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SUMMARY

This was a preannounced pre-approval inspection (PAI) and comprehensive GMP inspection of Eurofins Advantar Laboratories, Inc. a non-sterile Active Pharmaceutical Ingredient (API) manufacturer and control testing laboratory. This inspection was conducted per eNSpect Operation Id: 191560 and FACTS Assignment ID: 12085731, as part of the DPQO IV FY21 workplan and in accordance with Compliance Program (CP) 7356.002 (Drug Manufacturing Inspections); CP 7356.002F (Active Pharmaceutical Guidance Ingredient (API) (Process Inspection); and CP 7346.832 (Pre-Approval Inspections). Guidance for Industry titled, "Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients", was additionally utilized for guidance on CGMPs applicable to API manufacturers. Inspectional focus was given to laboratory operations related to NDA (b) (4) for (b) (4) . Profile classes LCP (Laboratory, Chemical/Physical Testing) and CSN (Non-sterile API by Chemical Synthesis) were covered during this inspection.

The firm supplies analytical testing and drug product development services for early and late phase programs for pharmaceutical companies, performs testing of commercial pharmaceutical products and manufactures an API for use in a commercial product ((b) (4)). The previous inspection, conducted 1/25/2016 – 2/3/2016, covered quality, production, laboratory controls, facilities and equipment, materials and packaging and labeling systems. The inspection also covered NDA (b) (4) submitted by applicant (b) (4) . The inspection resulted in a five-items FDA-483 issued to the firm for:

- No stability data for Active Pharmaceutical Ingredient (API) (b) (4) qualification lots completed and/or available for review during the inspection.
- Proposed and/or revised Master Batch Records (MBRs) for the manufacture of API (b) (4) (b) (4) , process validation lots, are deficient.

- Change control procedures do not specify changes to specifications and test methods,
- Change control procedures are not always followed.
- Laboratory investigation and Corrective and Preventive Action (CAPA) procedures are deficient.

Corrective actions to observations were observed as completed during this inspection.

This inspection covered the three primary objectives of the PAI program: readiness for commercial manufacturing, conformance to the application, and data integrity audit. A general six system approach to the inspection was performed with coverage of applicable systems including quality, facilities and equipment, materials, production, laboratory, and packaging and labeling systems. Records and documents reviewed included, but were not limited to non-conformance/deviations, out of specification investigations, change controls, method validations, release testing, stability, equipment qualification, laboratory computer systems, data integrity, master batch production records, annual product review, and applicable standard operating procedures.

The firm continues to provide analytical service, drug development and Non-sterile Manufacturing Services. No FDA-483, Inspectional Observations, was issued at the close of the inspection. No physical samples were collected. No refusals were encountered. The firm's registration is current. During the close-out meeting, the firm was informed that based on the inspection conducted, (b) (2), (b) (4), (b) (5) .

ADMINISTRATIVE DATA

Inspected firm:	Eurofins Advantar Laboratories, Inc
Location:	5451 Oberlin Dr Ste 100 San Diego, CA 92121-1716
Phone:	858-228-7788
FAX:	
Mailing address:	5451 Oberlin Dr Ste 100 San Diego, CA 92121-1716
Email address:	joepage@eurofinsus.com
Dates of inspection:	3/1/2021-3/5/2021
Days in the facility:	5
Participants:	**Santiago Gallardo Johnson, Investigator** **Nicholas L Hunt, Drug Specialist**

Non-FDA Participants: None

On 3/1/21 we (Gallardo Johnson and Hunt) presented our credentials and issued FDA-482, Notice of Inspection, to Joseph D. Page, President (**Attachment 1**). Mr. Page identified himself as the most responsible person at the firm. On 3/5/21, a closeout meeting was held to which Mr. Page was in attendance.

This was a team inspection conducted by Investigator Santiago Gallardo Johnson and Drug Specialist Nicholas L. Hunt. Both investigators were present for the entire inspection. Sections of this report were authored by team members as indicated by the following initials: SGJ (Santiago Gallardo Johnson) and NLH (Nicholas L. Hunt). "I" refers to the author of the report section as indicated by their initials. The term "We" refers to all team members present during the inspection at the time. The term "the firm and EALI" refers to the site of this inspection, Eurofins Advantar Laboratories, Inc. located at 5451 Oberlin Dr. Ste 100, San Diego, CA 92121-1716. The term (b) (4) refers to the application product (b) (4) No other in-plant inspectors or agencies were encountered during this inspection.

