May 31, 2020

RE: Request that the FDA recall of identified batches of metformin on the basis that, due to contamination with a probable human human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA

Docket ID: FDA-2020-P-0978

United States Food and Drug Administration

Dear Dr. Cavazzoni,

Thank you for your Partial Response Letter[1] dated May 28, 2020 and for taking action on our FDA Citizen Petition requesting recalls of the drug metformin.[2] We welcomed the opportunity to voluntarily provide samples to the FDA and appreciated the Agency's extensive analysis of these samples. We also applaud the FDA's action to request metformin product recalls from multiple firms[3] in an effort to safeguard the health of the American public.

However, we are very concerned that the current FDA statements target only a subset of the lots and manufacturers identified by Valisure as being unacceptably contaminated. Notably, the FDA has targeted extended release (ER) formulations of metformin, which account for about one quarter of prescriptions,[4] and not the immediate release (IR) formulations, which have also been identified by Valisure to contain unacceptable levels of NDMA. Additionally, the Agency states that their findings of NDMA in metformin "were generally lower than reported by the private laboratory [Valisure]" and the Agency states in its Partial Response Letter that "in most cases the Valisure results are 2 to 6 times higher than FDA values for the same product."

Both the focus on only ER and the Agency's different results from Valisure and Emery Pharma, which validated some samples from Valisure's petition, are very likely explained by the

[1] Partial Response Letter from FDA CDER to Valisure, LLC (May 28, 2020). (https://www.regulations.gov/document?D=FDA-2020-P-0978-0007)
[2] Citizen Petition from Valisure, LLC (March 2, 2020). (https://www.regulations.gov/document?D=FDA-2020-P-0978-0001)
[3] FDA Alerts Patients and Health Care Professionals to Nitrosamine Impurity Findings in Certain Metformin Extended-Release Products (May 28, 2020). (https://www.fda.gov/news-events/press-announcements/fda-alerts-patients-and-health-care-professionals-nitrosamine-impurity-findings-certain-metformin)
[4] Edney, Anna (May 27, 2020). FDA Finds Carcinogen in Some Versions of Popular Diabetes Drug. (https://www.bloomberg.com/news/articles/2020-05-27/fda-finds-carcinogen-in-some-versions-of-popular-diabetes-drug)

Agency's published method for the analysis of metformin not including an internal control.[5] Valisure requested in its March 2, 2020 FDA Citizen Petition that the Agency (highlight added):

4) update and revise FDA guidance document FY20-058-DPA-S,[5] to include the analytical methodology outlined in this petition and in Attachment A for improved quantitation of NDMA in metformin and to avoid underestimation of NDMA levels

In the Agency's Partial Response Letter, it is clear that this same FY20-058-DPA-S method from February 4, 2020 was used for quantitation and this method does not include any internal control. Valisure notes that the FDA performed multiple analyses and "the FDA tests used three different liquid chromatography columns and two different ionization sources" and reports "consistent results."[1] However, without an internal control, different columns or machines are expected to elucidate the same, incorrectly low and biased levels of NDMA.

Isotopic internal controls are considered scientific best practice by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[6] and are industry standard for the analysis of NDMA in complex samples like drinking water,[7] wastewater,[8] soil,[9] food,[10] beverages,[11] biological samples,[12] and pharmaceutical products[13] (including Singapore's published method for NDMA analysis in metformin[14]).

[5] LC-HRMS Method for the Determination of NDMA in Metformin Drug Substance and Drug Product (February 4, 2020). (https://www.fda.gov/media/134914/download)
[6] M10 Bioanalytical Method Validation (June 27, 2019). Regulations.gov. (https://www.regulations.gov/document?D=FDA-2019-D-1469-0002)
[7] U.S. Environmental Protection Agency, Method 521, Determination of Nitrosamines in Drinking Water by Solid Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry (MS/MS), Version 1.0, September 2004.
[8] Ngongang AD, Duy SV, Sauvé S. Analysis of nine N-nitrosamines using liquid chromatography-accurate mass high resolution-mass spectrometry on a Q-Exactive instrument. Analytical Methods. 2015;7(14):5748-59.
[9] Bednar et al., Determination of Low Level NDMA in Soils, U.S. Army Corps of Engineers, ERDC TN-EQT-09-01, December 2009. https://erdc-library.erdc.dren.mil/jspui/bitstream/11681/3699/1/ERDC-TN-EQT-09-01.pdf
[10] Chen et al., High Sensitivity Analysis of Nitrosamines Using GC-MS/MS, ThermoFisher Scientific Application Note 10315.
[11] Tipler, A., The Determination of Low Levels of Nitrosamines in Beer Using the Clarus 680 GC/MS and a D-Swafer System, PerkinElmer Application Note.
[12] Zeng T, Mitch WA. Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. Carcinogenesis. 2016 Jun 1;37(6):625-34.
[13] U.S. Food and Drug Administration, Combined Direct Injection N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), and N-Nitrosodibutylamine (NDBA) Impurity Assay by GC-MS/MS. 2019. https://www.fda.gov/media/123409/download
[14] Health Services Authority of Singapore, Determination of N-nitrosodemethylamine (NDMA) in Metformin Products by HRAM-GCMS, Ver002, May 2020. https://www.hsa.gov.sg/docs/default-source/announcements/safety-alerts/determination-of-ndma-in-metformin-products-by-hram-gcms.pdf

In a draft version of *International Council for Harmonization Guideline M10 - Bioanalytical Method Validation,* the document states "A suitable internal standard (IS) should be added to all calibration standards, QCs and study samples during sample processing."[6]

Valisure's inclusion of an isotopic control in the analysis of the samples in our metformin FDA Citizen Petition further allows for the analysis of recovery efficiency for each sample. When the isotopic control is added at a known amount in the sample, its detected amount in the sample after analysis is compared to the known starting amount to yield the recovery percentage. We have summarized this information for all 38 metformin batches in Table 1 below and in further detail on the 16 failed batches in Table 2.

