U.S. FOOD & DRUG ADMINISTRATION

Pharmaceutical Quality Investigation Branch
19701 Fairchild Road
Irvine, CA 92612
www.fda.gov

Via UPS
Return Receipt Requested

01/24/2019

Mr. Janmejay R. Vyas
Chairman
Dishman Carbogen Amcis Limited
Survey No. 47, Paiki Sub Plot No. 1
Lodariyal, Taluka Sanand-Bavla
Ahmedabad, Gujarat 382 220, India

Dear Mr. Vyas:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Dishman Carbogen Amcis Limited, FEI:3004161218, located at 47 Paiki Sub Plot No. 1, Survey No, Lodariyal, Gujarat, 382220 India from 10/22/2018 - 10/26/2018. FDA has determined that the inspection classification of this facility is "voluntary action indicated" ("VAI").[1] Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance with regards to current good manufacturing practice (CGMP).

A VAI inspection classification indicates that, although investigators found and documented objectionable conditions during the inspection, FDA will not take or recommend regulatory or enforcement action because the objectionable conditions do not meet the threshold for action at this time. Despite this facility inspection classification, FDA recommends that you address any observations noted on the Form FDA 483 issued at the the conclusion of the inspection or otherwise conveyed to you following the inspection. If not corrected, the same or similar conditions could lead to a future inspection being classified as "official action indicated" ("OAI").

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

An inspection classification of VAI for CGMP compliance will not directly negatively impact FDA's assessment of any pending marketing application referencing this facility. Please note, however, that application approval will depend on a product-and application-specific facility assessment conducted by the appropriate CDER or CVM review office. This letter does not address or reflect FDA's decision making with respect to any potential non-CGMP compliance issues.

FDA has concluded that this inspection is "closed" under 21 CFR 20.64(d)(3), and we are enclosing a copy of the narrative portion of the Establishment Inspection Report (EIR). It may reflect redactions made by FDA in accordance with the Freedom of Information Act (FOIA) and 21 CFR part 20. This, however, does not preclude you from requesting additional information under FOIA.

If you have any questions regarding this letter, you may contact me at (949) 608-3519 or email at Katherine.Jacobitz@fda.hhs.gov.

Sincerely,

Katherine E. Jacobitz -S

CAPT Katherine E. Jacobitz
Investigations Branch Director, Division IV
Office of Pharmaceutical Quality Operations

[1] See Inspection Classification Definitions, at https://www.fda.gov/ICECI/Inspections/ucm223231.htm.

Establishment Inspection Report	FEI:	**3004161218**
Dishman Carbogen Amcis Limited	EI Start:	10/22/2018
Lodariyal, Gujarat, 382220 India	EI End:	10/26/2018

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SUMMARY

This surveillance inspection of an active pharmaceutical ingredient (API) manufacturer was conducted at the request of CDER according to TRIP 2019-019D and eNSpect Operation ID 101033. The inspection was performed according to CPGM 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspections. The Quality, Materials, Production, and Packaging and Labeling Systems were chosen for coverage. Other systems had limited coverage during a walk-through of the facility. The products [redacted] and [redacted] (used in liposomal formulations) were chosen to facilitate systems coverage. Documents examined include training records, complaint investigations, change control records, deviations, SOPs, annual product quality reports (APQR), vendor qualifications, and batch records. The firm's API products fall under profile CSN. Additional information pertaining to this firm is in the CDER-prepared site dossier, **Attachment 2.**

The previous inspection took place 07/05-08/2016. It was a surveillance inspection that was classified VAI. At that time the firm was named Dishman Pharmaceuticals and Chemicals Ltd. The inspection covered the Quality, Facilities and Equipment, Laboratory Control, and Production Systems. The inspection concluded with the issuance of a two-item Form FDA 483, Inspectional Observations, for complaints not adequately investigated and out-of-specification events not adequately investigated.

The current inspection verified corrections related to the previous inspection. At the conclusion of the inspection, a two-item FDA 483 was issued to the most responsible person on-site for:

- blending in-specification and out-of-specification intermediate batches
- not conducting OOS investigations of intermediate batches

Firm management promised to address these observations and respond in writing within 15 business days.

The inspection was observed by a drugs inspector with the Central Drugs Standard Control Organization (CDSCO) of India. No samples were collected and no refusals were encountered during the course of the inspection.