Post inspectional correspondence and FMD-145 letter should be addressed to:
Joseph (Joe) D. Page, President
5451 Oberlin Dr. Ste 100
San Diego, CA 92121-1716
Phone: 858-228-7788
Email: JoePage@EurofinsUS.com

HISTORY (SGJ)
Advantar Laboratories was founded and incorporated in Delaware in 2008. In April 2016, Advantar Laboratories was acquired by Eurofins Scientific, headquartered in Brussels, Belgium and was renamed Eurofins Advantar Laboratories, Inc. The firm is a contract provider of drug development and non-sterile manufacturing services.

The firm's previous inspection conducted between 1/25/2016 – 2/3/2016 was classified VAI.
Business/Production hours are (b) (4).
The firm has been at the current location since 2012. Operations are conducted in a leased building approximately (b) (4) square feet. Number of Employees is (b) (4) The firm's website is https://www.eurofinsus.com/biopharma-services/biopharma-testing-services/biopharma-product-testing/us-locations/san-diego-ca/.

The firm's presentation is included as **Exhibit 1.**

INTERSTATE (I.S.) COMMERCE/JURISDICTION (SGJ)
The firm continues to supply analytical testing and drug product development services to pharmaceutical companies. The firm also performs testing of commercial pharmaceutical products and purifies API ((b) (4)) for use in commercial product, (b) (4) under NDA (b) (4) The firm obtains raw materials such (b) (4) from (b) (4)

(b) (4) which is used in the manufacture of the API (b) (4) Finished API is shipped to the manufacturing facility in (b) (4), for the manufacturing of finished the finished drug product.

The firm's API manufacturing and analytical testing operations are regulated by the Food, Drug, and Cosmetic Act (The Act) and applicable CGMPs delineated in the ICH Q7A guidance.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED (SGJ)(NLH)

Joseph (Joe) D. Page, Ph.D., President

Mr. Page is the most responsible person on-site and oversees the daily operations at the firm. He has been with the firm for over ten (10) years and with the pharmaceutical industry since 1991. He has a hiring and firing authority. He has (b) (6) Mr. Page received the FDA-482.

Joyce Riney, Director Quality Assurance

Ms. Riney has been with the firm since 2012 and 2 years in her current role. She oversees Quality Assurance Unit and the Control Document Unit. She manages the day to day operations as well as internal and external audits. Is responsible for the compliance of the site and a liaison between the EALI and global QA. She is responsible for conducting review and to report to clients and has the authority to recall products. Ms. Riney reports to Mr. Page and has the authority to hire and terminate. Ms. Riney provided the majority of the information included in this report and was the main contact and coordinator during the inspection.

(b) (6), Group Lead Quality Assurance

(b) (6) has been with the firm since 2011 and in her current role for approximately 3 years. She reports to Ms. Riney and has the same responsibilities as QA manager but no authority to hire and terminate employees. (b) (6) conducts client and regulatory audits and vendor qualification. (b) (6) accompanied us during the inspection.

Thomas Kovalcik, RPh, Ph.D., Vice President of Development and Manufacturing

Mr. Kovalcik reports to the President and has been employed at the firm since 2015. He has (b) (4) (b) (4) direct reports. He oversees the Manufacturing/Development Projects, Metrology, Facilities, Material Control Management, and IT. He approves batch records for use and has hiring and termination authority. Mr. Kovalcik has capital expenditures authority of $(b) (4) and reports to Mr. Page. He has been in the pharmaceutical industry for over thirty (30) years and has (b) (6) (b) (6).

Ryan Preston, Ph.D., Project Director Laboratory Operations

Mr. Preston joined the firm three years ago in his current position. As a Project Director, Mr. Preston is the primary contact between the firm and clients. His responsibilities include: writing

quotes, working with clients in experiment design, writes protocols, and manages investigations with clients. Mr. Preston manages (b) (4) analysts and has the authority to hire and terminate. He has a $(b) (4) expenditure cap. Mr. Preston reports to Ms. Nguyenle.

