DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	12/10/2018-12/18/2018 FEI NUMBER 3003144728

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Muralidhar Reddy Nomula, Site Head/VP Operations

FIRM NAME	STREET ADDRESS
Jubilant Generics Limited	No 18, 56, 57 & 58 Kiadb Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Nanjangud, Mysore, Karnataka, 571302, India	TYPE ESTABLISHMENT INSPECTED API Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Investigations are inadequate in that they do not evaluate all potential root causes of unexpected results nor are they adequately extended to potentially impacted products.

Specifically, investigations conducted to determine the root cause of the genotoxic and suspected human (b) (4) impurities (b) (4) which have been found in your (b) (4) API are deficient. For example:

A. Drug substances identified by your firm to possess a medium to high risk of contamination are not tested for (b) (4) impurities. As per your Risk Assessment (GEN/RAR/0046-R0), the manufacturing processes of multiple drug substances (such as (b) (4) ; (b) (4) ; were found to be at medium to high risk of formation of (b) (4) and (b) (4) impurities. The testing was limited to selected batches of (b) (4) API.
B. The site failed to extend the scope of the investigation and testing of the samples to include all possible sources of contamination such as analysis of raw materials, key starting materials, intermediates, process generated solvents, and recovered solvents.
C. The site failed to re-assess the cleaning validation program after the (b) (4) impurities were detected in (b) (4) API.

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		Dipesh Shah, CSO Saleem Akhtar, CSO Zedong Dong, Chemist	12/18/2018

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The site is continuously manufacturing (b) (4) and other APIs in Plant (b) (4) while all recommended actions during the risk assessment have not been implemented and the investigations are in progress. During the last year, the site has manufactured and shipped following (b) (4) APIs for the US market.

API Name	Batches Manufactured	Quantity (Kg)	Batches Shipped to US	Quantity Shipped into the US (Kg)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

OBSERVATION 2

Validated and/or transferred analytical methods are deficient.

Specifically, the analytical methods validated and transferred to detect and quantify (b) (4) impurities are deficient. For example;

A. The method validation for the GC-MS method for (b) (4) was not properly validated. For instance, your method validation protocol for (b) (4) (Protocol# QCD/PR/1099-R0) specifies that specificity shall be evaluated by verifying the retention time of (b) (4) in standard and spike preparations. You did not evaluate the interference due to the sample (b) (4)
B. The GC-MS methods was used for content determination of (b) (4) in the recovered solvents (b) (4) for the process validation studies without verification of their suitability for the intended use
C. Also, you have developed and validated a GC-MS method for (b) (4) at the analytical research department at (b) (4) site, and the method validation results were submitted to DMF (b) (4) Subsequently, the same GC-MS method was independently revalidated at the QC department at

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Nanjangud site. Significant response variability was observed in the method validation results between the two sites. For instance, the peak areas at LOQ level (b) (4) ppm) are (b) (4) and (b) (4) for the (b) (4) and Nanjangud sites, respectively. The response variability suggests significant issues with the reproducibility of the method.

D. Deficiencies were noted with the validation of the analytical method for the determination of (b) (4) content in (b) (4) by GCHSMS (protocol #MVP/VAL/013/00; report # MVR/VAL/013/00). Specifically, the method validation did not include the specificity studies.

E. The method transfer for (b) (4) content in (b) (4) by GCHSMS studies did not include the confirmation of the detection limit and the evaluation of the linearity (The calibration of GCMS # 333 used by QC lab did not include verification of the detector's response linearity). In addition, the reproducibility of the method is not properly demonstrated by comparing the results generated by different laboratories for samples with (b) (4) content above LOQ level. (Note: The (b) (4) sample chosen for the method transfer contained (b) (4) at "Below Detection Limit" level.)

OBSERVATION 3

The validation of your firm's cleaning process for non-dedicated equipment is deficient in that the cleaning process was not evaluated to demonstrate removal of residual contaminant(s) that could alter the safety, identity, quality or purity of the drug substance.

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	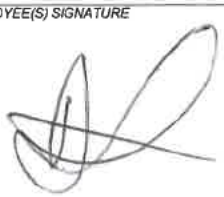	Dipesh Shah, CSO Saleem Akhtar, CSO Zedong Dong, Chemist	12/18/2018

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Specifically, your firm failed to evaluate the cleaning process for non-dedicated equipment located in production plant (b) (4) streams (b) (4) and (b) (4) The non-dedicated equipment in these streams are used in the manufacture of (b) (4) (Plant (b) (4) stream (b) (4), (b) (4) and (b) (4) (Plant (b) (4) stream (b) (4) These drug substance manufacturing processes were identified by your firm's Risk Assessment (GEN/RAR/0046-R0), to be either "Class I", high risk (b) (4) and (b) (4) or "Class II", medium risk (b) (4) for the formation of (b) (4) and (b) (4)

OBSERVATION 4 (REPEAT OBSERVATION)

Non-dedicated equipment used to manufacture drug substances is not maintained clean.

