June 12, 2020

David Light
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5 Science Park
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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). On May 28, 2020, the Food and Drug Administration (FDA or Agency) partially responded to this Petition to address a safety concern you raised in the first request in this Petition. That request asked FDA to recommend the recall of specific metformin products containing N-Nitrosodimethylamine (NDMA) in levels above the acceptable intake limit. Our partial response stated that the Agency recommended that five companies recall certain lots of metformin extended release (ER).[1] We noted that the Agency needed more time to respond to the remaining requests. This letter responds to the remaining four requests, which ask FDA to take the following actions:

- Conduct examinations and investigation under section 702(a) of the Federal Food, Drug and 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

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

- 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 level

[1] Subsequently, Amneal Pharmaceuticals, LLC (Amneal) announced a recall on June 1, 2020, and Marksans Pharma Ltd. (Marksans) announced the recall of the Time-Cap Labs, Inc. brand on June 5, 2020. Teva Pharmaceuticals USA, Inc. (Teva).announced a recall of the Actavis brand, and Apotex Corp. (Apotex) announced a recall of its products on June 5, 2020. Lupin Pharmaceuticals, Inc. (Lupin) announced a recall of one lot of its metformin ER product on June 11, 2020. See FDA's Recalls web page, available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts.

- 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.[2]

We have carefully considered your Petition, comments to the docket, and other information available to the Agency. We grant the first two requests and deny the remaining requests in the Petition.

I. BACKGROUND

A. FDA's Actions Regarding Metformin and Possible NDMA Impurities

Metformin hydrochloride (metformin) is an oral antihyperglycemic drug approved for the management of type 2 diabetes.[3] 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 (ER) tablets is 2000 milligrams (mg) in adults, and the maximum recommended daily dose of metformin immediate-release (IR) is 2550 mg.

NDMA has been classified as a probable carcinogen by the International Agency for Research on Cancer (IARC).[4] 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).[5] 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.[6] An acceptable intake for NDMA has been

[2] Petition at 2.

[3] 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.

[4] See original IARC review, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 1 (1972) NDMA at 95; IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, Vols. 1 to 42 (1987); Supp 7, NDMA at 67 (The 1987 IARC update for carcinogenic classification identifies NDMA as "Group 2A: Probably carcinogenic to humans."); as stated in supplement 7 (at page 31), the Group 2A "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." See, generally, IARC Monographs on the Identification of Carcinogenic Hazards to Humans, Amended Preamble, January 2019.

[5] 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.

[6] 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.

calculated as 96 nanograms (ng) per day.[7] Based on the maximum daily dose of metformin, 2000 mg for ER and 2550 mg for IR, the acceptable intake for NDMA in metformin ER is 0.048 parts per million (ppm), and for metformin IR, is 0.038 ppm.

FDA began an investigation into the possible presence of NDMA in metformin in December 2019. After FDA's Office of Testing and Research (OTR) tested samples of metformin, on February 3, 2020, FDA posted 10 test results on its website that showed either no detectable levels of NDMA, or low levels of NDMA that were below the acceptable intake for NDMA.[8] OTR tested these samples using a laboratory test method developed and validated for NDMA in metformin. The test methodology was also published on FDA's Metformin web page.[9]

After receiving Valisure's Petition, FDA informed applicants whose products had been identified in the Petition as having levels of NDMA above the acceptable limit and requested that they test their products to verify that they do not contain NDMA at unacceptable levels. The Agency also requested that these companies provide the Agency with product samples so that the Agency could conduct its own testing for NDMA in metformin. Additionally, FDA asked Valisure for samples of the metformin drug products it tested to verify the testing results Valisure obtained on 38 products identified in the Petition. FDA tested these products.

On May 28, 2020, FDA granted in part the first request in Valisure's Petition and announced that it had recommended to five companies that they recall their metformin ER products because FDA testing indicated that these products contained NDMA in levels above the acceptable limit. It also updated its Metformin web page to provide patients and healthcare professionals information on which products were recalled, and to remind patients to contact healthcare professionals before stopping any medication. Shortly thereafter, FDA published the companies' recall notifications.[10] On June 1, 2020, Amneal announced the recall of its lots of metformin ER, and on June 5, 2020, Apotex, Teva and Marksans announced the recall of their affected ER metformin products. Lupin announced the recall of a lot of metformin ER on June 11, 2020.

To ensure that other metformin ER products did not contain NDMA above the acceptable intake

[7] 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 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)).

[8] These and other test results are available on FDA's web page on metformin, which is available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin (Metformin web page).

