U.S. FOOD & DRUG ADMINISTRATION
CDER Office of Compliance
Office of Manufacturing Quality

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Date April 28, 2021

From **Christina Capacci-Daniel, Compliance Officer**
Global Compliance Branch IV (GCB IV)
Division of Drug Quality II (DDQII)
Office of Manufacturing Quality (OMQ)
Center for Drug Evaluation and Research

Subject **For Cause Inspection Request – High**
eNSpect Assignment #198621
CMS Work Activity # 348691
ORA Concurrence: MP2021042601
PAC Code(s): 56D800, 56030A, 56002

Firm: Valisure, LLC
5 Science Park
New Haven, CT 06511-1966

POC: Mr. David Light
Chief Executive Officer
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FEI: 3012063246

To **Alonza Cruse, Director**
Office of Pharmaceutical Quality Operations (OPQO)

Through **Milind Ganjawala, Director** for MG Tracie H. Sharp -S
Division of Drug Quality II
Office of Manufacturing Quality (OMQ)

Francis Godwin, Director
Office of Manufacturing Quality (OMQ)

We are requesting a for cause inspection of Valisure, LLC located at 5 Science Park, New Haven, CT. Valisure, LLC ("Valisure" or "the firm") is a pharmacy and a wholesale distributor with an analytical laboratory conducting testing of drugs it both distributes to hospitals and pharmacies, and dispenses directly to patients. Valisure also offers contract laboratory testing for manufacturers.

BACKGROUND INFORMATION

Valisure advertises itself as being the first and only pharmacy in America that chemically analyzes every medication it sells, at no additional cost to the consumers. Valisure states that it tests medications for correct dosage, major inactive ingredients, proper dissolution, and the presence of carcinogens such as, N-Nitrosodimethylamine (NDMA) using "proprietary analytical technology in addition to standard FDA and USP assays." The company has also stated that it rejects over (b) (4) % of marketed medication batches based on its testing standards. Valisure's

results are described in a unique Valisure Certificate of Analysis (COA) that accompanies distributed batches and is provided to patients with prescriptions.

Valisure's website now states that it also offers services to the pharmaceutical industry: Valisure can test products "at any level of the supply chain, from manufacturers who want to differentiate their generic products from competitors, to retail and hospital pharmacies" (Attachment: "Product Certification" Website, February 22, 2021). Additionally, Valisure's website also advertises its "chemical validated generic" medications that "have a substantial improvement in quality assurance backed by a batch-specific certificate of analysis."

According to its website, Valisure also advertises itself as having the ability to wholesale its "validated" product to "clinics and dispensing practices." The Connecticut State Department of Consumer Protection (DCP) lists Valisure as having a current and active wholesale distributor license in Connecticut (expiration date June 30, 2021), and Valisure has information available on their website describing their wholesale distribution capability and services. In addition, Connecticut DCP also lists ValisureRX as having a current and active pharmacy license (expiration date August 31, 2021).

Valisure has expanded its operations to perform contract release testing for drug product manufacturers as now described on its website. These contract testing operations have not been evaluated for compliance with Current Good Manufacturing Practice (CGMP).

INSPECTIONAL HISTORY

FDA traveled to Valisure in August 2018 to conduct a new registrant surveillance inspection per MARCS OpID: 9732. At the time of the visit, Valisure was a privately-owned company founded in 2015. Valisure is a parent company of three wholly owned business entities: ValisureWS, LLC; ValisureCL, LLC; and ValisureRX, LLC. Valisure registered as a Control/Analytic Laboratory in February 2018. The firm was not operational at the time of the visit, but the firm expected to be operational by October 2018. The investigator explained that based on the nature of the laboratory testing, the firm was not required to perform testing in accordance with the CGMP, and therefore the firm's registration is not required, and the registration type would be updated to voluntary. This was documented in an OP13 Memo (Attachment: OP13 Valisure memo). Now the firm appears to be performing release testing for manufacturers which would mean that its laboratory operations are subject to CGMP.