Other personnel who provided relevant facts, documentation and/or escort assistance during the EI included:

Linh Nguyenle, Ph.D., Head of Laboratory Operations
Ziaollah Rashidi, Technical Operations Manager
David Yeakel, Director, IT Operations
Dan Beidler, Director, Product Development
(b) (6), Metrology Technician
(b) (6), Associate Scientist
(b) (6), Group Lead, Senior Scientist
Dan Murphy, Metrology Manager

Exhibit 2 includes a copy of the firm's organizational chart.

FIRM'S TRAINING PROGRAM (SGJ)
I reviewed the firm's written procedure SOP3000-C003, Rev. 6 "Training Procedure," effective 4/1/2019, which defines procedures for conducting and documenting training for employees at the firm. GMP training is provided during introductory training and (b) (4) at a minimum. I reviewed the training records for employees (b) (6) Associate Scientist and (b) (4) Group Leader I, Senior Analyst. No deficiencies were noted.

MANUFACTURING/DESIGN OPERATIONS (SGJ)(NLH)
This was a pre-approval inspection for NDA (b) (4). The application holder, (b) (4) This product is currently manufactured at (b) (4). Eurofins Advantar Laboratories, Inc. performs stability testing (except (b) (4)) of (b) (4) drug product registration batches; stability storage, release testing (appearance, (b) (4), container content for (b) (4)).

Application coverage included a review of records from the (b) (4) manufactured exhibit batches, observation of analytical processes, review of change control records associated with the release and stability testing, storage of stability samples, review of analytical data and equipment, and review of investigations and deviations.

General GMP systems coverage to support product commercialization with focus, where applicable, on the firm's commercial analytical services. Coverage included: Quality, Facilities and Equipment, Materials, and Laboratory systems.

OBJECTIVE 1: READINESS FOR COMMERCIAL MANUFACTURING
Review was performed on the firm's analytical records for commercial scale exhibit/submission/stability batches, non-conformances/deviations, change controls associated analytical methods, finished product and stability testing, supplier qualification. Coverage of specific records and practices are discussed in detail in various sections of this report including Quality System and Laboratory System. Records reviewed appeared to be complete and adequately documented.

OBJECTIVE 2: CONFORMANCE TO APPLICATION
Release test records, stability data, supporting documents and reports, and procedures which we reviewed during this inspection appeared to conform with the chemistry and manufacturing controls (CMC) section of the submitted application. Verification of elements of the CMC section of the application was performed by direct observations of raw data and analytical methods. Raw data records were reviewed for lots supporting the stability of the product described in the application.
Records were consistent with the general description of processing methods identified in the application. Records appeared to be in conformance to submitted records and no deviations from the application were noted. No missing records or lack of original electronic records was noted.

OBJECTIVE 3: DATA INTEGRITY AUDIT
CMC data integrity audits were performed on deviations, investigations, laboratory analyst notebooks, and release and stability testing. Conformance to prescribed processing methods was verified. Original methods along with instrument and sequence audit trails were reviewed. Computer systems and retention of raw data was challenged including mock data integrity changes, permission levels of analysts, and ability to alter audit trails. Data sets reported by the site are complete and accurate. No data integrity concerns were noted during the inspection.

QUALITY (SGJ)(NLH)

Quality Agreements

We reviewed (b) (4) between Eurofins Advantar Laboratories and (b) (4) (b) (4) included as **Exhibit 3.** We also reviewed the Quality Agreement between (b) (4) and EALI effective 22 March 2020.

Annual Product Reviews (SGJ)

I reviewed "(b) (4) API Annual Product Quality Review (APQR) Advantar Part No. (b) (4) . Review period Jan 2020 – December 2020. The document represents the firm's initial APQR for (b) (4) with assigned product number (b) (4) batches were manufactured during the period. All

batches were released. No batches were rejected, re-processed or reworked. No deficiencies noted.

Exceptions (NLH)

Exceptions include out-of-specification (OOS), out-of-trend (OOT), out-of-alert (OOA), out-of-tolerance (OOT), non-representative result (NRR), planned deviation, unplanned deviation, protocol acceptance criteria failure, client request, and other categories. List of (b) (4) Exceptions for the last two years is included as **Exhibit 4**. We examined exceptions for (b) (4) (b) (4) API, and (b) (4) drug product. The majority of OOS were related to impurity specifications at the (b) (4) time point during (b) (4) temperature and humidity stability studies. The investigations determined these were expected results for a product intended to be stored in (b) (4) conditions. Corrective and preventive actions (CAPAs) were opened and executed for exceptions when appropriate. We did not observe deficiencies during our review of the following exceptions and their related CAPAs:

OOS

(b) (4)

Deviations

(b) (4)

Complaints (SJG)

Complaints received for the firm's analytical services or API manufacturing are handled via procedure SOP2000-C0012, "Complaint Handling Procedures". Quality Agreements between EALI and (b) (4) outline the responsible parties. In both agreements, EALI will assist the sponsor in the event of a recall, complaints, adverse event, or field alerts.