ADMINISTRATIVE DATA

Inspected firm:	Dishman Carbogen Amcis Limited
Location:	47 Paiki Sub Plot No 1, Survey No Lodariyal, Gujarat, 382220 India
Phone:	(++91)2717669600
FAX:	(+91)792642 0198
Mailing address:	47 Paiki Sub Plot No 1, Survey No Lodariyal, Gujarat, 382220 India
Email address:	
Dates of inspection:	10/22/2018-10/26/2018
Days in the facility:	5
Participants:	**Alan P Kurtzberg, Investigator**

On 10/22/2018, I initially displayed my credentials to Parashat Vaishnav, Sr. GM for QA in the firm's conference room. When Janmejay R. Vyas, Chairman, entered the conference room, I also displayed my credentials to him. Mr. Vyas identified himself as the most responsible person on-site. No Form FDA 482, Notice of Inspection, was issued due to the nature of a foreign inspection.

Drugs Inspector Shashi Paul of the CDSCO acted as an observer during the inspection.

On 10/28/2018, I issued an FDA 483 to Mr. Vyas. The observations listed on the form were discussed with Mr. Vyas and management representatives during a closing meeting.

Note that dates listed in this report are in the format mm/dd/yyyy. Dates on exhibits collected from the firm are in the format dd/mm/yyyy.

HISTORY

The company was founded in 1983 as Dishman Pharmaceutical and Chemicals Ltd. In 1996, the inspected site was established to produce bulk intermediates and APIs. In 2017, the company name was changed to Dishman Carbogen Amcis Ltd. The company has a global presence with 10 manufacturing sites and 1400 employees in India, Switzerland, Netherlands, UK, France, and China. See **Exhibit 1** for a list of the addresses of the corporate headquarters and India manufacturing sites. **Exhibit 2** lists all manufacturing sites. Dishman is a public company listed on the Bombay Stock Exchange. Globally, the company provides APIs, intermediates, vitamins, disinfectants, and has a major business in contract research services. The major markets for the company are the U.S., the EU, and Japan.

The inspected site employs about 700. Office hours for the firm are 9:00am - 5:30pm, Monday - Saturday. Production is done in three shifts: 7:00am - 3:00pm, 3:00pm - 11:00pm, 11:00pm - 7:00am. The facility closes each year for 7-10days for Diwali.

The firm was last inspected by FDA 07/05-08/2016. The surveillance inspection was classified as VAI. The firm was also inspected 02/10-13/2015. This inspection was also VAI. The site has also been inspected by Australia's TGA (most recent in 2013) and Japan's PMDA in 2017.

The U.S. agent for the firm is:
Bhavesh Oza
Dishman USA Inc
476 Union Avenue, Second Floor
Middlesex, NJ 08846
phone: (732) 560-4300
email: bhaveshoza@dishmangroup.com

FMD 145 and other correspondence should be addressed to:
Janmejay R. Vyas, Chairman
Dishman Carbogen Amcis Limited
Survey No. 47, Paiki Sub Plot No. 1
Lodariyal, Taluka Sanand-Bavla
Ahmedabad, Gujarat 382 220, India

INTERSTATE (I.S.) COMMERCE/JURISDICTION

The firm manufactures intermediates and APIs for manufacture into human drug products. **Exhibit 3** is a list of products which have been supplied to the U.S. market since 2016. This list includes the

product code and therapeutic category. **Exhibit 4** is the same list of products with quantities shipped to the U.S. shown. **Exhibit 5** shows products with a filed DMF. **Exhibit 6** shows which of those products have been referred to in an NDA or ANDA. A complete list of products with product codes is given in **Exhibit 7**. Approximately 19% of sales are for the U.S. market.

Major suppliers of the firm's key starting materials are India-based companies. Those companies along with the firm's major U.S. customers are listed in **Exhibit 8**.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

See page 9 of **Exhibit 9** for an organizational chart to better understand reporting relationships.

During the inspection, my primary points of contact were Parashat Vaishnav and Kirti Rawal. They answered my questions, provided requested documents, and requested subject matter experts when needed. Ms. Rawal also accompanied me to and from the firm each day.

Senior General Manager - QA Parashat Vaishnav has been with the company since September 2006. He has been in his current role since June 2015. Mr. Vaishnav is responsible for quality assurance operations at the site. He establishes and implements the Quality Management System (QMS), approves level 1 documents, decides Validation/Qualification strategy, and acts as technical advisor during investigations. Mr. Vaishnav reports to Himani Dhotre, CEO.