INSPECTIONAL COVERAGE

Please conduct an inspection to assess the nature of the operations performed at Valisure to determine whether the firm is subject to CGMP (21 CFR 210 and 211). Valisure's contract release testing as an available service for drug product manufacturers would subject its testing to CGMP standards.

Because the firm holds drugs prior to introduction into interstate commerce, its wholesale distribution activities are subject to inspection under section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as the provisions of section 501(j) of the FD&C Act.

Valisure is also a trading partner subject to the Drug Supply Chain Security Act (DSCSA) product tracing and verification system requirements.

This inspection will focus on (I) whether Valisure's operations are subject to CGMP and evaluation of these operations; (II) compliance with the DSCSA; (III) distribution decisions based on testing, and (IV) drug storage and holding conditions.

In preparation for the possibility that the laboratory operations are in scope for a full CGMP inspection, we recommend the investigation team include an experienced Chemist with expertise in analytical method validation and LC/MS methodology.

SCOPE OF FDA JURISDICTION

Valisure also engages in pharmacy dispensing operations. **Pharmacy operations are outside the scope of this inspection. Therefore, investigators should not review prescriptions, individual patient records, or other documents specifically related to the dispensing of prescriptions to individual patients.**

The exclusion of inspectional authority described in the third sentence of 704(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) does not apply pharmacies meeting certain criteria, see section 704(a)(2). This exclusion is limited such that firms that manufacture, prepare, propagate, compound or process drug for sale may be subject to inspection. If investigators find evidence that Valisure is engaging in the manufacture, preparation, propagation, compounding or processing of drugs for sale, contact James L. Dunnie, Jr. to schedule a teleconference to discuss.

Valisure, as a wholesale distributor, holds drug product for introduction into interstate commerce which is subject to inspection per FD&C Act § 704(a)(1) and CGMPs at FD&C Act § 501(a)(2)(B). Likewise, there is evidence that the firm may be analyzing drug products for manufacturers to satisfy the CGMP regulations at 21 CFR 211 for the purposes of product release which would make them generally subject to the laboratory and related requirements in 21 CFR 211.

As a wholesale distributor and dispenser, Valisure is subject to the product tracing and verification system requirements of DSCSA.[1] Valisure must retain records related to an investigation of suspect or illegitimate product for a period of six years.[2] Upon request by FDA to investigate suspect or illegitimate product, Valisure must produce transaction information within one business day (sections 582(c)(1)(C) and 582(d)(1)(D)). Valisure must also report any illegitimate product in its possession or control to FDA using FDA Form 3911 within 24 hours of its determination that the product is illegitimate. (sections 582(c)(4)(B)(ii) and 582(d)(4)(ii)).[3]

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[1] Wholesale distributor is defined in section 581(29) and Dispenser, includes pharmacy, is defined in section 581(3).

[2] Sections 582(c)(4)(A)(iii) and 582(c)(4)(B)(v) for wholesale distributors and sections 582(d)(4)(A)(iv) and 582(d)(4)(B)(v) for dispensers.

[3] Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry https://www.fda.gov/media/88790/download

INSPECTIONAL GUIDANCE – PART I, CGMPs

In the EIR, please include answers to each of the points or questions listed in this For Cause assignment.

A. DETERMINATION OF CONTRACT LABORATORY TESTING OPERATIONS

1. Does Valisure conduct any testing on behalf of a drug product manufacturer (including drug product repackager) to fulfill a CGMP requirement? If Valisure does conduct contract laboratory testing:

    - Collect a list of drug manufacturers and drug suppliers that contract release testing with Valisure and copies of any quality agreements or similar documents with Valisure. Determine when these agreements were signed and how much testing has been already performed by Valisure as part of this contract.
    - Collect a list of products tested and testing performed. Proceed to the Testing Section below for additional guidance on laboratory coverage.
    - Also request quality agreements or similar documents between Valisure and (b) (4) and other wholesale drug distributors it sources from.