Change Control

The firm tracks changes for documents, software, and equipment through the following procedures:

SOP1000-C0003, Rev. 14, "Procedures for the Generation Review and Processing of Compliance Policies and Procedures Documents"; SOP1000-C0006, Rev. 11, "Test Method Creation and Management"; SOP1000-C0009, Rev. 9, "Specification Creation and Management"; SOP1000-C0010, Rev. 6, "Equipment Change Control Procedures"; and SOP1000-C0009, Rev. 4, "Software Change Control Procedures". We reviewed change control records for (b) (4) , and (b) (4) Changes were primarily updates to analytical methods and narrowing of specifications. We did not observe deficiencies.

(b) (4)

We reviewed the following Specification Change Requests:

Specification Title; Release and Stability Specifications for (b) (4)
(b) (4)

Specification Title: Release and Stability Specifications for (b) (4)
(b) (4)

Specification Title: Release and Stability Specifications for (b) (4)
(b) (4)

(b) (4)
(b) (4)

(b) (4)
(b) (4)

FACILITIES AND EQUIPMENT (NLH)(SGJ)

Temperature and Humidity Monitoring

(b) (4) provides remote monitoring and alerts for low and high excursions. The firm has data loggers installed on storage chambers as a local backup for the remote monitoring service. We examined the following chambers used to store stability samples for (b) (4)
(b) (4)
. There were no issues with temperature and humidity monitoring.

Equipment Calibration and Qualification (NLH)

Ziaolla Rashidi, Technical Operations Manager, and (b) (6) , Metrology Technician; provided most of the information related to calibration and qualification.

I reviewed (b) (4), Equipment Qualification Protocol for the Calibration and Maintenance or Any Secure Storage Area Controlled/Monitored for Temperature and Humidity, effective 05/30/18. The firm used this protocol to perform (b) (4) qualifications for stability chambers. Qualifications assessed uniformity and consistency of temperature and humidity over (b) (4). The technician performed an open-door study at the end of the (b) (4) data collection. Temperature and humidity probes for routine monitoring were placed in the worst-case locations identified during qualification. I did not observe deficiencies when I reviewed the two most recent sets of qualification records for chambers used to store stability samples for (b) (4), selected chromatography equipment, balances, and (b) (4) equipment:

Stability Chambers

(b) (4)

HPLC

(b) (4)

(b) (4)

Balances

Dan Murphy, Metrology Manager, explained calibration and maintenance of equipment at the firm. The firm experimentally sets the operating range which does not exceed the upper limit set by the manufacturer for balances. Minimum net weights are established. Analysts document (b) (4) verification of the upper and lower limits. I did not observe deficiencies when I reviewed the two most recent sets of calibration records for balances (b) (4) (b) (4)

(b) (4)

(b) (4) Calibration and Maintenance of the (b) (4) System, (b) (4) issued 08/03/18, approved 10/29/18

Cleaning

I reviewed (b) (4), Equipment Qualification Protocol for Cleaning of and (b) (4). The qualification established clean and dirty hold times, contained detailed instructions, and listed the approved cleaning agents.

MATERIALS (NLH)(SGJ)

Warehousing and Controlled Room Temperature Storage

Warehouses we examined were clean and organized. (b) (4), Controlled Room Temperature Storage, is a secure area within the firm's warehouse used to store finished products, reserve samples, excess production materials, quarantined finished products, and other items. There were additional secure areas within the warehouse for ambient storage of finished products. Materials management personnel located every item we requested using the established processes.