[9] 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 web page and is available at https://www.fda.gov/media/134914/download. The limit of detection is 1.0 ng/milliliter (mL) or 0.01 ppm. The limit of quantitation is 3.0 ng/mL, or 0.03 ppm. The range is 3.0 to 10 ng/mL, or 0.03 to 0.1 ppm.

[10] See FDA's Recalls web page, available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts. See also Metformin web page, footnote 8.

limit, FDA sent information requests to all metformin ER applicants with product on the market, requesting that they review their manufacturing procedures to look for the potential risk of NDMA impurities in their products. The information requests asked applicants to test specifically for NDMA and stated that the testing should be performed using FDA's published method or another validated method that has been demonstrated to be equivalent to the published FDA method. Applicants were asked to provide the full method verification package if their product is tested using an FDA published method, or to provide the method validation package if a method other than the FDA method is used. Also, as part of its investigation, FDA requested applicants to provide to the Agency samples of their metformin ER product that represented different times during the product's shelf-life.

On June 5, 2020, FDA provided an update on its sampling results for metformin products on the Metformin web page. And on June 9, 2020, the Agency also released details of an additional testing method that other regulators and industry could use to test for NDMA in metformin.[11] This alternative test protocol is a liquid chromatography-electrospray ionization-high resolution mass spectrometry testing method that can detect eight different nitrosamine impurities, including NDMA, in metformin drug substances and drug products. This validated, orthogonal method was used by FDA to confirm OTR's testing results with the original Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) method.[12] This second method has a slightly better limit of quantitation for NDMA than the original method (0.01 versus 0.03 ppm). Although the method can detect additional nitrosamines in metformin, to date only NDMA has been detected.

B. Legal Framework

1. Inspections and Examinations Conducted by FDA

Under section 704(a)(4)(A) of the FD&C Act, FDA may conduct factory inspections to obtain records from an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a drug in advance or in lieu of an inspection. Section 704(a)(1) of the FD&C Act broadly defines factory, warehouse or establishment inspections to include such facilities where prescription drugs or nonprescription drugs are manufactured, processed, packed or held, and includes inspection of records, files, papers processes, controls and facilities. Furthermore, FDA may request and evaluate information from applicants and manufacturers to ensure that approved drug products continue to be safe and effective, and to ensure that drug products meet applicable standards under current good manufacturing practice (CGMP).[13] The

[11] This additional test methodology is available at https://www.fda.gov/media/138617/download.

[12] See footnote 10.

[13] The regulations in parts 210 and 211 (21 CFR parts 210 and 211) contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the FD&C Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess (21 CFR 210.1(a)). The failure to comply with any regulation set forth in parts 210 or 211 will render such drug to be adulterated under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), and such drug, as well as the person who is responsible for the failure to comply, will be subject to regulatory action (§

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

2. Providing Information to the Public

FDA makes it a priority to disclose information to the public on drugs that may harm the public health. The recall regulations specifically address the need for FDA to issue public warnings when there is a company-initiated or FDA-recommended recall of a product under 21 CFR part 7, subpart C (7.42(b)(2)).[16] The purpose of a public warning under this section is to alert the public that a product being recalled presents a serious health risk. FDA may issue public warnings in a variety of forms, including but not limited to press releases, emails, and web and social media postings.[17] It is important that a public warning be distributed in a way that ensures that the information conveyed in the warning reaches the public.

Timely communication of important drug safety information provides healthcare professionals, patients, consumers and other interested persons with access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed treatment choices.[18]

210.1(b)). The term "manufacture, processing, packing or holding of a drug product" includes packaging and labeling operations, testing, and quality control of drug products (21 CFR 210.3(b)(12)).

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

[15] 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)).

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

[17] Id. at 5 and 10.

[18] See generally, FDA draft guidance for industry *Drug Safety Information – FDA's Communication to the Public* (March 2012, Revision 1) (when final, this guidance will represent FDA's current thinking on this topic); FDA guidance for industry *Drug Safety Information – FDA's Communication to the Public* (March 2007).