2. Does Valisure utilize any other testing lab(s) to confirm its testing results and/or to validate/verify its methods? If so, collect a list of laboratories and any quality or similar agreements. Specifically, confirm whether Emery Pharma is utilized. (Valisure has publicly stated it uses Emery Pharm as an outside lab that has been FDA inspected/compliant with CGMP. See Attachment Emery Pharma EIR.)
    - Determine scope of testing (i.e. time period of testing, specific drug products tested) conducted by Emery Pharma under contract with, or on behalf of, Valisure. Determine whether Emery, when testing on behalf of Valisure: followed CGMP during testing, validated testing methods according to CGMP, and/or used another standard (such as ISO).
    - Request a table of all Emery Pharma results vs Valisure results. Did any results differ, and what is Valisure position/follow up to discrepancies in their lab vs their contractor?

B. EVALUATION OF ACTIVITIES SUBJECT TO CGMP

Once a general assessment of Valisure's operations is conducted, please contact James L. Dunnie, Jr. to schedule a teleconference to make a preliminary determination of whether the firm is subject to CGMP and whether laboratory coverage is warranted. Daily meetings during the inspection may also be requested for additional guidance.

If during the initial assessment of Valisure's operations, it is determined that Valisure's laboratory operations are subject to CGMP, proceed with the following sections evaluating the firm's testing operations and analytical methods.

General laboratory practices and controls are covered in items 1 – 8. The adequacy of analytical methods should be evaluated through items 9 – 11 below; the control of data and the computerized systems used to collect analytical data is covered in item 12 below.

1. Does the firm have adequate resources (e.g. trained personnel and equipment) to adequately perform all laboratory analyses? Assess the adequacy of training and qualifications of employees engaged in laboratory operations. Confirm if Valisure performs both analytical and microbiological analyses.

2. If the firm conducts microbiological analysis, determine the adequacy of the firm's microbial test methods (preservative effectiveness, growth promotion, USP test methods, etc.). Include details regarding how the firm identifies all bioburden in its products to ensure no objectionable microbes are present.

3. Assess the firm's internal standards qualification program and respective expiration date of the standards.

4. Is system suitability performed as part of each test?

5. Obtain a list of out-of-specification (OOS) and out-of-trend (OOT) investigations and any recommendations or reports provided to clients following Valisure's own investigation of their laboratory results and practices.

6. Review and collect the procedure for OOS investigations to ensure sound scientific rationale is applied throughout the investigation, determination of a laboratory root cause if applicable, and identification and implementation of corrective actions as needed. Assess the adequacy of investigations and collect all pertinent documents related to product release or distribution decisions.

7. If results were invalidated, but no investigation was performed confirming laboratory error, then document and indicate the firm's rationale, if any, for invalidation.

8. Collect equipment maintenance dates and calibration schedules for key pieces of analytical equipment (i.e. HPLC, IR and Raman instruments).

C. METHOD VALIDATION AND ANALYTICAL PROCEDURES

Investigators should utilize FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics, and FDA's Guide to Inspections of Pharmaceutical Quality Control Laboratories to the extent that CGMP is determined to apply to Valisure's laboratory testing.

9. Evaluate method validation in support of the current analytical methods used for assay and impurities testing for all drug products intended for U.S. distribution. If no formal method validation has been conducted, collect what the firm can provide to demonstrate the method is fit for purpose.

10. Specific to method validation related to the nitrosamines, determine if any analytical methods developed by the firm were adequately validated. Evaluate how specificity for NDMA in metformin was established.

11. If Valisure uses its own nitrosamine-related test methods, determine if it conducted comparison studies demonstrating that its in-house methods are equivalent or superior to FDA's methods. (See Attachments: FDA Analytical Method and Guidance for Industry)
    - For NDMA testing, conduct an audit of the raw data from the analytical equipment used to generate any technical reports supporting method validity.
    - Collect any specifications for the impurities of nitrosamines including NDMA and all associated test methods related to release testing of angiotensin receptor blockers (ARBs).
    - Verify if impurities were observed and/or unknown impurities were observed. Collect evidence related to the impurity profiles. If unknown impurities were observed, collect any associated investigations.