General Manager - Regulatory Affairs Kiri Rawal has been with the company for 20 years. She assumed her current duties in August 2010. Ms. Rawal is responsible for preparation, submission, and life cycle management of regulatory filings in the U.S. and other countries. Ms. Rawal reports to Himani Dhotre, CEO.

The top management officials present were Chairman Janmejay R. Vyas and Chief Executive Officer Himani S. Dhotre. Dr. Dhotre reports to Mr. Vyas. They were present for the opening and closing meetings as well as some of the daily wrap-ups. Other members of the firm's management were available as needed.

FIRM'S TRAINING PROGRAM

Training is governed by the SOP BDQA-293 revision 04, Training, effective 03/20/2018. Training types include OJT (SOP and practical), orientation and induction (new employee training done by department), internal (GMP and other topics), and external. Employees may not conduct independent work until their OJT is complete. Internal training which is evaluated by a questionnaire

requires minimum score of 80% or retraining occurs. The procedure defines criteria for the firm's trainers. A list of qualified trainers is maintained by the HR department.

I examined the training records of Dharmendra Kumar H. Zala, a trainee in the production area with a start date of 01/18/2018. Introductory training was given 01/18/2018. Basic GMP was recorded on 01/19/2018. SOP training is listed over the period 01/30/2018 - 07/31/2018. Hetal Kumar R. Prajapati is a senior offocer in the warehouse with a start date of 06/20/2013. A record of induction training was not available. The firm indicated that documentation practices have improved since that time. The most recent GMP training is recorded as 05/17/2018. The most recent training on the SOP for receipt of materials is recorded on 07/27/2018.

MANUFACTURING/DESIGN OPERATIONS

I walked through the facility on 10/22/2018. In the microbiology laboratory, I observed the analysts wearing sandals which exposed much of the foot. See **Discussion Item 2.**

QUALITY SYSTEM

I examined a number of SOPs. Also see sections on training, complaints, and recalls. SOPs are reviewed by the firm, at a minimum, every three years.

I reviewed SOP BDQA-210 revision 16, Handling of Deviation, effective 11/10/2016. This SOP covers unplanned deviations only. Planned deviations are covered in the firm's change control procedure. Deviations are categorized by their potential impact to quality. Minor deviations must be closed within 15 days. Major deviations must be closed within 30 days. Critical deviations closing requirements are not defined by the procedure. A form is included to document the process and approvals.

I examined deviation [redacted], initiated for batch [redacted] of [redacted] 03/12/2018. The firm has a requirement that stage I material have not more than [redacted] of impurity [redacted]. When analyzed, this batch yielded a result of [redacted]. No OOS investigation was performed on this result. See **Observation 2.** The deviation investigation indicated that the impurity could be due to an improper pH adjustment at [redacted]. The firm made the pH requirement [redacted] at [redacted] a critical parameter. Samples must now go to the QC lab for measurement in addition to the production samples. Operators were also retrained on pH meter calibration. The deviation was classified as major. Accelerated stability studies were recommended for the packaged batch, but no long-term studies were requested. See **Discussion Item 3.** On 03/30/2018, a report was signed that the material would not pass finished API specifications if allowed to proceed in production. and the material would be kept on hold pending further decision. However, the R&D

group subsequently recommended that the material could be blended with other batches. The failed batch was used in [redacted] manufacturing blended with other batches that met the [redacted] requirement. The first of these [redacted] batches was manufactured beginning 04/10/2018. See **Observation 1**.

I reviewed deviation [redacted], initiated for [redacted] on 01/18/2018. During preparation of the annual product review (APR) for this product, it was discovered that samples had not been pulled in 2017 for routine, on-going stability studies. QA received retraining on pulling samples.

I reviewed the 2017 APR for [redacted], document APR-[redacted]17. This product's DMF is held by the company's [redacted] site. The product is currently manufactured in Unit 6B. The manufacturing process and critical parameters are listed. The storage condition for this product is given as not more than 25°C. A total of five batches were packaged in 2017. There were no OOS, deviations, or reprocessed/reworked batches. Two complaints were received and investigated concerning product seal. No stability data were included as stability studies are performed by the customer. I also examined the 2017 APR for [redacted], document [redacted]. A total of [redacted] (which includes packaging) batches were manufactured in 2017. This product is manufactured in [redacted] The manufacturing process and critical parameters at each stage are listed. There were no OOS, deviations, or reprocessed/reworked batches. Three complaints were received and investigated concerning extraneous material. The impurities for two batches were noted at the specification limit of not more than [redacted].