3. Laboratory Testing and Analysis

FDA has authority to regulate and oversee certain laboratory testing as it relates to the pharmaceutical industry.[19] When an analytical procedure is used as part of a new or abbreviated drug application or a biologics license application, it becomes the FDA-approved analytical procedure for the approved product.[20] Analytical test procedures that support other Agency regulatory decisions, such as approvals of supplements, must also be based on approved procedures that are suitable for their intended purpose.[21] Similarly, manufacturers must rely on validated or approved test procedures in making manufacturing decisions.[22] An approved analytical procedure may originate from FDA-recognized sources (e.g., a compendial procedure from the U.S. Pharmacopeia/National Formulary) or a validated procedure an applicant submitted that was determined to be acceptable by FDA.[23] An analytical procedure is developed to test a defined characteristic of the drug substance or drug product against established acceptance criteria for that characteristic. Similarly, testing for impurities must meet FDA's standards regarding the use of accepted analytical procedures.[24]

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[19] General regulations for laboratory controls are found at § 211.160; regulations concerning the documentation of test methods are found at § 211.165(e) and regulations relating to laboratory records are found at § 211.194.

[20] See 21 CFR 314.50(d)(1), 314.94(a)(9), 601.2; see also FDA guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* at 2-3 (July 2015) (guidance on Analytical Procedures and Methods Validation).

[21] See 21 CFR 314.70(e) "an applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate lack of adverse effect for specific types of manufacturing changes on the identity, strength, quality, purity and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."

[22] See 21 CFR 211.22 (Responsibilities of quality control unit), 211.80 Control of components – general requirements), 211.84 (Testing and approval or rejection of components), 211.100 (Production and Controls, written procedures, deviations), 211.160 (Laboratory Controls – general requirements), 211.165(a) and (e) (Testing and release for distribution); see also, FDA guidance for industry on *Analytical Procedures and Methods Validation* at 2 (a risk-based approach on the need for revalidation of existing analytical methods may need to be considered when the manufacturing process changes during the product's life cycle).

[23] FDA guidance for industry on *Analytical Procedures and Methods* at 3; see 21 CFR 314.50(d)(1)(i) and (ii) and 314.94(a)(9)(i), citing to § 314.50(d)(1). Subsection 314.50(d)(1)(i) requires submission of "specifications necessary to ensure the identity, strength, quality, and purity of the drug substance…, including for example, tests, analytical procedures, and acceptance criteria related to stability, sterility, particle size and crystalline form. The NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph." Similar language appears in 314.50(d)(1)(ii) with respect to a drug product. See also 21 CFR 601.2(a) and 601.2(c) regarding biologics and the need to meet requirements for safety, purity and potency.

[24] See 21 CFR 211.165(e) "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2)." See also ICH guidance for industry *Q3A Impurities in New Drug Substances* at 4 (June 2008 (Revision 2)) (an applicant should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B guidances on analytical validation); ICH guidance for industry *Q3B(R2) Impurities in New Drug Products* at 3 (July 2006 (Revision 2)) (an applicant should include documented evidence that the analytical procedures have been validated

Testing for impurities can be either a quantitative test for the content of the impurities or a limit test for the control of impurities, and the analytical procedures used must be validated.[25] Validation is the process of demonstrating that an analytical procedure is suitable for its intended purpose.[26] As indicated above, validation can be through use of a compendial analytical procedure or a procedure previously agreed upon by FDA. Otherwise validation will need to be established[27] and submitted to the Agency.[28] The objective of the analytical procedure should be clearly understood by the entity developing the test procedure because this will govern the validation characteristics that will be evaluated. Typical validation characteristics for an impurity include: accuracy, repeatability (precision), specificity, detection limit, quantitation limit, linearity and range.[29] Developing and validating a method requires selecting appropriate analytical techniques, optimizing operation conditions, and designing strategies for sample and standard preparations. A method developed and validated for certain types of drugs or formulations is not appropriate for use on other drugs or formulations without separate validation.

II. DISCUSSION

Your Petition contains four outstanding requests based on metformin testing conducted by Valisure. We are granting the requests that FDA conduct investigations and provide information to the public. We are denying your requests that FDA adopt your testing protocol for NDMA in metformin as described in the Petition and that the Agency promulgate regulations requiring (and in the interim, publish guidance recommending) independent third-party testing of all pharmaceuticals.

A. FDA Has Investigated Whether Certain Metformin Products Contain NDMA Impurities and Provided That Information to the Public

As discussed above, FDA began an investigation in December 2019 into potential NDMA impurities in metformin. By May 28 when we confirmed that some metformin products should

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and are suitable for the detection and quantitation of degradation products (see ICH Q2A and Q2B guidances on analytical validation).

[25] 21 CFR 211.165(e); 21 CFR 211.194((a)(2) Records shall include a statement on the location of the data that established the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. See also ICH guidance for industry *Q2A Text on Validation of Analytical Procedures* at 2 (March 1995).