The firm uses two written procedures to manage incoming materials. SOP5000-C0001, "Laboratory Materials Receipt Procedures", Rev. 12, effective 11/25/19 and SOP5000-C0011, "Manufacturing Materials Receipt and Quarantine Procedures", Rev. 8, effective 03/11/19. Both procedures are included as **Exhibits 5** and **6.**

Laboratory materials flow is as follows: (b) (4)

(b) (4)

Raw materials flow is as follows: (b) (4)

(b) (4)

Supplier Validation (SGJ)

Vendors/suppliers used for GMP/GLP activities must be qualified before use per the written procedure. SOP2000-C0009, "Vendor/Supplier Qualification and Audit Process," effective 2/11/2021 is used to manage the program. Procedure is included as **Exhibit 7** The type of audit depends on the criticality level of the materials/services. We did not observe deficiencies during our review of the firm's list of approved Vendor/Supplier or the following vendor qualifications: (b) (4) for (b) (4), conducted 01/11/21; (b) (4) for (b) (4) conducted 01/11/21; (b) (4) for (b) (4), conducted 05/09/19; and (b) (4) for (b) (4) (b) (4) approved 02/14/19. The most current Approved Vendor List is included as **Exhibit 8.**

Water System

We reviewed the firm's (b) (4) Water system trend report for the years 2019, 2020, and 2021. The water generated by the (b) (4) System is used for manufacturing equipment cleaning and in the preparation of reagents. Water used as a material in manufacturing is (b) (4) We conducted a walkthrough of the water system and reviewed Equipment Log Book for (b) (4) Water System, (b) (4). No deficiencies noted. Water system P&ID and trend report is included as **Exhibit 9.**

PRODUCTION (NLH)(SGJ)

(b) (4) API Production

(b) (4) API is the only commercial product produced by Eurofins Advantar Laboratories, Inc. The firm produces approximately (b) (4) of (b) (4) API (b) (4) in Room (b) (4). The general process flow includes (b) (4), and packaging. All productions steps occur in (b) (4) room with dedicated equipment. Investigator Gallardo Johnson observed production of lot (b) (4) on 03/04/21. There were no deficiencies.

(SGJ)

On 4 Mar 2021, I observed the (b) (4) and packaging of (b) (4) Lot No (b) (4) in room (b) (4)

(b) (4) operators are authorized in the room at one time during operations. The API material was already in the room's (b) (4). All packaging material and labels are staged in the room and inspected as part of the room clearance process. (b) (4) handled the product while (b) (4) (b) (4) observed and verified everything was performed according to the batch records.

After the (b) (4) , operator collected (b) (4) QC sample using a (b) (4) . After the QC sample is collected (b) (4) is collected as a retain sample.

Packaging and Labeling (SGJ)

One label is applied to one of the liners. The operator applied a duplicate of the label on the batch record. Senior QA, (b) (6) , reviewed the labels on the batch record and on the liner.

The empty liners are placed inside the pail and the product is poured into the double liners until the required weight of (b) (4) is reached. Once the balance registers (b) (4) and the operators verify the weight, the inner bag is sealed with a zip tie. The bag with the remaining product is also sealed and stored with the QC sample. Per. Mr. Kovalcik, the excess material is kept with the QC sample and turned into Material Control. We verified the practice during a visit to Control Room Temperature Storage (b) (4) where we saw retain samples stored with the excess material.

The second plastic liner is also sealed and then the top is placed on the pail. A serialized cable tie is used to seal the pail providing tamper proof.

Front label is applied, and QA verifies label and the cable tie serial number against the batch record. QA exits and operator applies a warning label on the opposite side of where the product label was placed. QA enters and verifies the warning label on the pail against the label placed in the batch records. No issues noted during the process.

Batch Production Records (NLH)

Thomas Kovalcik, V.P., Manufacturing and Development; explained the production process and records for (b) (4) . The firm executes batch records per an approved protocol. Technical Protocol: Preparation, Initial Testing, and Repackaging of (b) (4) , Active Pharmaceutical Ingredient for Use in Clinical Supplies and/or Commercial Product. We did not identify any issues during our review of executed batch records for lots (b) (4) (b) (4) . **Exhibit 10** includes a list of (b) (4) commercial lots.

LABORATORY (NLH)

Overview of Analyses Performed for Commercial Products

(b) (4) API: release and stability testing (b) (4) drug product: release testing for (b) (4) API, release testing of drug product, stability testing of drug product (b) (4) (pending approval): release testing of drug product, stability testing of drug product, plan to cease release testing of (b) (4) drug substance (**Note**: firm performed QC release of drug substance for the registration batches)

Data Integrity

QC release and stability testing records for each batch of (b) (4) and (b) (4) we examined appeared complete and consistent with information contained in the laboratory notebooks. We did not observe unexplained discrepancies or deviations from the approved procedures.

