July 27, 2021

Response to Form 483

OBSERVATION 1

> **The firm failed to adequately validate and/or verify analytical methods used in the evaluation of pharmaceutical products in that the firm failed to document the validation/verification process, acceptance criteria, and an evaluation of the validity of the method outlining its intended use.**

VALISURE'S RESPONSE:

As described in the Cover Letter, Valisure is unrelated to the drug manufacturing process, and therefore it is not subject to the cGMP standards set forth by FDA, including for validation and verification of analytical methods. The testing Valisure performs is purely voluntary and not intended for any regulatory purpose, such as for product release or approval specifications.

Nevertheless, the analytical methods Valisure uses are accurate and reliable. As described in Valisure's publicly available certificate of accreditation (available on the Perry Johnson Laboratory Accreditation website, https://www.pjlabs.com/search-accredited-organizations, and attached as **Exhibit 1**), the purpose of Valisure's methods is to broadly screen medicinal products and dietary supplements. The laboratory conducts its testing activities pursuant to its ISO/IEC 17025:2017 certification, and per ISO standards, Valisure's clients are made aware of the specifications or standards used by Valisure.

Valisure methods are validated pursuant to ISO standards, which reference ICH and FDA validation procedures. The following method characteristics are established at Valisure:

- Accuracy
- Precision
- Repeatability
- Reproducibility
- Intermediate Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Linearity
- Range

In addition to proficiency testing, Valisure conducts (b) (4) recalculation of its test methodology. Ongoing method validation includes, but is not limited to, control charting to establish detection limits and instrument performance. Valisure maintains records of reviewed validation data for all its tests.

Corrective Action:

Valisure intends to review and revise its claims to customers and on the website to further clarify that Valisure's services are not intended for and not appropriate for any regulatory purpose.

Based on feedback from FDA, Valisure will (b) (4)

OBSERVATION 2

The firm's equipment qualification program is inadequate.

VALISURE'S RESPONSE:

As described in the Cover Letter and response to Observation 1, Valisure is not an entity that is integral to the drug manufacturing process, and therefore it is not subject to the cGMP standards set forth by FDA, including for equipment qualification. As a corrective action, the company intends to (b) (4) upon confirmation by FDA.

Although Valisure may not have a documented program for qualifying its laboratory equipment pursuant to FDA standards, Valisure maintains objective evidence that its equipment can correctly perform all testing specified in the certifications it provides. For example, Valisure maintains uniquely identified instrumentation and equipment, which is labeled to identify the calibration status. All equipment is maintained on a calibration schedule ranging from (b) (4) to (b) (4) or (b) (4) . Service, in-house maintenance, and preventative maintenance actions are scheduled and logged, as per ISO/IEC 17025:2017 standards. Valisure uses a third party ISO accredited calibration laboratory or on-site service provider to calibrate its equipment. In addition to calibration, and calibration checks, equipment is qualified each use with certified reference standard samples and criteria for sensitivity and resolution. The company maintains documentation of its (b) (4) proficiency testing of its equipment.

In addition, all equipment operators are systematically trained and assessed for competency prior to operating equipment; this training is documented. Only authorized laboratory staff are permitted to operate laboratory equipment. Relevant manuals provided by the manufacturer of the equipment are controlled and are made readily available for use. Instructions on the use and maintenance of all equipment are kept up to date and are readily available.

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OBSERVATION 3

The firm has failed to adequately control data access within analytical equipment used for the analysis of pharmaceutical products.

For example,

The ICP-MS, (b) (4) GC-MSs, LC-HRMS, and the (b) (4) HPLCs have no controlled access (i.e., no passwords required). Furthermore, each analyst has administrative access to these systems.

VALISURE'S RESPONSE:

As described in the Cover Letter and response to Observation 1, Valisure is not an entity that is integral to the drug manufacturing process, and therefore it is not subject to the cGMP standards set forth by FDA, including for control of data access within analytical equipment. As a corrective action, the company intends to deactivate FDA registration upon confirmation by FDA.

Further, Valisure has strong processes to control data access to equipment used to analyze drug products.

- Document Control: All electronic testing and method calibration results are identified, filed, and stored in a secure cloud-base storage that provides document tracking for auditing purposes and automatic back-up of multiple document versions. All internal quality, procedural, and policy documents are stored, managed and shared using this system. Obsolete documents are archived in Valisure (b) (4) and permissions to view are managed by the Quality Manager. All electronic testing and method calibration results and records are recorded at the time they are made in such a way that they are identified with the time, the task, operator, and reviewer.

