA so that the Agency could perform its own testing.

A. FDA Testing of Metformin for NDMA

FDA started conducting tests of NDMA in metformin in January 2020, and as of May 19, 2020 the Agency has tested 106 metformin samples. Some of the metformin drug product was obtained through pharmacy purchases, some of the product was from samples applicants sent to OTR and some samples were directly provided by Valisure to FDA.[33] Different doses were tested, 500 mg, 750 mg, and 1000 mg, and both IR and ER metformin formulations were tested.

For purposes of responding to this Petition, the most relevant testing conducted by the Agency was testing of the samples of metformin FDA received from the 38 lots Valisure tested.[34] The Petition requests that of these 38 lots of metformin Valisure tested, FDA should request a recall of 16 lots (Petition at 11-12). Based on our test results, FDA has determined that 8 of these identified lots of metformin contain NDMA levels above the acceptable intake limit.[35] Of the 8

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as two different companies. See Petition at 4. For our internal review, we considered them to be one company.

[31] The Petition also indicates the number of tablets that are commonly taken per day. According to the Petition, three tablets from each batch were tested individually and the NDMA detected is reported as an average, along with the standard deviation of the result from the three tablets (Petition at 8).

[32] Petition at 4-8, and Attachment B.

[33] At the request of FDA, Valisure provided the Agency with 10 tablets from each of the 38 lots it had sampled.

[34] Although Valisure requested recall of the specific 16 lots identified in the Petition, it was important for FDA to verify all 38 of the testing results submitted to have confidence in any of the sampling results.

[35] See further discuss below in section III.B.

remaining lots that the Petition asks FDA to recall, 6 were IR tablets, and FDA testing demonstrated that none of the 15 IR lots showed detectable NDMA amounts. Of the remaining two ER lots Petitioner recommended for recall, one had NDMA levels below the acceptable intake limit and one had no detectable NDMA.

FDA has requested that five companies voluntarily recall 8 lots of metformin ER. These requests are based on OTR's testing of NDMA in metformin using the Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) method published by FDA.[36] FDA scientists have confidence that the LC-HRMS method can consistently and accurately determine the level of NDMA in metformin. For each lot, 4 samples were tested, and the LC-HRMS method results were verified by two different validated analytical procedures. The FDA tests used three different liquid chromatography columns and two different ionization sources (electrospray ionization and atmospheric pressure chemical ionization) on a high-resolution mass spectrometry platform. The consistent results from each of these test methods supports the accuracy of FDA's test methodology.

We acknowledge the efforts Valisure has made to identify this impurity in metformin, but the overall disparity between our test results and those of Valisure on the same lots raises questions about the credibility of the results obtained using the Valisure NDMA test methodology. With respect to the 38 samples we obtained from Valisure, in most cases the Valisure results are 2 to 6 times higher than FDA values for the same product. In many cases, Valisure observed NDMA amounts where none is detected by FDA testing (false positives). In several cases, the FDA tests show low levels of NMDA present in lots where Valisure found no detectable levels. Additionally, none of the IR lots FDA tested showed detectable NDMA amounts. Overall, these data suggest that the Valisure NDMA test methodology may not be reliable for detection of NDMA in metformin.[37]

B. Manufacturer Recall and FDA Actions

In general, FDA advises companies to voluntarily recall products when the products present a risk of injury or are in violation of applicable laws and regulations. More specifically, FDA advises firms to take voluntary recall action when laboratory testing using validated test methods confirms that impurity levels in their drug products exceed acceptable intake limits. Based on the results of OTR's testing of metformin ER products, FDA has requested five companies to voluntarily recall certain lots of metformin ER products from the U.S. market. These companies are Amneal Pharmaceuticals (Amneal), Actavis Pharma Inc. (Actavis), Apotex Corp. (Apotex), Lupin Pharma (Lupin), and Marksans Pharma Limited (Marksans).[38]

[36] See footnote 29.

[37] The Petition states that Valisure modified the FDA protocol for testing NDMA in metformin published on the FDA Metformin webpage to improve the precision of the method (Petition at 4). The Petition specifically requests FDA to update and revise FDA's methodology to include the Valisure methodology outlined in the Petition to avoid underestimating NDMA levels (Petition at 2). We are currently evaluating that methodology and will address that request in a separate response.

[38] In the Petition, you identify Time Cap Laboratories, Inc. as a company whose product you tested. For our notification purposes we notified the application holder, Marksans Pharma Limited.

In addition to requesting this voluntary recall, FDA will request that these companies release-test all lots of metformin ER to verify that any N-nitrosamine is not above the acceptable intake limit. FDA is not recommending that manufacturers recall any metformin IR tablets because our testing showed that NDMA levels in the Valisure samples were not detectable.

As a result of OTR's testing, FDA is also sending information request letters to all metformin ER applicants requesting that they assess the risk of NDMA in their products, test their products for NDMA, to confirm that NDMA levels, or other N-nitrosamine levels, are not above the acceptable intake limit, and to send samples of their products to FDA for evaluation.

Accordingly, FDA grants your request to ask for a recall in part. We have requested that Actavis, Amneal, Apotex, Lupin and Marksans voluntarily recall those lots of metformin ER that FDA testing has confirmed have levels of NDMA above the acceptable intake limit. The specific lots included are:

Company	Dose and Formulation	Lot
Actavis	750 mg ER	1354471A
Amneal	750 mg ER	AM18077A
	500 mg ER	AM190107AA
	500 mg ER	HD03319A
	500 mg ER	HM02918A
Apotex	500 mg ER	NE5801
Lupin	500 mg ER	G901203
Marksans	500 mg ER	XP9004

We are denying your request that the Agency ask for a recall of the remaining lots of metformin identified in the Petition.

FDA's investigation into the potential for metformin drug products to contain unacceptable levels of NDMA is continuing. The Agency will continue to update the public, physicians, and other health care providers as we obtain additional information. With respect to the remaining requests in your Petition, we are evaluating those requests and will respond when we have completed our review.

IV. CONCLUSION

For the foregoing reasons, FDA responds to the first request in your Petition asking for FDA to request a recall of identified lots of metformin by granting it in part and denying it in part.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002411843, cn=Patrizia A. Cavazzoni -S
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