July 6, 2020

RE: Request that the FDA to issue a regulation, revise industry guidance, and take such other actions

Docket ID: FDA-2019-P-2869

Filed June 13, 2019

United States Food and Drug Administration

Dear Sir or Madam:

We are writing in addendum to Valisure's FDA Citizen Petition filed June 13, 2019 regarding detecting very high levels of the probable human carcinogen N,N-Dimethylformamide ("DMF") in specific lots of metformin drug products. Specifically, we report below (Table 1) DMF levels detected in metformin products previously described in Valisure's FDA Citizen Petition on metformin (FDA-2020-P-0978)[1] and using the United States Pharmacopeia method for detection and quantification of residual solvents. In many cases, levels of DMF in metformin drug products tested exceed the high levels found in valsartan drug products reported June 13, 2019 and can expose patients to DMF in the order of milligrams per week. These findings of DMF in metformin are in agreement with the recent FDA statement posted July 2, 2020 on metformin[2] where the "interfering substance" is DMF.

As stated in our petition, DMF is a chemical that was reclassified in 2018 as a Group 2A probable human carcinogen by the World Health Organization ("WHO") and International Association for Research of Cancer ("IARC").[3] DMF is classified by the FDA as a Class 2 solvent[4] and is commonly used in the production of pharmaceutical active ingredients. According to the FDA, Class 2 solvents "should be limited in pharmaceutical products because of their inherent toxicity."[5] Petitioner notes that the WHO and IARC reclassified DMF to Group 2A probable human carcinogen status in 2018, while the most recent revision of the FDA regulation of residual solvents is dated June 2017. Thus, Valisure requests an expeditious review of DMF in

[1] Light, David; Kucera, Kaury (June 13, 2019). Request that the FDA to issue a regulation, revise industry guidance, and take such other actions. *FDA Citizen Petition*. (https://www.regulations.gov/docket?D=FDA-2019-P-2869)
[2] Food and Drug Administration. "7/2/2020: UPDATE – The AAPS Journal publishes FDA paper on metformin testing."
[3] International Agency for Research on Cancer and World Health Organization, *IARC Monographs on the Identification of Carcinogenic Hazards to Humans,* Volume 47, 71, 115 (2018). (https://monographs.iarc.fr/list-of-classifications-volumes/)
[4] Food and Drug Administration, *Q3C – Tables and List* (June 2017), page 3. (https://www.fda.gov/media/71737/download)
[5] *Id.* at 6.

drug products and that the FDA take action to significantly lower the acceptable daily intake limit for DMF.

Metformin is now the second major drug product to be recalled for N-Nitrosodimethylamine ("NDMA") contamination that appears to concurrently contain very high levels of DMF. As is suggested from the valsartan contamination case, DMF can form NDMA,[6] further making it a potentially dangerous impurity that appears to be increasingly found in conjunction with NDMA. Furthermore, as mentioned in Valisure's DMF petition, a review by the California Environmental Protection Agency had expressed concern regarding the potential genotoxicity and permeation-enhancing activity of DMF whereby it "may act as an escort to facilitate the easy entry of either endogenous or exogenous carcinogens."[7] As FDA's July 2, 2020 post and linked FDA analytical paper describe, the DMF contamination is so large it can make the precise determination of NDMA levels difficult, though the permeation-enhancing activity of DMF can make any detectable level of NDMA potentially dangerous.

In our petition, we requested that FDA revise the standards for limits on DMF in medications. In light of recent findings and recalls of metformin drug products, we further urge the FDA to investigate and address our requests from Valisure's June 13, 2019 Citizen Petition and to include metformin drug products as part of the agency's consideration.

Labeler	Dose (mg)	Type	Lot	NDC	Exp Date	DMF ng/tablet	CV	DMF Exposure milligrams/week
ACI Healthcare USA, Inc.	500	IR	D105061	71093-132-06	Aug-22	3,000	8%	0.09
ACI Healthcare USA, Inc.	500	IR	C105019A	71093-132-04	Feb-21	3,500	17%	0.09
ACI Healthcare USA, Inc.	500	IR	D105019	71093-132-05	Mar-22	3,000	7%	0.08
Actavis Pharma, Inc.	500	ER	1376339 M	62037-571-01	Sep-21	54,500	10%	1.52
Actavis Pharma, Inc.	750	ER	1354471A	62037-577-10	Feb-21	114,000	15%	1.60
AiPing Pharmaceutical, Inc.	500	ER	190300211	11788-037-60	Feb-21	4,000	12%	0.11
AiPing Pharmaceutical, Inc.	1000	ER	190200411	11788-038-60	Jan-21	7,000	15%	0.10
American Health Packaging/(Zydus)	1000	IR	184759	60687-162-01	Sep-20	7,000	9%	0.10

[6] Anna Edney, Susan Berfield & Evelyn Yu, *Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.*, BLOOMBERG BUSINESSWEEK, Sept. 12, 2019. (https://www.bloomberg.com/news/features/2019-09-12/how-carcinogen-tainted-generic-drug-valsartan-got-past-the-fda)

[7] California Environmental Protection Agency, *Evidence on the Carcinogenicity of N,N-Dimethylformamide (Draft)* (August 2008), page 31. (https://oehha.ca.gov/media/downloads/proposition-65/chemicals/dmfhid080808.pdf)