Unplanned deviation (b) (4) was opened for an incorrectly integrated chromatogram of (b) (4) drug substance. The impurity was not reported with a shoulder drop and the entire peak region was not reported with proper endpoints. The peak was (b) (4) to the baseline and the impurity was reported with a shoulder drop. We compared the original chromatogram and raw data in (b) (4) to the reintegrated data. The reintegration appeared appropriate. There was slightly higher impurity for the lot, but the result remained within the approved specification. The firm executed a CAPA to clarify the integration instructions in the analytical method. The updates were intended to ensure all impurities were reported and all peaks were integrated along the baseline.

Analytical Software

The firm uses the current version of (b) (4) software for all its chromatographic systems. The system administrator is located at Eurofins Lancaster, but there is a local administrator with permissions to create and remove user accounts. SOP8000-C0004, (b) (4) Chromatography Data System Procedures; provides guidelines for the overall management of the software by the firm. Topics such as access controls and integration instructions are addressed. Chromatographic systems include (b) (4). (b) (4) data examined during this inspection included system policies, user roles, user groups, audit trails, (b) (4) (b) (4) sequences, system suitability, integration parameters, system methods, consistent integration of endpoints for peaks, and other information. We performed a detailed review of raw data in (b) (4) for the following analyses of registration batches:

(b) (4)

Analytical Methods and Validation

We examined analytical methods for all release and stability tests for (b) (4) The firm validated methods using (b) (4) commercially available lots of (b) (4) Method validations included identity, (b) (4) . Assessments of robustness for each method were performed in separate protocols from the other validation elements. Robustness included (b) (4) . Methods appeared to be stability-indicating. Validations established expiration dates for sample solutions and (b) (4) . We reviewed validations for the following methods:

(b) (4) **Drug Substance**

- Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Substance; (b) (4), approved 02/12/20
- Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Substance; (b) (4) approved 07/17/20

(b) (4) **Drug Product**

- (b) (4)
  - Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 02/13/20
    - Identity, assay, percentage purity, percent individual and total impurity/degradation products (related substances) for (b) (4) API and (b) (4) drug product
  - Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 07/17/20
  - Technical Protocol; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation, (b) (4) approved 01/23/20
  - Technical Report; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation, (b) (4) approved 05/20/20
- (b) (4)
  - Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 06/05/20
  - Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 12/11/20
  - Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 06/05/20
  - Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 07/17/20
  - Technical Protocol; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation; (b) (4) approved 09/25/19
  - Technical Report; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation; (b) (4) approved 03/02/21
- (b) (4)
  - Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 01/22/20
  - Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Product; (b) (4) approved 07/10/20
  - Technical Protocol; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Substance; (b) (4) approved 05/29/20
  - Technical Report; ICH Compliant Validation of (b) (4) Test Method (b) (4) (b) (4) for Analysis of Drug Substance; (b) (4) approved 11/23/20

- Technical Protocol; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation; (b) (4) approved 10/31/19
- Technical Report; Robustness Assessment of (b) (4) Test Method (b) (4) (b) (4) to Supplement the ICH Compliant Validation; (b) (4) approved 01/30/20

(b) (4)

- Technical Protocol; (b) (4), Verification of Compendial Test Methods (USP Monograph) for (b) (4) API (Active Pharmaceutical Ingredient), dated 11/19/15
- Technical Report; (b) (4), Verification of Compendial Test Methods (USP Monograph) for (b) (4) API (Active Pharmaceutical Ingredient), dated 02/12/16
  - (b) (4) Impurities ((b) (4)), (b) (4)

Analytical Method Observation

We observed Associate Scientist (b) (6) prepare samples of (b) (4) on 03/02/21. Ryan Preston, Project Director, explained the formulation was slightly different from the (b) (4) product formulation, but the sample preparation was the same. We did not observe deficiencies during sample preparation and setup of the analytical equipment.

Laboratory Notebooks

The firm generated protocols for all release, stability, and validation analyses. We examined protocols and the associated laboratory notebooks used to document method validations, release testing, and stability testing for registration batches of (b) (4) and (b) (4) batches of (b) (4) Documents included:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Analytical Balances

Dan Murphy, Metrology Manager, demonstrated the access controls for analytical balances. No system menus could be accessed without a password which was maintained by personnel without direct responsibility for approving laboratory data. Scientists in the laboratory could weigh, print, and perform calibrations. They did not have access to the date and time functions.