D. CONTROL OF COMPUTERIZED LABORATORY SYSTEMS

12. Conduct an audit, including audit trails, of material that passed, and material that has failed Valisure testing:
    - Focus should be on material that fails compendial specifications first.
    - Evaluate the firm's electronic and hard copy raw data retention policy.
    - Assess the firm's technical data review process including but not limited to audit trail verification, manual integration procedures, system suitability criteria, any calculation spreadsheet validation, verification of integration parameters, processing methods and reprocessed data.
    - Verify and collect if there is any evidence of data deletion or renaming of any aborted or failed injections that are not included as part of the final data package.
    - Verify if there is any evidence of destruction of chromatographic related documents or other laboratory records such as notebooks and balance printouts.
    - Determine if all equipment is appropriately maintained on a regular maintenance schedule.
    - Review the audit trails. Determine if the firm regularly reviews the audit trails and review the recycle bin for deleted documents.
    - Determine if the firm has automated data processing techniques and is consistent. Determine if the automated processing is overridden to alter the parameters.

INSPECTIONAL GUIDANCE – PART II, COMPLIANCE WITH DRUG SUPPLY CHAIN SECURITY ACT (DSCSA)

Based on the publicly available information, it appears Valisure is both a dispenser and a wholesale drug distributor. As such, the firm has different requirements based on whether the firm is acting as a wholesale distributor or acting as a dispenser in a specific instance. As a wholesale distributor under section 581(29) of the FD&C Act, Valisure has obligations to comply with certain requirements of section 582(c) of the FD&C Act. As a dispenser under

section 581(3) of the FD&C Act, Valisure has obligations to comply with certain requirements of section 582(d) of the FD&C Act.

A. CURRENT STATUS OF VALISURE WHOLESALE DISTRIBUTOR LICENSE(S)

1. Determine licensure status for Valisure as a wholesale distributor. As required by section 503(e), "No person may engage in wholesale distribution… unless they are licensed by the state from which the drug is distributed… and if the drug is distributed interstate, is licensed by the State into which the drug is distributed if the State into which the drug is distributed requires the licensure of a person that distributes drugs into the State."
    - Collect any and all information about Valisure's status as a licensed wholesale distributor in Connecticut, or in any other state. Determine the earliest date Valisure became a licensed wholesale distributor.
    - Verify compliance with wholesale distributor annual reporting requirements as required by section 503(e)(2).

2. Authorized Trading Partner Requirement
    - As required by section 582(s)(3), the trading partners of a wholesale distributor and a dispenser may be only Authorized Trading Partners. Valisure may only transact with manufacturers, repackagers, wholesale distributors, or utilize third-party logistics providers who are up to date with their requisite licensure requirements as outlined in DSCSA.
    - Document the procedures the firm utilizes to verify that its direct trading partners are authorized as required by DSCSA.

B. SUSPECT AND ILLEGITIMATE PRODUCT INVESTIGATIONS AND FDA 3911 NOTIFICATION OF ILLEGITIMATE PRODUCTS

When a trading partner determines that a product in its possession or control is illegitimate, it must notify FDA and its immediate trading partners. An example of where it appears that Valisure made a determination of an illegitimate product involves Valisure's testing of metformin, announcing on its website on March 2, 2020 that it had tested several batches of metformin and found that "several batches contained over 10 times the daily acceptance intake limit of NDMA, a carcinogen, and that there was significant variability from batch to batch, even within a single company."[5] Valisure announced its filing of a citizens petition with FDA and "urged FDA to request recalls for the identified lots."[6] Based on Valisure's statements regarding these lots of metformin it appears that Valisure determined that these lots were illegitimate. Valisure believed that it had credible evidence that the product was unfit for distribution because it would be reasonably likely to result in serious adverse health consequences. If it had determined that those lots of metformin were illegitimate, Valisure was required to submit a FDA 3911 and notify its trading partners with 24 hours of its findings.