Specifically, two non-dedicated (b) (4) (equipment ID: (b) (4) -62104 and (b) (4) -62105) located in Unit (b) (4) Stream (b) (4) are not maintained clean. Both equipment are used to manufacture (b) (4) APIs (such as (b) (4) (b) (4) in Unit (b) (4) Stream (b) (4) On December 10, 2018, we observed:

A. White mass that appeared to be a product build up on the potential product contact surface of the (b) (4) -62105) was observed on December 10, 2018; a non-dedicated equipment. This equipment was most recently used to manufacture (b) (4) (batch # (b) (4) on December 5, 2018. Batch to batch and product change over cleaning was performed on December 6, 2018 and December 9, 2018 respectively to manufacture (b) (4)
B. A white plastic piece that appears to be part of a (b) (4) gasket was observed on December 10, 2018 to be sticking inside the product transfer line of (b) (4) 62104); a non-dedicated equipment. This (b) (4) is a non-dedicated equipment and the (b) (4) gasket along is not taken

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out during cleaning of the equipment. This equipment was most recently used to manufacture (b) (4) (batch # (b) (4) on 12/5/2018. Batch to batch and product change over cleaning was performed on 12/6/2018 and 12/9/2018 respectively to manufacture (b) (4)

C. Dispensing and Sampling Booth (DB-61001) located in Plant (b) (4) Stream (b) (4) is not maintained clean. On December 11, 2018, we observed sticky material that appeared to be product residue on the inside walls of the booth. This sampling booth is dedicated for (b) (4) and was cleaned on December 8, 2018. The site performs sampling and dispensing of the finished APIs in this area. The site has not established a use logbook for this sampling booth.

OBSERVATION 5

Production equipment is not stored appropriately to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Specifically, the production equipment such as (b) (4) (b) (4) are not stored appropriately to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API. On December 10, 2018, during the inspectional walkthrough of the site, we observed the aforementioned production equipment stored outside (in the open air under the sun) in the back of the Engineering and Projects shed. The equipment such as (b) (4) (b) (4) Storage Tank – SS304, (b) (4) MSGL was observed in an unwrapped condition with bird droppings. There is no procedure in place to clean or evaluate equipment after being stored in these uncontrolled conditions prior to reincorporating them in manufacturing processes.

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OBSERVATION 6

Finished APIs are not adequately segregated in the storage areas to prevent mix-up.

Specifically, on December 10, 2018, we observed co-mingled products in the Cold Room in Plant-(b)(4) In this room drug substances (such as (b)(4) (b)(4) etc.) with different status such as Approved, Quarantined, Rejected, returned, and Retest were not adequately segregated. The firm's control procedure (# PL6/SOP/029-R0) requires segregation of all materials stored in this room.

OBSERVATION 7

Manufacturing equipment is not maintained adequately.

Specifically, Air Handling Units (AHU-63104 and AHU-62107) that supply clean air to equipment wash area and Finished Goods Storage Area are not maintained adequately. For example:

A. On December 11, 2018, during the inspection of AHU-63104, we observed the return air duct connected with the AHU was not properly sealed and the return air was leaking. At another location on the return air duct, we observed about eight holes drilled into the duct. The firm was not sure as to why these holes were drilled.

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	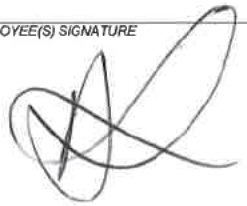	Dipesh Shah, CSO Saleem Akhtar, CSO Zedong Dong, Chemist	12/18/2018

B. During the inspection of Air Handling Unit (AHU-62107), we observed the pressure gauge (MG-462) connected to this AHU was not working. AHU-62107 supplies clean air to Finished Goods Area. We observed most of the surface of the intake air filter was clogged with dust.

OBSERVATION 8

There is inadequate control over the quality of starting materials and intermediate produced by the contract manufacturers.

Specifically, the Key Starting Materials (KSM) as intermediates used for manufacturer of (b) (4) drug substance are not verified for quality (for example impurity analysis). In lieu of conducting a comprehensive assessment on the quality of the KSM and intermediates, your quality unit accepts the certificate of analysis from the contract manufacturers. The lack of a comprehensive review and verification of the quality of the KSM and intermediates was confirmed through interviews during the inspection.

OBSERVATION 9

Appropriate controls have not been established for APIs.