[26] ICH guidance for industry *Q2B on Validation of Analytical Procedures: Methodology* at 1 (November 1996).

[27] 21 CFR 211.160; 211.165(e), and 211.194.

[28] 21 CFR 314.50(d)(1)(i)(ii) and 314.94(a)(9) and see footnote 24.

[29] See footnotes 25 and 26. In November 2005, ICH incorporated the guidance Q2B on methodology with the parent guidance Q2A and retitled the combined document *Q2(R1) Validation of Analytical Procedures: Text and Methodology*; see FDA guidance on *Analytical Procedures and Methods Validation* at 3 and 7.

be recommended for recall, we also recognized we needed to alert all application holders of metformin ER products that we had measured NDMA in some metformin ER products above the acceptable intake limit. We requested that applicants verify their products do not contain NDMA, or any other nitrosamine impurity, in amounts that might expose patients to NDMA or any other nitrosamine above the acceptable limits. At the same time, we requested that applicants provide information to the Agency on the potential risk for their products to contain NDMA, and to provide information on testing. We note that your request for examinations and investigations includes a request for effective labeling revisions as needed. Based on our investigation, we have determined that at this time, no labeling changes are recommended. Our investigation continues as the Agency receives and evaluates responses to information requests from applicants.

Additionally, as noted above, FDA has been providing information to the public on a regular basis about the recalls and our investigation into NDMA impurities in metformin.[30]

B. Valisure's Methods for Testing NDMA in Metformin

In the Petition, you request that FDA revise its testing methodology for the analysis of NDMA in metformin to include those methods used by Valisure and described in the Petition (Petition at 5-8 and Attachment A). You state that Valisure's test method improves and optimizes the test method identified by FDA by using Valisure's in-house instrumentation to achieve a lower limit of detection, lower limit of quantitation and wider reportable range, and that Valisure's test method has a lower risk of underestimating NDMA levels than FDA's methodology (Petition at 8, Attachment A at 1).

FDA has reviewed the information you provided on its testing methodology, and based on the data provided, we conclude that the Valisure method has not been appropriately validated to demonstrate its specificity for measuring NDMA in metformin. Specifically, we do not agree that the method is suitable for analysis of NDMA in metformin drug products because it fails to account for an interfering substance.

FDA's analysis of the samples tested by Valisure reveals a clear correlation between the NDMA values reported by Valisure and the amount of dimethylformamide (DMF)[31] in these samples. In the Valisure method, DMF and NDMA co-elute[32] and if sufficient mass accuracy[33] is not applied

[30] See Section I.A.

[31] DMF is a common solvent used in pharmaceutical manufacturing and residual levels in drug products are allowed up to 880 ppm. ICH guidance for industry *Q3C (R6) Impurities: Residual Solvents* (October 2016).

[32] Co-elution occurs when two or more compounds do not chromatographically separate because both compounds have retention times that differ by less than the resolution of the method.

[33] Mass accuracy is defined by an equation that averages the number of individual mass errors, where a mass error is defined as the difference between the accurate measured mass and the expected or calculated exact mass. For further discussion, see Brenton, AG and Godfrey, AR, "Accurate Mass Measurement: Terminology and Treatment of Data" J Am Soc Mass Spectrom., vol 21: 1821-1835 (2010).

in the measurement or analysis, the presence of certain nitrogen isotopes in DMF that cause it to have similar (but not exactly the same) mass as NDMA will interfere with the detection and quantitation of NDMA. In contrast, the FDA published test methodology applies the appropriate mass accuracy to distinguish DMF from NDMA. FDA's testing shows little correlation between DMF amounts present in the samples and the measured amount of NDMA in the same Valisure-submitted samples. Our data suggest DMF is an interfering substance in the Valisure results. This interference makes the reported NDMA values unreliable and raises questions about the validity of the protocol because it cannot meet the validation standard for specificity.

Valisure's analytical procedure uses an isotope-enriched NDMA standard as an internal control, which we agree is a common control approach used in LC-MS based measurements. The purpose of a stable isotope enriched standard for NDMA in mass spectrometry-based detection is to control for losses that may occur in the native unlabeled NDMA impurity in the metformin tablet during preparation of the sample for analysis or during the mass spectrometry measurement. Such losses may occur if the tablet composition, including the excipients and drug substance (the matrix), impacts the recovery of NDMA in the sample preparation steps or impacts the measurement of NDMA in the mass spectrometer from tablet to tablet. An internal standard can control for such matrix effects.

