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 of a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

Specifically,

On 09/16/2021 during stability study sample analysis of Solution 1% Batch (9-Month Long Term), the test result did not comply with specification limit. The observed test result was %, while the Limit was NMT %. OOS-IO-153-21-0027 was initiated on 09/16/2021. The investigation did not identify any errors. Hence, the Out of Specification (OOS) result stood valid. The manufacturing investigation concluded that surface imperfections/aberration observed on some QC Batch have led to product loss under conditions of stability study at a certain orientation. However, this batch underwent a successful incoming material inspection when they were received at the warehouse and was released by your QA on 09/11/2020. No issues of surface imperfections/aberration were reported at that time.

Your firm performed Impact Assessment and the subject OOS Batch was recalled (RCL/IN2/21/04 10/18/2021). More batches of the same batch were also recalled (RCL/IN2/21/04 10/18/2021). The investigation further identified the defective Batch...
OBSERVATION 2 (Repeat)

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. Your firm failed to document deviations/equipment failures occurring during manufacturing and packaging in the batch record, initiate investigations, including risk assessments, and appropriate corrective and preventive actions (CAPAs) into the breakdown of critical process equipment/critical breakdown notifications in the manufacturing area for several US marketed products in

You recorded 1695 breakdown notifications from January 2019 to March 2023 for and 64 breakdown notifications for However, you investigated 41 breakdown notifications for and 7 breakdown notifications for
B. Deviation investigations are not thoroughly investigated by your firm and appropriate actions are not taken to prevent recurrence. For example,

a) Deviation #DEV-IO-136-20-0062 revealed that a foreign filled capsule was found by your inspector during the visual inspection of [redacted] mg Capsules in Batch no. [redacted] in Inspection area on October 20, 2020. The investigation revealed the foreign empty capsule was supplied in your shipment by your vendor and is a different specification. You utilized the capsule Batch # [redacted] where the foreign capsule was found to encapsulate [redacted] Capsules mg Batch # [redacted] that were released to the US market. However, you failed to file a field alert report (FAR).
b) Deviation #DEV-IO-136-22-0003: Manufacturing data was not captured in the data acquisition software for [Redacted] mg Batch # [Redacted] (US market). You lost manufacturing data for 10 minutes which is a critical step according to your Manager of Production and stated there was no product impact. However, this is a recurring deviation and you initiated an ineffective CAPA (CAP-IO-136-21-0022) for manufacturing data previously lost and where you proposed to capture data manually in the batch records.

c) Deviation #DEV-IO-136-19-0034: During the activity of Lot- [Redacted] mg for [Redacted] tablets of [Redacted] mg Batch # [Redacted], production person noticed that the [Redacted] was not started at the time of [Redacted] in [Redacted] material. You attributed the root cause to human error where you stated the operator might have missed to switch the “ON” power button although you stated in the investigation report there was no identification available whether the [Redacted] was on or off. However, you failed to interview the operator prior to reaching the root cause and the batch record does not delineate any instructions for the operator regarding turn on/off the switch.

C. Your firm failed to implement controls to support the integrity of your data. You recorded 16 breakdown notifications where manufacturing data was not captured in the data acquisition software for some manufacturing and packaging equipment during batch operations for the following US marketed products. However, you only investigate one out of [Redacted] of the breakdown. In addition, you released all the batches.
In addition, you recorded two repeated critical breakdown notifications (Notification ...(ti)(l)
where data was not captured and ...(ti)(l) were aborted. Notification ...(ti)(l) occurred.
D. Assigned root causes for laboratory OOS result are not always scientifically justified. Specifically,

a) OOS/C/19/IN2/SS/014 was initiated on 07/27/2019 for the OOS result observed in dissolution test analysis in product [redacted] Tablets USP during Batch [redacted] at 3 months (M) long term (LT) stability study. An observed OOS result of [redacted]% for Tablet [redacted] at [redacted] hour did not pass the specification limit of No Less Than (NLT) [redacted]% of the labelled amount as per USP requirement. One of your hypothesis studies demonstrated that wrong filter usage and without discarding aliquots would cause a similar OOS result. The investigation thus concluded the OOS result was attributed to laboratory error (human error). However, your investigation did not contain confirming information because the conclusion of wrong filters used was not substantiated by the analyst interview and the filters had been discarded. No manufacturing investigation was conducted. The observed OOS result was invalidated, results were within specification, and Batch [redacted] (Mfg. [redacted]) remained in the U.S. market with an expiration date of 01/31/2021.

b) OOS/C/20/IN2/SS/004 was initiated on 04/30/2020 for the OOS result observed in the Related Substances test of [redacted] Tablets USP during stability study at 24 M [redacted]. An individual unspecified impurity result [redacted]% was OOS for the specified limit of No More Than (NMT) [redacted]% . The hypothesis study and investigation concluded the root cause for unknown impurity peak was due to contamination of sample solution with [redacted] during sample preparation. However, the contamination was not admitted by the analyst. Further, the assigned root cause referenced an unrelated OOS investigation, where an experiment was conducted by [redacted] during sample preparation. No different probable contamination sources were assessed. The root cause that [redacted] contamination attributed to the observed impurity in Batch [redacted] was unsupported. No manufacturing investigation was conducted. The observed OOS result was invalidated, results were accepted, and Batch [redacted] (Mfg. [redacted]) remained in the U.S. market with an expiration date of 01/31/2021.
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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DATE(S) OF INSPECTION
03/21/2023 - 03/29/2023

PET NUMBER
3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Amit Sarseen, Site Head and Sr. Vice President - Manufacturing

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STREET ADDRESS
Unit - 2, Plot No. M2 and M2A, SEZ, Phase II, Misc. Zone, Apparel Park, Dist. Dhar

TYPE ESTABLISHMENT INSPECTED
Drug Manufacturer

OBSERVATION 3 (Repeat)

Written records of investigation of a drug complaint do not include the findings of the investigation and the follow-up.