PRODUCTION SYSTEM
The site covers an area of 300,000m^2. Production is divided into 18 manufacturing units. Nine of the units are for API manufacturing. Six of the units are for intermediate production. During my walk-through of the facility, I went into Unit 9 (high potency manufacturing) and Unit 2 (API manufacturing of medium batch size). Unit 9 is not in commercial production, but plans include the manufacture of the cancer API, [redacted]. The unit features its own dispensing area (as opposed to the warehouse dispensing area).

I was told that for US marketed products, reprocessing is permitted. Rework is not allowed.

I reviewed the manufacturing record for batch [redacted] for [redacted] For a summary of the manufacturing process, see **Exhibit 10**. The equipment in this manufacturing process is dedicated and batch to batch cleaning is noted in the batch record. I also reviewed the manufacturing record for batch [redacted] for [redacted]. See **Exhibit 13** for a summary of the manufacturing process. The equipment in this manufacturing process is not dedicated. There

were no major issues in documenting the manufacturing steps in these records.

On 10/25/2018, I observed production of batch [redacted] of [redacted] in [redacted]. I watched material being transferred to the centrifuge. Two centrifuges were available, and the batch was split into two sub-lots for this process. Three operators were in the area at the time. Batch record entries appeared contemporaneous.

I examined the process validations of [redacted] performed in 2017 and [redacted] performed in 2011. No issues were noted in the protocols or associated reports.

MATERIALS SYSTEM

Raw materials are unloaded, de-dusted, and inspected. Cold (2-8^{0}C) material storage is available. Temperature is recorded two times a day in the cold storage area. When I observed the area on 10/22/2018, I noticed a small puddle of standing liquid on the floor that appeared to be water. See **Discussion Item 1**. A cool (15-25^{0}C) storage area is also available. The firm uses a combination of paper forms and SAP to manage inventory. Labels for materials are generated by SAP. Material status is controlled in SAP. Labels have a color-coded area that indicates status (green: approved, yellow: on-test, red: rejected). A chained-off area is used to segregate materials on-test. QC staff pulls samples. Rejected materials are stored in a locked area with limited access. A reject log is used to record RM rejects.

I reviewed SOP BDWH-152 revision 17, Receipt and Storage of Raw Materials and Packaging Materials, effective 08/01/2018. The procedure adequately describes the entry of material into the Inward Register and into the SAP system. The procedure includes checklists for inspection of the in-coming delivery vehicle and for an initial inspection of the material.

I examined SOP BDQA-292 revision 08, Vendor Approval, effective 08/01/2018. Samples are to be evaluated by QC and R&D. For key starting materials, an on-site audit is required a minimum of every three years. Foreign suppliers do require an on-site audit.

I reviewed the vendor qualification of [redacted] Chem Ltd, the back-up supplier for [redacted]. [redacted] is a key starting material for the manufacture of [redacted]. This qualification is dated 02/10/2017. The qualification includes a questionnaire, a sample evaluation by QC and R&D, and an on-site audit performed in 10/2016. I also checked the qualification of Dishman (Netherlands) BV, supplier of chloesteryl acetate. Cholestryl acetate is a key starting material for [redacted]. This qualification is dated 10/31/2017. The qualification includes a questionnaire and an assessment of batches manufactured. No on-site audit was performed.

API leaves the facility by company truck or contract freight. Destinations for the material are generally Mumbai or the Ahmedabad airport.

PACKAGING AND LABELING SYSTEM

Packaging of API is done into 30-80L plastic drums or into fiber drums. The drums are double-lined with polyethylene (PE) bags. Drums have numbered seals which say "Dishman." Labels on the drums are printed and issued by QA. I observed the packaging area in Unit 2. The room was supplied with HEPA-filtered air. Every six months, a HEPA filter integrity test is performed. If criteria are not met, the filter is replaced. The test is currently being performed by Validair Engineers of Ahmedabad. I looked at the last three filter integrity tests and found no issues. The humidity specification for the room was less than 65% and the temperature less than 27°C. Samples of the packaged material are taken to QC. The packaged drums wait in a quarantine area until released by QA. They are then taken to the finished goods warehouse.