However, a suitable protocol for the measurement of an analyte should control for substances that interfere with the quantification of the analyte. In this case, DMF, which shares similar physicochemical properties with NDMA, may be present in the metformin as a residual solvent. As a result, testing metformin appropriately for NDMA requires the application of sufficient mass accuracy to distinguish NDMA from DMF. Valisure's method did not apply sufficient mass accuracy to distinguish the DMF impurity from the NDMA impurity. It is FDA's opinion that the higher NDMA values Valisure reported are due to the presence of DMF, an interfering substance that co-elutes with NDMA, causing Valisure to overestimate the amount of NDMA in the sample.

Valisure suggests that FDA underestimates NDMA when using the first laboratory method it published for testing NDMA in metformin (see Petition at 2, 5, 6, and 8). When OTR repeated the measurements on the same samples with the stable isotope internal standard Valisure used, the testing results were the same as those obtained with the FDA method as published. Therefore, the Agency disagrees with Valisure's suggestion that our testing methodology underestimates NDMA levels and FDA is confident in its testing methodology and sampling results. As indicated in the published methodology, FDA relied on the principles stated in the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* to develop the protocol.[34] We specifically adopted a reasonable approach to demonstrate the accuracy of the method that relied on recovery of a spiked standard (in this case unlabeled NDMA) in test samples to avoid underestimating NDMA in metformin tablets. With the spiked standard approach, a known amount of NDMA is added to samples and the recovered amount is measured. Typically, a spike recovery of 80 to 120 percent is specified as acceptable in a validation protocol. If the recovery observed in this part of the method validation falls within the

[34] See footnote 29. As identified in the methodology, this guidance is the basis for the development of FDA's method.

specified range, the analytical procedure is considered suitable for its intended use.

FDA observed good analytical procedure performance for the primary and secondary testing methods based on results of the validation data. Furthermore, as an added check, FDA validated the secondary method and an additional orthogonal method that uses different ionization sources for the mass spectrometry detection and different columns and gradients for the chromatographic conditions. Comparable NDMA results were observed across the three methods on the 38 samples from Valisure. If there were matrix effects with one method, it is unlikely the effects would be the same with a second method and even more unlikely with a third method. Overall, the Agency has a high degree of confidence in the NDMA measurements that were produced using these methods.

On May 31, 2020, Valisure submitted a comment to the docket for this Petition (Comment). In that document Valisure discusses what it perceives to be a fault with FDA's laboratory analysis of NDMA in metformin. You suggest that the reason FDA's laboratory test results differ from those of Valisure is because FDA has failed to use an "internal control" in its testing (Comment 2-3). As described above, the FDA method uses an alternative approach to account for the potential problem with NDMA recovery or other matrix effects in the test. However, in an abundance of caution, some FDA measurements were repeated using the same internal control used by Valisure. FDA obtained the same results that were achieved using its unlabeled spiked recovery method. Thus, the difference between the Valisure and FDA values for NDMA cannot be attributed to the use of the stable isotope-labeled standard used by Valisure.

In the Comment, Valisure refers to the draft ICH guidance for industry *M10 Bioanalytical Method Validation*,[35] which is intended to help applicants validate bioanalytical methods for use in human clinical pharmacology, bioavailability and bioequivalence studies requiring validation of testing methods for testing in matrices such as blood and tissue, as support for the need for an internal control. However, as the metformin drug products being analyzed are in less complex matrices than blood or tissue, the more appropriate guidance for analytical procedure validation of the current measurement is ICH Q2(R1).

FDA does not agree with Valisure that the Agency's sampling results of NDMA in metformin are underestimated. Additionally, we do not agree that the test methodology proposed by Valisure has been appropriately validated to measure NDMA in metformin. FDA cannot adopt laboratory test methods that fail to meet appropriate analytical procedure performance characteristics when evaluating the on-going safety of a marketed drug. FDA will only rely on appropriately validated test methods to recommend the recall of a drug product or to otherwise remove a drug product that is no longer safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. Valisure's methodology does not meet that standard.