- Physical Equipment Access: The Valisure Laboratory facilities are in a building with (b) (4) security guards, including an (b) (4) guard that patrols at least (b) (4). Valisure requires (b) (4) for access to laboratory facilities. Additionally, Valisure maintains an alarm system with (b) (4) and (b) (4) to track physical access to equipment, reagents, and computers.

- Electronic Equipment Access: Valisure has a dedicated administrator who controls access to all equipment workstations and can modify access. Valisure staff

maintain unique passwords to access shared laboratory equipment, which include complexity requirements and are changed every (b) (4) . Managerial staff will revoke a staff member's password if there is reasonable cause to believe the password has been created, used or disclosed in a manner not compliant with Valisure Policy. To date, there have been no instances in which Valisure has needed to revoke access to equipment.

It is important to note that FDA's descriptions about access to Valisure's equipment in this observation are inaccurate. FDA states: "The ICP-MS, (b) (4) GC-MSs, LC-HRMS, and the (b) (4) HPLCs have no controlled access (i.e., no passwords required)." Each of these machines do require a password to access the software. Valisure passwords are unique for employee user account, and the passwords are controlled by a dedicated administrator.

FDA also incorrectly states that "each analyst has administrative access to these systems," which implies uncontrolled access to the equipment. For each piece of equipment, only one to three accounts have administrative access to make software changes. These accounts include the dedicated administrator and, in some cases, the senior scientist in charge of that equipment or the instrument vendor for initial software installation and subsequent updates.

OBSERVATION 4

The firm's laboratory investigations are inadequate.

For example,

The firm's process for laboratory discrepancies and investigations is inadequate in the fact that the firm has had at least 45 out-of-specification events and failed to perform any documented Investigations from 06/07/2019 – 06/02/2021. In addition, the firm does not have an SOP instructing an employee to open an investigation when products do not meet their specifications.

VALISURE'S RESPONSE:

As described in the Cover Letter and response to Observation 1, Valisure is not an entity that is integral to the drug manufacturing process, and therefore it is not subject to the cGMP standards set forth by FDA, including for laboratory investigations. As a corrective action, the company intends to (b) (4) upon confirmation from FDA.

Because it is not a drug manufacturer nor subject to cGMP, Valisure does not have specifications for specific products that require investigation. Valisure does not typically run product-specific methodologies or perform method transfers to run such methods. The company's activities are limited to conducting independent testing and screening of products; therefore, testing is reviewed by Valisure's Quality Manager and any investigations are made after consideration of the results in the context of the specific methodologies and products evaluated. Valisure's testing may overlap with some of the FDA-required specifications but there are additional standards that Valisure applies to determine whether the drugs receive Valisure certification.

In the observation, FDA notes that the firm does not have an SOP instructing an employee to open an investigation when products do not meet their specifications. Per ISO 17025:2017, Valisure maintains a process applicable to all employees for reporting and documenting corrective actions within the ISO quality management system and it trains its employees on this process as part of their on-boarding training. This process requires employees to log any discrepancies that require correction and is not limited to product or screening specifications. The company maintains a log of Corrective Action Reports that documents any discrepancy in the quality management system and the corrective action that was taken after investigation to address the issue. Therefore,

corrective actions are logged on a continuous basis, reviewed (b) (4) by management, and the entire system is reviewed (b) (4)

OBSERVATION 5

There are no systems in place to enable compliance with the requirements of the Food Drug and Cosmetic Act Section 582(c)(A) & (B) and (d)(A) & (B). Your firm has none of the verification systems required by the Drug Supply Chain Security Act (DSCSA). When asked, your firm stated that it had not previously heard of the DSCSA.

VALISURE'S RESPONSE:

Until recently, Valisure owned ValisureRx, LLC, which operated as an online pharmacy and distributor focusing on helping to ensure the safety, quality and consistency of medications and supplements distributed and dispensed to the public. During the relevant times, all drug products distributed or dispensed by ValisureRx were batch-certified by Valisure. Such testing, using ISO standards, supplemented the testing performed by manufacturers/suppliers as part of cGMP. This process helped ensure that any drug product distributed or dispensed by ValisureRx would meet expected quality standards. In addition, Valisure established procedures to identify product that was potentially "unfit" for distribution or dispensing, consistent with the DSCSA requirements for identification of suspect products. Any products identified through the certified testing process would be immediately "quarantined." As FDA noted in the Form 483, in the examples cited: Bupropion XL lot NB900240 and Metformin lot MTSB19003-A, ValisureRx ensured that such product was not distributed or dispensed.