I reviewed the packaging record for batch [redacted] for [redacted]. The inner bag for this product is a white antistatic PE bag. It is labeled. The outer bag is a black antistatic PE bag. The bags are inserted into 15 x 21in fiber drums. A net weight of 25kg is contained in each drum. A copy of the drum exhibit label is provided as **Exhibit 11**. Label reconciliation is done by QA in a separate logbook. I also reviewed the packaging record for batch [redacted] for [redacted]. This material (1kg) is scooped into a 12 x 14in laminated pouch. Ten pouches are packed into each blue HDPE drum.

MANUFACTURING CODES

The procedure for lot numbering is SOP BDQA-227 revision 11, Batch Numbering System, effective 11/10/2017. The SOP excludes Unit 10 which is used for formulation work. According to the SOP, API lots are coded in the format 1XXYYYAZZZ where:

the number 1 is used to represent the inspected site (Bavla plant, Lodariyal, Gujarat)
XX represents the last two digits of the year manufactured
YYY is a three-character product code (see **Exhibit 7** for a list of product codes)
A is a character used to represent the stage of the batch - the number 0 is used for the final, packaging, stage
ZZZ represents a three-character sequence starting with 001 - after 999, the sequence goes to A01 - after A99, the sequence goes to B01

COMPLAINTS

I reviewed SOP BDQA-212 revision 07, Handling Customer Complaints, effective 01/12/2018. The firm classifies complaints into categories of critical, major, and minor. All complaints received are forwarded to QA using the form attached to the procedure. An initial acknowledgement is required within two working days. An investigation must be complete within 30 days. After an additional 30 days (or after customer feedback, if received sooner) the complaint may be closed. Annual trending of complaints is required.

I reviewed complaint CC/2017/012, received on 08/03/2017. The complaint was that a customer found a cap nut on a sieve that batch [redacted] ([redacted]) had passed through. The firm classified the complaint as major. After receiving the sample from the customer, the firm identified the cap nut as the type used in their mill. However, there were no cap nuts missing from the equipment. It was concluded that the nut was replaced and not documented. As corrective action action, the firm implemented a new system for reporting issues with items such as nuts, bolts, and gaskets. The system adds a reporting form which is reviewed by QA.

I looked at complaint [redacted], received on 05/29/2018. A black hair was found by the customer while sifting batches [redacted], [redacted], and [redacted] ([redacted]). The firm indicated that the packaging area is a class 100,000 area. The firm's documents and practices were reviewed. One possible source for a hair was considered to be from gowning that was improperly laundered. As corrective action, the firm changed the laundry facility for their gowning.

I examined complaint [redacted], received on 04/25/2017. This complaint was for batch [redacted] ([redacted]) having a leaking seal. The complaint was classified as major. Operators were retrained on applying a seal and the batch record was revised to provide greater detail in these steps.

RECALL PROCEDURES

I reviewed SOP BDQA-248 revision 07, Recall of Goods, effective 07/04/2017. A recall decision is required as soon as suspected product is identified by QA. Recalls are classified as Class I, II, or III. The recall timeline depends on the recall class. Class I is 24 hours, Class II is 10 days, and Class III is 30 days. Recalled material is placed in a quarantine status and kept under lock and key. The head of QA or the customer will inform the appropriate regulatory agency in the event of a recall immediately after the recall decision is made. The firm conducts a mock recall every three years (if no actual recall has been performed).

No actual product has been recalled since the previous FDA inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483
PRODUCTION SYSTEM
1.) Blending of in-specification with out-of-specification (OOS) intermediate batches is performed.

Specifically, [redacted] ([redacted] intermediate) batch [redacted] tested OOS for impurity [redacted]. The batch was manufactured starting on 03/05/2018. QC testing of this batch yielded a result of [redacted] for the impurity against a specification of less than or equal to [redacted]. Deviation investigation [redacted], written for this incident, calls for this batch to be blended with other batches that have an in-specification result for [redacted] manufacturing. The OOS batch was blended with in-specification material as follows:
A.) [redacted] kg of batch [redacted] blended with [redacted] kg of batch [redacted] to manufacture [redacted] batch [redacted]
B.) [redacted] kg [redacted] blended with [redacted] kg of batch [redacted] and [redacted] kg of batch [redacted] to manufacture [redacted] batch [redacted]
C.) [redacted] kg of batch [redacted] blended with [redacted] kg of batch [redacted] to manufacture [redacted] batch [redacted]
D.) [redacted] kg of batch [redacted] blended with [redacted] kg of batch [redacted] and [redacted] kg of batch [redacted] to manufacture [redacted] batch [redacted]