Stability

Ryan Preston, Project Director, explained the process for stability pulls. We examined stability set (b) (4), Protocol (b) (4), lot (b) (4) for (b) (4). We physically counted multiple sets of stability samples in chamber (b) (4) and reconciled the number with the firm's sampling records. There were no discrepancies. We verified samples were stored per the orientation indicated in the stability commitments.

Reserve Samples

The firm stores reserve samples in the controlled room temperature storage room, (b) (4) (b) (4). We examined reserve samples for (b) (4), lot (b) (4). The sample quantity matched what

was listed in the executed batch record, and there was no obvious evidence of deterioration. Per Ms. Riney, all reserved samples are evaluated (b) (4) .

PACKAGING AND LABELING (SGJ)

Label Management

I reviewed the "Label Creation, Receipt, Quarantine, Inspection, Release and Reconciliation" SOP9000-C0005, Rev. 4, effective 20 Nov 2020, included as **Exhibit 11.** Labels are maintained and controlled by the Control Document Unit.

Labels are printed from a template housed in the (b) (4) system. Anyone with access to (b) (4) can access and print labels; however, labels used in production need to be issued by the Control Document Unit. Ms. Riney explained the process as follows:

- When the batch record is printed by the Control Document Unit, operators log into (b) (4) and print the labels per specification (b) (4) .
- Once the labels are printed, they are submitted to the Material Control Management who reviews the labels and ensures the data is accurate
- Once approved, the labels are taken to the Control Document Unit where they are stored in quarantine
- QA releases the labels to production

No discrepancies noted with packaging and labeling operations.

MANUFACTURING CODES (SGJ)

Manufacturing codes are assigned in accordance with Quality Manual CPD9000, "Compliance Policy Document for Manufacturing Control System", Rev. 8, effective 01/22/21.

Per the procedure, for each manufacturing project, a completed Notebook Record serves as Master Batch Record. For each manufacturing project, a completed Notebook Record serves as a Batch Production Record. Finally, a technical report describes the outcome of each manufacturing activity. Batch number or lot numbers are assigned as the Notebook Record document (b) (4) (e.g. (b) (4)) unless otherwise directed by the sponsor. Written procedure is included as **Exhibit 12.**

RECALL PROCEDURES (SGJ)

Recalls are handled via procedure SOP2000-C0013, "Product Recall Procedure." Per Ms. Riney, the firm has not had any recalls or withdrawals.

GENERAL DISCUSSION WITH MANAGEMENT (SGJ)

On 03/05/21, we, Investigator Gallardo Johnson and Drug Specialist Hunt, held a closeout meeting with firm management. In attendance in the room were Mr. Page, Ms. Riney, Ms. Nguyenle, Mr. Kovalcik, Mr. Preston, Mr. Beidler, and (b) (6) . During the closeout meeting, the firm was informed no significant objectional conditions were observed and no Form

FDA-483, Inspectional Observations, was issued. Additionally, we also informed the firm that based on the inspection conducted, (b) (2), (b) (5)

EXHIBITS COLLECTED

1 EALI's presentation, 19 pages
2 EALI's Org Chart, 4 pages
3 EALI and (b) (4) Quality Agreement, 18 pages
4 List of (b) (4) Exceptions (Last 2 years), 2 pages
5 Laboratory Materials Receipt Procedure, 22 pages
6 Manufacturing Materials Receipt and Quarantine Procedures, 18 pages
7 Vendor/Supplier Qualification and Audit Procedure, 43 pages
8 Approved Vendor List, 2 pages
9 Water P&ID and trend report for 2019, 2020, and 2021, 2 pages
10 List of Commercial Lots of (b) (4) 1 page
11 Label Creation, Receipt, Quarantine, Inspection, Release and Reconciliation, 8 pages
12 Compliance Policy Document for Manufacturing Control System, 14 pages

ATTACHMENTS

1 FDA 482 Issued to Mr. Page, 3 pages
2 Initial Field Recommendation (IFR), 2 pages

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Office of Pharmaceutical Quality Operations 4

Nicholas L. Hunt -S
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