Accurately testing drug products, active pharmaceutical ingredients, and impurities is complex

[35] ICH draft guidance for industry *M10 Bioanalytical Method Validation* (June 2018), notice of availability published in the *Federal Register* of June 27, 2019 (84 FR 30732) (when final, this guidance will represent FDA's current thinking on this topic).

and requires the use of appropriately validated methods. If the test methodology is inaccurate, the results can affect patient treatment, or cause confusion and distrust among consumers. If the testing methodology produces an inaccurately high level of an impurity, then based on the results of that inaccurate test, patients may decide to forego or change treatment. If the methodology used for testing leads to a conclusion that levels of an impurity are low, when in fact they are high, those results may likewise affect patient safety. To help ensure that safe and effective drugs are sold in the United States, FDA tests selected drugs in state-of-the-art FDA laboratories and through research contracts and grants. The testing program includes drug substances and finished drug products and uses the same standards that are part of the drug approval process for establishing identity, strength, quality and purity. When a drug product is suspected of having an unexpected impurity, appropriately validated test methods must be developed that can ensure testing is suitable for its intended purpose.[36]

C. Promulgation of Regulations and/or Guidance Requiring Independent Chemical Testing and Verification of Pharmaceuticals Is Not Necessary

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

FDA's CGMP regulations set minimum requirements for drug product manufacturers to use in adequately controlling their manufacturing operations.[37] This formal system of controls helps to prevent instances of contamination, mix-ups, deviations, failures, and errors and assures that drug products meet the quality standards identified in regulations. FDA guidance recommends that similar controls be exercised by manufacturers of active pharmaceutical ingredients before they release a batch of active pharmaceutical ingredient for use by drug product manufacturers.[38] In addition, every establishment that is registered to engage in the manufacture, preparation,

[36] See 21 CFR 211.22 (Responsibilities of quality control unit), 211.80 (Control of components – general requirements), 211.84 (Testing and approval or rejection of components), 211.100 (Production and Controls, written procedures, deviations), 211.160 (Laboratory Controls – general requirements), 211.165(a) and (e) (Testing and release for distribution). See also footnote 24.

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

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

propagation, compounding or processing of a drug is subject to an inspection under section 704 of the FD&C Act. FDA's inspection programs provide additional oversight of manufacturing.[39]

FDA guidance provides recommendations to industry on how to assure quality standards are met by manufacturers of active pharmaceutical ingredients and drug product manufacturers.[40] If a new risk is identified, it is expected that the manufacturer will assess that risk and, as appropriate, take steps to address it -- for example, by updating control strategies. Manufacturers are the most familiar with their own processes, facilities, and supply chains, and are therefore best positioned to assess a risk.

As discussed above, analytical test procedures must be based on approved or recommended product specific validated procedures.[41] The use of unvalidated testing procedures, such as those Valisure used to test metformin products can lead to inaccurate results creating confusion and thereby causing a public health risk. Manufacturers may choose to use an independent third party to perform certain tests if they have reason to be concerned about the reliability of their own results or desire to access sophisticated methods or equipment that may not otherwise be available to them. However, that choice is based on the familiarity they have with their manufacturing process. Independent testing does not generally provide a unique insight into risks and is therefore generally not warranted.

Similarly, FDA does not agree that guidance recommending independent chemical batch-level testing and verification of the chemical content of all pharmaceuticals is necessary. Because FDA does not agree that regulations should be implemented to require third-party independent testing of all pharmaceuticals, we also do not agree that a guidance on this topic should be developed in the interim. In addition, we note that implementation of such a system would be difficult. As a general principle, the degree of regulatory scrutiny over batch-level testing should be commensurate with the degree of risk and an independent tester cannot evaluate the risk without sufficient knowledge of all manufacturing processes. Additionally, testing methods can only be developed with a target analyte in mind; testing of all possible chemical impurities or contaminants is not feasible. Beyond the problem of the volume of potential impurities to test, an independent third party would need information concerning the formulation and manufacturing of a product to determine which chemical tests are appropriate and to develop suitable methods for detection of impurities.

We note that this request for new regulations and guidance on third-party testing was also requested in Valisure's previously submitted petition relating to ranitidine.[42] FDA responded to

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

[40] See e.g., the following ICH guidance for industry *Q8 (R2) Pharmaceutical Development* (November 2009, Revision 2); *Q9 Quality Risk Management* (June 2006) and *Q10 Pharmaceutical Quality System* (April 2009).

[41] 21 CFR 314.50(d)(1), 314.94(a)(9), 601.2; see 21 CFR 211.165(e).

[42] FDA April 1, 2020, response to Valisure Petition, Docket No. FDA-2019-P-4281, available at

that petition on April 1, 2020. Our response to that same request in this Petition is the same. FDA's opinion has not changed since that time, and you have not presented any new information in this Petition that would alter our opinion. However, the Agency will reevaluate and update our policy as appropriate.

III. CONCLUSION

For the foregoing reasons, the remaining requests in your Petition are granted in part and denied in part.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
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