The manufactured [redacted] batches were used in the production of packaged lots [redacted], [redacted], [redacted], [redacted], and [redacted] of [redacted]

Supporting Evidence and Relevance:
Exhibit 14 is a copy of deviation [redacted], dated 03/12/2018. Page 7 of the exhibit states that the batch does not conform to specifications. Line item 7 on that page shows the OOS result for impurity [redacted]. The investigation indicates that lack of pH control at [redacted] in the manufacturing process may have contributed to the OOS. The material produced at [redacted] is an intermediate to used (all or in part) in the next process ([redacted]) with a separate batch number to produce the API. At the bottom of page 35, it states in part, "...the quality of final API...does not comply...by using the Batch No. [redacted]...it is concluded that material of deviated batch cannot be used to proceed for further stage." Corrective action 4 on page 36 states to hold the material for a further decision but corrective action 6 on the next page indicates to blend the OOS material with in-spec material from other batches.

Exhibit 15 contains pages 1 and 3 of each blended [redacted] batch using the OOS [redacted] material. This exhibit shows the quantities of each batch used as stated in the observation.

Discussion with Management:
Management indicated that the recommendations came from R&D. I told the firm that intermediate specifications should be carefully set and followed. If an intermediate does not meet its specifications, it could be an indication of an uncontrolled processing parameter. In this case, the pH of the [redacted] batch may have varied. The firm indicated that they understood the observation and intended to respond in writing within 15 business days.

LABORATORY CONTROL SYSTEM
2.) Laboratory investigations for OOS intermediate batches are not conducted.

Specifically, according to SOP BDQC-311 for OOS investigations (effective 07/16/2018), OOS is to be conducted on "...all quantitative and qualitative tests of...intermediates..." An investigation of an OOS impurity result in the [redacted] intermediate, batch [redacted], for [redacted] was not conducted.

Supporting Evidence and Relevance:
Exhibit 16 is a copy of SOP BDQC-311. Page 1 of the exhibit contains section 2.0, Scope. The scope includes intermediates. No investigation was performed on the referenced intermediate batch.

Discussion with Management:
Management stated that it is not their practice to conduct OOS investigations for material at this stage. They indicated that they understood the observation and would respond in writing within 15 business days.

REFUSALS
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

On 10/26/2018, I met with a group of the firm's management to discuss my findings during the inspection. Present for that meeting were the following individuals.

- Janmejay R. Vyas, Chairman

- Himani S. Dhotre, Chief Executive Officer
- Parashat Vaishnav, Senior General Manager - QA
- Armanino Paolo, Senior Vice President
- Kirti Rawal, General Manager - Regulatory Affairs
- Digant Chokshi, Vice President - Engineering & Maintenance
- Paresh Patel, Senior General Manager - Production
- Amit Patel, General Manager - Production
- Kesavarao Teki, General Manager - QC & ADL
- Rajesh Acharya, Associate General Manager - QA

Also present at this meeting was Shashi Paul, Drugs Inspector for the CDSCO.

During the meeting, the following **Discussion Items** were presented.

1. A standing liquid with the appearance of water was observed on the floor of the cold storage warehouse. The firm indicated that the liquid was water left from cleaning activities. They stated that they would be using a wringable mop in the future. I was given documentation, **Exhibit 17**, concerning corrections made.
2. Sandals worn in the microbiology lab leave feet exposed. The firm said that no product is exposed in the area and gave me a risk assessment, **Exhibit 18**.
3. Long term stability should be performed on [redacted] API product affected by deviation [redacted]. The firm agreed with this and presented me with documentation, **Exhibit 19**, to show the initiation of a study.

An FDA 483 was issued to Mr. Vyas and discussed with those present. The firm indicated that they understood the observations as presented and committed to a written response within 15 business days. I provided the firm contact information for submitting their response.

ADDITIONAL INFORMATION

During the inspection, I stayed at the Courtyard Marriott Ahmedabad. The hotel provided shuttle transportation to the airport. A one-way trip from the airport to the hotel is about 30 minutes depending on traffic. The hotel has amenities including free wi-fi and breakfast buffet. The firm provided transportation to and from the facility. A one-way trip from the hotel to the firm is about 45min depending on traffic.

SAMPLES COLLECTED

No samples were collected during the course of this inspection.