Amneal Pharmaceuticals LLC	750	ER	AM180770A	65162-179-10	May-20	112,000	22%	1.57
Amneal Pharmaceuticals LLC	500	ER	AM190107AA	65162-178-10	Dec-20	64,000	21%	1.79
Amneal Pharmaceuticals of New York LLC	500	ER	HD03319A	53746-178-90	Apr-21	51,500	18%	1.44
Amneal Pharmaceuticals of New York LLC	500	ER	HM02918A	53746-178-01	Jan-21	57,000	14%	1.59
Amneal Pharmaceuticals of New York LLC	850	IR	AM180405A	53746-219-05	Mar-20	71,500	17%	1.00
Apotex Corp.	500	ER	NE5801	60505-0260-1	Apr-21	6,000	16%	0.17
Apotex Corp.	750	ER	NG2595	60505-1329-1	May-20	< 500	--	--
Ascend Laboratories, LLC	1000	IR	4200061B	67877-563-01	May-22	118,500	22%	1.66
Ascend Laboratories, LLC	500	IR	4980028B	67877-561-01	May-21	6,000	17%	0.17
Ascend Laboratories, LLC	1000	IR	4200024C	67877-563-01	Jan-21	12,500	17%	0.17
Aurobindo Pharma Limited	500	IR	MTSA19016-B	65862-008-01	Jan-23	7,500	14%	0.21
Aurobindo Pharma Limited	500	IR	MTSA19070-C	65862-008-99	Jul-22	6,500	11%	0.19
EPIC PHARMA, LLC	500	ER	190101111	42806-405-60	Dec-20	3,500	16%	0.10
Granules Pharmaceuticals Inc.	500	ER	4910134A	70010-491-01	Jun-22	9,500	4%	0.27
Heritage Pharmaceuticals Inc.	850	IR	4510157A	23155-103-10	Apr-22	146,500	12%	2.05
Heritage Pharmaceuticals Inc.	500	IR	4500753A	23155-102-01	Apr-20	62,500	18%	1.75
Heritage Pharmaceuticals Inc.	1000	IR	4521630A	23155-104-10	Jun-22	13,000	16%	0.18
Ingenus Pharmaceuticals, LLC	1000	ER	19388005	50742-634-60	Dec-20	11,500	15%	0.16
Lupin Pharmaceuticals, Inc.	500	ER	G901203	68180-336-07	Dec-20	18,000	30%	0.51
Megalith Pharmaceuticals Inc	1000	IR	442180318	71717-106-11	Feb-20	5,500	13%	0.07
Mylan Pharmaceuticals Inc.	1000	ER	3090719	0378-6001-91	Sep-20	14,000	18%	0.19
Nostrum Laboratories, Inc.	1000	ER	MEF290206	29033-032-06	Apr-21	8,500	12%	0.12
Oceanside Pharmaceuticals	500	ER	19D125P	68682-021-50	Mar-23	< 500	--	--
Sun Pharmaceutical Industries, Inc.	750	ER	JKU0880A	62756-143-01	Feb-22	7,500	13%	0.10

Sun Pharmaceutical Industries, Inc.	500	ER	JKU2539A	62756-142-02	Jun-22	4,500	14%	0.13
TAGI Pharma, Inc.	500	ER	5841910035	51224-007-50	Oct-21	5,000	21%	0.13
TAGI Pharma, Inc.	500	ER	5841905129	51224-007-60	May-21	5,500	8%	0.15
TIME CAP LABORATORIES, INC	500	ER	XP9004	49483-623-01	Dec-20	5,000	12%	0.14
Westminster Pharmaceuticals, LLC	500	IR	B105067B	69367-180-05	Oct-20	3,000	7%	0.08
Westminster Pharmaceuticals, LLC	1000	IR	B107261B	69367-182-05	Oct-20	< 500	--	--

Table 1. Metformin products for which Valisure previously included NDMA information annotated with DMF detection. Levels are reported as the average of three or more measurements and the CV for replicates is reported. DMF exposure in milligrams per week is calculated assuming the common maximum daily intake of metformin of 2000 mg.

Valisure used the USP <467> Residual Solvents method to screen metformin drug products. Specifically, Analytical Procedures for Class 1 and Class 2 Residual Solvents and a GC-MS with headspace injection and modified to use mass spectrometry detection. Parameters including the split ratio were optimized for detection of DMF resolution and sensitivity. An Agilent 7697A Headspace Sampler, 7890B GC System, and 5977B Mass Selective Detector were used. All samples were prepared with approximately 500 mg powdered and homogenized material and levels of DMF measured were adjusted for individual tablet sampling. Samples included a deuterated DMF standard to determine recovery across samples (data not shown). The lower limit of detection for this method is 500 ng DMF and the lower limit of quantification is 1,500 ng DMF per sample.

The USP <467> Residual Solvents method described above has less sensitivity for DMF than the method described in Valisure's DMF petition, which has a lower limit of detection of 25 ng. Valisure's petition utilized FDA recommended NDMA and N-Nitrosodiethylamine ("NDEA") combined detection method utilizing GC/MS headspace analysis (FY19-005-DPA[8]). The DMF contamination levels in metformin are significantly higher than that observed in valsartan and therefore a less sensitive but regulatory-accepted method was used, which was still able to detect these elevated contamination amounts in most products.

[8] Food and Drug Administration, *Combined N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay,* FY19-005-DPA-S (January 2019). (https://www.fda.gov/media/117843/download)

In summary, the probable human carcinogen DMF continues to significantly contaminate drug products in the United States including not only valsartan, but also metformin. Valisure detected levels of DMF in metformin that exceed those detected in valsartan and in some cases appear to expose patients to over 2 milligrams of DMF per week. Valisure reiterates its request from June 13, 2019 that the FDA review and significantly lower the acceptable intake/permitted daily exposure limit of DMF and investigate products with high levels.

Respectfully submitted,

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