Specifically, controls for (b) (4) have not been established when these impurities were detected in (b) (4) API. For example;

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A. Your risk assessment suggests that the reagents and recovered solvents used for the production of [(b) (4)] are likely to be the source for [(b) (4)] generated during the [(b) (4)] Furthermore, you have detected [(b) (4)] in the recovered solvents. However, you have not established appropriate controls for these two genotoxic impurities in the [(b) (4)] drug substance.

B. Your internal [(b) (4)] specifications and revision history indicate that the test for heavy metals is removed effective April 06, 2018. However, you have not submitted a risk assessment report to the regulatory Agency to justify the removal of the test.

C. Your risk assessment concludes that [(b) (4)] are in the high-risk category for [(b) (4)] However, you have not established any control on these two impurities in the aforementioned drug substances.

OBSERVATION 10

Buildings and facilities are not adequately maintained to prevent contamination of the drug substances manufactured at the site.

Specifically, the mezzanine area (where Air Handling Units-AHUs for Plant [(b) (4)] are located) is not maintained properly to prevent leakage of the volatile organic compounds from other areas into the mezzanine area and thus causing these volatile organic compounds being sucked by the AHUs into the Clean Areas. AHUs located in this mezzanine area provide clean air to manufacture drug substances in Plant [(b) (4)] Stream [(b) (4)] . The firm manufactures [(b) (4)] APIs (such as [(b) (4)] in Plant [(b) (4)]

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OBSERVATION 11

Deficiencies were noted with the calibration, handling and usage of the laboratory equipment.

Specifically,

A. The firm failed to properly control and monitor the temperature for the refrigerators and freezers in the chemistry and micro laboratories. In particular, the temperature was monitored during the working day only. The digital Min-Max thermometers used for the temperature monitoring were not checked for possible temperature excursions happened outside of the business hours. The following temperature excursions were noted during the audit:
B. The maximum temperature reading of 23.1°C was observed for the refrigerator used for the secondary standards storage (The refrigerator's labelled range was 2 – 8°C).
C. The maximum temperature reading of 24.9°C and the minimum temperature reading of 5.1 °C were observed for the freezer QC/RFT/082 used in the Microbiological laboratory (The labelled range was -18°C to -27°C). The lab personnel were not aware of these temperature excursions.
D. Deficiencies were noted with the usage of balances. The minimum weight calculated from the repeatability test was not always followed. For example, the balance #QC/ABM/248 was found to be labeled with two different minimum weight values: 1mg for qualitative analysis and 20 mg for quantitative analysis. The minimum balance weight determined during the balance calibration was 13.99 mg. During the discussion with the QA personnel, it was noted that this was not an isolated incident but rather the firm's routine practice to disregard the minimum weight determined during balance calibration and use it as per manufacture's manual for qualitative analysis. However, there was no assessment of the impact of weighing below the established minimum weight on the accuracy of the results generated.
E. Deficiencies were noted with the calibration and usage of pH meters:

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	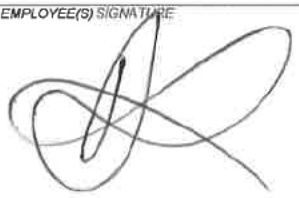	Dipesh Shah, CSO Saleem Akhtar, CSO Zedong Dong, Chemist	12/18/2018

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1- The calibration of the pH meter did not include a verification of a buffer with a pH value between pH values of the calibration buffers and verification of the slope and offset criteria as per current USP requirements.
2- In addition, two two-point calibrations were done consecutively for the routine pH meter (b) (4) calibration and entire range was considered as a pH meter calibration range. For example, pH meter QC/PHM/054 was calibrated on December 11, 2018 twice using two points calibration: buffers 4 and 7 were used for first two-point calibration and buffers 7 and 11 were used for the second two-point calibration. The actual calibration range is pH 7.00 – 11.00. However, the firm considered that the pH meter was calibrated for the pH range from 4.00 to 11.00 and pH= 4.33 was measured for the in-process sampie (b) (4) batch (b) (4)
3- The pH meter QC/PHM/054 was used beyond its upper calibration range 11.00 on December 12, 2018: pH=12.57 was measured for the in-process sample (b) (4) batch (b) (4)

F. The calibration of GCMS # 333 did not include verification of the detector's response linearity.

OBSERVATION 12

The creation, maintenance, processing, and/or review of laboratory data is inadequate.

Specifically,

A. The integration of the chromatograms was not always done properly. For example, the peak at RT (b) (4) min was improperly integrated and the peak at RT (b) (4) min was not integrated at all for the recovered (b) (4) purity testing (Sample set GLC_064_1802093).
B. The raw data was not always complete. For example, the titrant used for the assay by titration testing was not recorded for (b) (4) solution, batch numbers (b) (4) and (b) (4)

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