VOLUNTARY CORRECTIONS

Corrections to observations from the previous inspection were verified. The observation is quoted in italics below. My observations concerning corrections follow.

Observation 1: "*...Complaint #[redacted] dated 8/21/14 regarding lumps in [redacted] determined that the root cause of the lumps was due to the customer not properly closing the product packaging after sampling...it was determined that the complaint investigation was performed on a different grade of [redacted]*.." The only grades supplied by the firm are IP (India Pharmacopeia) and USP. Both grades are manufactured the same, just tested to different specifications. Both grades are labeled to protect from moisture/humidity. In this case, the customer was sold the IP grade for the domestic market. The customer acted as a distributor and resold the material to the end user. I read the extended investigation, dated 09/27/2014 and the addendum to the investigation, approved 07/07/2016 (**Exhibit 12**). The addendum indicates that the end user may have misused the API. The addendum indicates that the end user appeared to be doing dry powder vial filling. Only sterile powder is suitable for dry powder filling and the firm does not manufacture a sterile product. In addition to potential misuse, the addendum also indicates that the distributor may have repackaged the product prior to it reaching the end user. The firm reports no additional complaints for lumps have been received on this product and I found no investigations lacking in depth.

Observation 2: "*...OOS Investigation Report for [redacted] dated 2/21/15 regarding an OOS purity by HPLC for [redacted] concluded that a root cause could not be identified. A year later in OOS Investigation Report# [redacted] dated 4/16/16 the same OOS purity by HPLC for [redacted] occurred...the investigation of [redacted] concluded that the root cause of the OOS were the sampling technique for intermediate analysis of [redacted] and the temperature of the reaction mass in [redacted] of the manufacturing process. These root causes were not investigated or evaluated in the prior OOS investigation...*" I reviewed both investigations mentioned in the observations. The firm did not go back and examine data from the first incident while investigating the second incident. The firm has not had a repeat incident since modifying the temperature during [redacted] manufacturing. I looked at a more recent OOS report to see if they are being performed with better attention to detail. I looked at OOS investigation [redacted], dated 07/31/2018. The investigation was performed for batch [redacted] of [redacted] having an out-of-specification unspecified impurity. The investigation was thorough and found that the impurity was not being picked up at the in-process stage due to the window of non-integration (for the API peak) being too large. This was solved with a modification to the customer-supplied method (reduce the size of the window of non-integration).

EXHIBITS COLLECTED

1 Addresses for Dishman in India, dated 10/23/2018, 1 page
2 Dishman Manufacturing Sites, dated 10/23/2018, 3 pages
3 List of Products Supplied to the U.S. with Product Codes, dated 10/11/2018, 1 page
4 List of Products Supplied to the U.S. Market Including Quantities, dated 10/12/2018, 1 page
5 List of DMF Filed Products, dated 10/11/2018, 1 page
6 List of Products Referred in an NDA/ANDA, dated 10/11/2018, 1 page
7 List of Products, dated 12/08/2017, 2 pages
8 Marjor Suppliers and U.S. Customers, dated 10/23/2018., 2 pages
9 Opening Presentation, 30 pages
10 Process Flow Diagram for [redacted], 9 pages
11 Exhibit Label from [redacted] Batch [redacted], 1 page
12 Addendum to the Investigation Report [redacted], approved 07/07/2016, 1 page
13 [redacted] Process Flow Diagram, 6 pages
14 Deviation [redacted], dated 03/12/2018, 46 pages
15 Pages 1 and 3 of the Following [redacted] Blended Batches: [redacted], [redacted], [redacted], and [redacted], all issued by QA on 04/06/2018, 8 pages
16 SOP BDQC-311 Revision 16 Investigation into Out of Specification (OOS) Results, effective 07/16/2018, 16 pages
17 Compliance Report for Water Found on Cold Storage Floor, 3 pages
18 Compliance Report for Exposed Feet in the Microbiology Lab, 6 pages
19 Compliance Report for Initiation of Long Term Stability Studies of Batches [redacted] to [redacted], 4 pages

ATTACHMENTS

1 Form FDA 483 Issued to Janmejay R. Vyas, Chairman, on 10/26/2018
2 Site Dossier for GMP Surveillance Inspection, 2 pages

Alan P. Kurtzberg -S

Digitally signed by Alan P. Kurtzberg -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001403102, cn=Alan P. Kurtzberg -S
Date: 2018.11.30 08:34:35 -07'00'