Valisure issues a Certificate of Analysis for products batch-tested by its laboratory. Thus, Valisure creates a specific record of whether a drug has passed or failed its certification testing. In those cases where Valisure determined that certain products obtained by ValisureRx had failed, the Quality Manager would inform the Pharmacy Manager that these lots were not fit for distribution. This was the case for the two examples cited by FDA: Valsartan lot (b) (4) and Metformin lot (b) (4). In addition, for all products tested by the Valisure laboratory with failing results, Valisure sent these products to a reverse distributor to ensure such products were removed from the distribution chain and either destroyed or otherwise handled according to directions from the manufacturer. That process and specific notification to manufacturers, ensured that manufacturers were notified about potential quality issues with their products. This enabled manufacturers to take appropriate action related to these products, for all of their customers.

Valisure's use of a reverse distributor also facilitated notification to the manufacturer and provided an opportunity for the manufacturer to make further inquiries

about the product, including requesting samples, to further investigate issues raised by Valisure's testing.

The DSCSA requires that a trading partner should establish procedures to identify, quarantine and investigate suspect product. In addition, trading partners should appropriately notify other trading partners, including the manufacturer of the product determined to be suspect and/or illegitimate. ValisureRx's policies and procedures related to its use of Valisure's certified testing program in regard to the review, testing, quarantine and disposal of any products determined to be unfit, were consistent with DSCSA requirements to investigate and document products determined to be suspect or illegitimate products. These procedures provided sufficient documentation as to steps taken consistent with the intent of DSCSA related to suspect and illegitimate products.

As noted, as of April 2021, Valisure has discontinued distribution and dispensing of any drug products and sold the ValisureRx entity and its associated business to Medly Pharmacy.

Finally, to clarify, Valisure and ValisureRx were familiar with the DSCSA, however, we would concede that some staff were not previously familiar with DSCSA's specific reporting requirements for pharmacies related to product that could be defined as "suspect" or "illegitimate." As evidenced by FDA's recent revisions to guidance documents on June 3, 2021 related to these terms, the understanding and education on these requirements among the regulated industry continue to evolve, especially among pharmacies and pharmacists.

OBSERVATION 6

Trading partners must have systems in place to make a notification of illegitimate product to FDA and immediate trading partners within 24 hours after making such a determination. There is no documentation to indicate that your firm has such procedures. Furthermore, your firm failed to make timely (within 24 hours) notifications to immediate trading partners or FDA once your firm became aware that it was in possession of an illegitimate product.

VALISURE'S RESPONSE:

As FDA acknowledged, while ValisureRx is alleged to have not met the specific notice requirements under DSCSA, e.g., the Form 3911, it did provide notice to both FDA and its trading partners related to product that could be defined as suspect or illegitimate. In addition, once the product was so identified, it was removed from the distribution chain.

For example, Valisure provided results of the testing and detailed information related to issues with the quality of certain lots of these products. This includes the examples cited by FDA: Metformin lot (b) (4) and Valsartan lot (b) (4). Such information was more than sufficient for manufacturers and other trading partners to determine that the product would meet the definition of illegitimate product under the DSCSA.

The same is true for notification to FDA. On June 13, 2019, Valisure filed a Citizen Petition with FDA related to contamination concerns with certain lots of Valsartan, including the example cited by FDA in the Form 483. Also, on March 2, 2020, Valisure filed a Citizen Petition with FDA related to concerns about high levels of NDMA in specific batches of prescription drug products containing Metformin. The Citizen Petitions filed by Valisure provided detailed information about the testing conducted by Valisure and the concerns about the product. Such filings provided information that could be used to determine whether the products were "unfit," thus meeting the definition of suspect and illegitimate product.

Similarly, Valisure has notified the manufacturers of products that were rejected by Valisure's testing program. These notifications provided sufficient information for the manufacturer to review and determine whether such product was "unfit" and met the definition of illegitimate under the DSCSA. Moreover, such information would have been sufficient for the manufacturers to notify other trading partners about these potential issues.

As discussed above, ValisureRx is no longer owned by Valisure.

Exhibits

1	Accreditation issued by Perry Johnson Laboratory Accreditation, Inc.
2	Agreement between Valisure and (b) (4)
3	(b) (4) May 26, 2021 Statement
4	June 1, 2021 Statement