	ALL	ER	IR
Average Recovery %	34.9%	39.3%	28.8%
Standard Deviation	17.7%	17.3%	16.4%
Number of samples	114	66	48

Table 1: Summarized recovery values of isotopic control for 114 samples (38 batches with 3 tablets each)

Two critical points are illustrated by this data:

1) **Relatively low and variable control recoveries.** *FDA is likely underestimating NDMA contamination in all metformin samples.*
   With an overall average of 34.9% recovery, it would be expected that without the use of an internal control, NDMA quantification would incorrectly be roughly 3 times lower. Furthermore, the high variability in recovery percentages suggests a broad range above and below that value. This aligns closely with the observations stated in the Partial Response Letter.

2) **Significantly lower control recovery for IR than for ER formulations.** *FDA is particularly prone to missing contamination in IR formulations.*
   An important observation is that there exists strong evidence that the ER and IR formulations affect NDMA recovery at different rates, with ER recovery being significantly more efficient than IR recovery. A two-tailed, homoscedastic T-Test comparing ER to IR gives a p value of .001, meaning the lower recovery for IR is strongly statistically significant. This presents a strong case that IR formulations are particularly difficult to analyze and, without using an internal control, the NDMA values for IR will be incorrectly measured even lower than ER samples.

Company	Dose (mg)	Type	Lot	NDC	Exp Date	NDMA (ng/tablet)	FDA Voluntary Recall Request	Average Recovery Efficiency (%)
ACI Healthcare USA, Inc.	500	Metformin IR	D105061	71093-132-06	Aug-22	31 ± 4	No	37.6 ± 3.2
Actavis Pharma, Inc.	500	Metformin ER	1376339M	62037-571-01	Sep-21	182 ± 2	No	58.4 ± 9.3
Actavis Pharma, Inc.	750	Metformin ER	1354471A	62037-577-10	Feb-21	320 ± 25	Yes	62.0 ± 8.2
Amneal Pharmaceuticals LLC	750	Metformin ER	AM180770A	65162-179-10	May-20	450 ± 100	Yes	25.7 ± 6.6
Amneal Pharmaceuticals LLC	500	Metformin ER	AM190107AA	65162-178-10	Dec-20	395 ± 53	Yes	59.1 ± 39.5
Amneal Pharmaceuticals of New York LLC	500	Metformin ER	HD03319A	53746-178-90	Apr-21	283 ± 27	Yes	45.4 ± 15.8
Amneal Pharmaceuticals of New York LLC	500	Metformin ER	HM02918A	53746-178-01	Jan-21	282 ± 67	Yes	30.5 ± 10.6
Amneal Pharmaceuticals of New York LLC	850	Metformin IR	AM180405A	53746-219-05	Mar-20	235 ± 17	No	14 ± 1.6
Apotex Corp.	500	Metformin ER	NE5801	60505-0260-1	Apr-21	90 ± 3	Yes	53 ± 3.4
Ascend Laboratories, LLC	1000	Metformin IR	4200061B	67877-563-01	May-22	529 ± 107	No	25.9 ± 14.7
Aurobindo Pharma Limited	500	Metformin IR	MTSA19016-B	65862-008-01	Jan-23	30 ± 7	No	27.9 ± 8.5
Granules Pharmaceuticals Inc.	500	Metformin ER	4910134A	70010-491-01	Jun-22	41 ± 5	No	28.9 ± 16.3

Heritage Pharmaceuticals Inc.	850	Metformin IR	4510157A	23155-103-10	Apr-22	254 ± 12	No	58.4 ± 2.5
Heritage Pharmaceuticals Inc	500	Metformin IR	4500753A	23155-102-01	Apr-22	206 ± 20	No	20.0 ± 7.2
Lupin Pharmaceuticals, Inc.	500	Metformin ER	G901203	68180-336-07	Dec-20	122 ± 11	Yes	24.9 ± 5.2
TIME CAP LABORATORIES, INC	500	Metformin ER	XP9004	49483-623-01	Dec-20	53 ± 12	Yes	43.7 ± 11.3

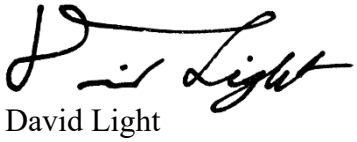
Table 2. Sixteen metformin products for which Valisure requested recalls annotated with the FDA recall decision and recovery efficiency as an average and standard deviation of triplicate measurements.

These details are extremely important as roughly 18 million Americans[15] are currently taking metformin and approximately 13 million Americans are currently taking IR formulations of metformin. All are at risk of continued exposure to unacceptable levels of NDMA.

Valisure is willing to voluntarily provide further samples of tablets from all 38 batches identified in our March 2, 2020 FDA Citizen Petition, if useful, or provide any assistance the Agency deems helpful.

[15] Graedon, Joe (May 28, 2020). ALERT | Metformin Carcinogen Contamination Confirmed! (https://www.peoplespharmacy.com/articles/alert-metformin-carcinogen-contamination-confirmed)

Respectfully submitted,



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