1. Wholesale Distributor Verification

[5] https://www.valisure.com/blog/valisure-news/valisure-detects-high-levels-of-ndma-in-metformin/

[6] Id.

- As required by section 582(c)(4), a wholesale distributor shall have systems in place to conduct verification of suspect and illegitimate product.
- Verify whether the firm has been a party to any investigations involving suspect or illegitimate product, either based on its own discovery of suspect or illegitimate product, or by being contacted by a trading partner as a part of the trading partner's investigation into a suspect or illegitimate product.
    - If yes, collect all information available related to the investigation including information related to communication with trading partners with respect to the investigation, quarantine, and disposition of the products.
- Determine whether Valisure submitted a form FDA 3911 for any illegitimate products within the past two years as required by section 582(c)(4)(B)(ii).
    - If yes, collect all information available related to the form FDA 3911.
- Determine whether Valisure returned any illegitimate products as saleable or unsaleable returns and collect those records. See 582(c)(1)(B).

2. Dispenser Verification
    - As required by section 582(d)(4), a dispenser shall have systems in place to conduct verification of suspect and illegitimate product.
    - Verify whether the firm has been a party to any investigations involving suspect or illegitimate product, either based on its own discovery of suspect or illegitimate product, or by being contacted by a trading partner as a part of the trading partner's investigation into a suspect or illegitimate product.
        - If yes, collect all information available related to the investigation, including trading partners related to the investigation, quarantine, and disposition of the products.
    - Determine whether Valisure submitted a form FDA 3911 for any illegitimate products within the past two years as required by section 582(c)(4)(B)(ii).
        - If yes, collect all information available related to the form FDA 3911.
    - Determine whether Valisure returned any illegitimate products as saleable or unsaleable returns and collect those records. See 582(c)(1)(B).

C. DISTRIBUTION DECISIONS BASED ON TESTING

The August 2018 OP13 investigation found that prior to distributing over-the-counter and prescription medications, Valisure conducts additional analytical testing, including dissolution and spectral analysis (HPLC and/or Raman). Medications determined to have an assay within +/- (b) (4) % of the manufacturer's stated dosage strength are deemed acceptable to be dispensed to patients through its pharmacy (ValisureRX) with a valid prescription. Medications determined to be outside of the +/- (b) (4) range are to be returned to the distributor, (b) (4)

If Valisure is testing to make a distribution decision, inspectional coverage should include the scope of testing and how this information is communicated to its clients.

- Collect a list of all tests Valisure uses to determine if a drug product batch should be distributed. Confirm that the acceptance/rejection criteria is the same for each unique

drug. Collect product specifications or equivalent criteria and limits for rejection for several products, including the most rejected drug products.

- The firm states that its analysis is summarized in a Valisure COA, which is supplied to the customer after testing of the drug product is complete. Collect examples of Valisure COAs for multiple batches of several drug products.
- Examine at least exemplary Valisure COAs for ranitidine and metformin batches. Collect the information provided to Valisure by the drug product manufacturer (such as release testing or COAs).
- Collect Valisure COAs that are issued to different customers (e.g. patients vs. pharmacies vs. manufacturers) and determine if there are different claims or information on the COA based on the intended audience.
- Compare the results of Valisure's testing to the manufacturer's results to see if there are discrepancies between the test results on a manufacturer's drug product COA and Valisure's testing results which are then provided on its COA to customers, particularly for the NDMA impurity.
- Collect any procedures for the return of rejected material and any formal communication between Valisure and its suppliers (e.g (b) (4) regarding the rejection of material, including any test results or investigations performed by Valisure demonstrating that a drug product batch is unacceptable.
- Determine how Valisure has handled drug recalls over the past two years. Has the firm participated in a manufacturer initiated recall caused by a batch failure and how did this information compare to testing done by Valisure? Has Valisure or would Valisure update its COA provided to customers for a batch that is later recalled?

D. DRUG STORAGE AND HOLDING PRACTICES

Because Valisure holds drugs, its wholesale distribution operations are subject to section 501(a)(2)(A) provisions of the FD&C Act. Investigators should not evaluate operations or elements related to the practice of pharmacy and can only evaluate pharmacy dispensing spaces if significant violations are suspected.

Document how the firm receives drugs and where they are stored.

- Is the area clean?
- Is the area temperature-controlled, and does the firm store any drugs that are temperature sensitive outside of the labeled conditions? A list of drugs can be sent to CDER during the inspection to evaluate this.
- Are any light-sensitive drugs stored in a manner that could lead to degradation?
- How does the firm handle expiration dates on drugs from its suppliers, and factor them into release for distribution or dispensing decisions?
- Collect an inventory of drugs currently held at the facility or any other facility under the control of the firm (e.g., off-site warehouse).
- Collect a spreadsheet from the firm that contains its receiving and shipping records since August 2018 (FDA's last OP13 investigation of this firm as noted earlier in this assignment).
- Collect storage and warehouse procedures.

- Collect a list of all drugs received and sent back to its supplier since August 2018, including reason for rejection.

REGULATORY STRATEGY

If the inspection finds the firm is subject to CGMP and deficiencies that pose a risk to patients, we may pursue a warning letter or other compliance action. If the firm is not found to be subject to CGMP, the validity of methods and its onsite use will be evaluated to determine whether a potential FD&C Act section 301 violation exists for introduction or delivery for introduction of adulterated drugs, distribution of drugs in violation of 503(e) or a violation of the DSCSA.

SAMPLE COLLECTION

Physical samples, if appropriate, should be collected according to the IOM. Physical samples may be requested for collection under this assignment and sample analysis will be coordinated by ORS/CDER. Contact James L. Dunnie, Jr. with questions regarding sample size, etc. Documentary samples may be requested after determination of evaluation of operations.

PAC REPORTING

Accomplishments are to be entered into eNSpect under PAC 56D800, 56030A and 56002, as applicable. We estimate that it will take approximately 80 hours for each team member to accomplish this assignment.

TELECONFERENCE SCHEDULING

Please contact James L. Dunnie, Jr. at james.dunnie@fda.hhs.gov upon receipt of this assignment to schedule a pre-inspection teleconference with ORA HQ and CDER.

Once a general assessment of Valisure's operations is conducted, please contact James L. Dunnie, Jr. to schedule a teleconference with CDER for a preliminary determination of whether the firm is subject to CGMP and whether laboratory coverage is warranted. For inquiries about this assignment, contact Christina Capacci-Daniel in CDER.

ORA HQ and CDER would like to have a teleconference prior to closing out the inspection(s) to discuss any significant findings and the issuance of a FDA-483 (if warranted). Please coordinate this meeting with James L. Dunnie, Jr.

TARGET DATE

The inspection should be completed as soon as feasible from the date of this memo.

PAC: 56D800, 56030A, and/or 56002, as applicable (PAC CODE LINK):
(http://inside.fda.gov:9003/PolicyProcedures/GuidanceRegulations/PACMasterList/default.htm)

Priority: High

Rick L. Friedman -S

Digitally signed by Rick L. Friedman -S
Date: 2021.04.28 13:38:54 -04'00'

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
CDER for Drug Evaluation and Research, FDA

Attachments:

1. "Product Certification" Website February 22, 2021 and Screenshot March 3, 2021
2. FINAL OP13 VALISURE LLC FEI 3012063246.PDF and RE VALISURE ATTACHMENTS.MSG
3. NAJAFI PHARMA INC DBA EMERY PHARMA 3012759597 FY19 EIR.PDF
4. VALISURE LABEL AND COA EXAMPLE.JPG
5. FDA method: "*Liquid Chromatography-Electrospray Ionization-High Resolution Mass Spectrometry (LC-ESI-HRMS) Method for the Determination of Nitrosamine Impurities in Metformin Drug Substance and Drug Product*" https://www.fda.gov/media/138617/download
6. FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs https://www.fda.gov/media/141720/download