Specifically, your complaint investigations are deficient. You have received several repeated market complaints for Capsules USP mg, mg Batch during stability study at 3M, Assay test result of % for content was OOS for the specified limit of % of label claim. The content result of % was within specification. The hypothesis study and investigation concluded the root cause for the observed OOS result was due to improper shaking during sample solution preparation. However, the assigned root cause was unsupported because the analyst stated applicable STP was followed. Further, Investigation Study PR-OOS/C/20/IN2/SS/006/02 demonstrated the different combinations of did not produce passing results on the batch. Your firm lacked scientific justification that improper shaking attributed to only OOS result. The observed OOS result was invalidated, retest results were accepted, and Batch remained in the U.S. market with an expiration date of 12/31/2021.

A. You received several complaints for foreign tablets/capsules including two complaints for Capsules USP (Complaint #DPC-IO-134-21-0041 on July 19, 2021 and DPC-IO-134-22-0069 on July 1, 2022) where the complainant reported that a foreign tablet with no marking...
were found in a sealed bottle. You concluded in your investigations that they did not occur at your facility which were unconfirmed. However, I observed you processed Deviation #DEV-IO-136-20-0062 where a foreign filled capsule with different marking was found by your visual inspector during visual inspection of product ___________Capsules 16 mg, batch no. _______ in Inspection area on October 20, 2020.

In addition, we observed during our inspectional walkthroughs that your packaging lines are not equipped with a vision system for detecting foreign capsules and tablets. We also observed collected in-process samples (tablets) from _______equipment (ID #TCM303) are returned to the equipment/batch during our inspectional walkthrough on March 21, 2023.

B. You recorded at least 40 complaints for short-count/underfilled and for different products from 2019 to date. You have not taken any appropriate actions to prevent recurrence although you concluded they did not happen at your facility through deficient investigation. We observed during our inspectional walkthroughs that you only challenge your checkweighers at the end of manufacturing and packaging operations. In addition, we observed that you recorded 18 notifications from the equipment breakdowns for checkweighers during operations where the checkweighers were not working or the _______was not working (as reported in Observation 2).

OBSERVATION 4 (Repeat)

Employees engaged in the manufacture, processing, packing and holding of a drug product lack the training required to perform their assigned functions.

You failed to monitor and ensure that personnel complete their assigned training by the due date. Training is assigned in SABA software (which was validated in 2011) and you do not assign the due dates in SABA. For example, the following personnel were assigned training in SABA and they are currently overdue. In addition, you failed to provide on-going CGMP training to contracted personnel at least:

- Employee ID #_________ (Manager, ______ – Overdue on _______ For New Joinee in _______Production assigned on 09/28/2016 and not yet completed.)
OBSERVATION 5

The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically.

A. You failed to adequately classify and assess Change control #CCP-MM-941-21-0003 initiated on January 14, 2023 for upgrading the Windows operating system from 2008 to 2016. You classified the change as “Minor” where revalidation is required and did not perform an assessment of the change.

B. You have not established quality agreements with the following suppliers:

Facilities & Equipment System

OBSERVATION 6

Equipment for adequate control over air pressure, humidity, temperature is not provided when appropriate for the manufacture, processing, packing or holding of a drug product. Specifically, you failed to requalify the HVAC systems (HEPA) for Building/Unit classified as ISO Class 8 per ISO standard utilized by your firm. You requalified the HVAC for Building, However, ISO 14644-2:2000 (E) states they must be performed at maximum time interval.
In addition, your requalification documents for HVAC system and equipment with HEPA listed below failed to include the service provider/third party who performed the requalification including their reports although the documents were approved by your Quality Assurance.

- Document #SR/3/044-02 (Requalification of HVAC System and Equipment with HEPA Filter, 09/29/21 approval date).

**OBSERVATION 7**

Substances required for equipment operations such as lubricants and coolants come in contact with drug product containers, closures, and drug product so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. Specifically,

A. During our inspectional walkthrough of the packaging operations on March 21, 2023, we observed the firm utilizes Laminar Air Flow (ID #LAF-303) in Bulk Packing which is classified as ISO Class-8 during operation where the bottles are However, the firm does not perform testing of the bottles operations.

B. You have not established action limit, alert limit, and limit for environmental monitoring (EM) of which is being utilized in area for bags that are filled with raw materials going to manufacturing In addition, we reviewed several sampling for where you recorded the following EM testing results and you concluded that all counts:

- June 29, 2020 sampling: Location The Limit for states “Informative”.

**E. O. A. Liu, Investigator**

**Yvins Dezan, Investigator**

**DATE ISSUED** 03/29/2023
Production System

OBSERVATION 8 (Repeat)

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

The Electronic Logbook (eLog) System V1.0.0 is used for Instrument, Equipment, Area Operation and Cleaning usage log for Production, Warehouse, and Quality Control departments of Lupin Limited. The eLog is not adequately controlled.

A. Your firm cannot assure us that access to the eLog system is adequately controlled. According to Annex_MUM_ITP_004403 (page of SOP_MUM_ITP_004150 Rev. 4.0 (User Management for Elog System)), the Service Vendor/Service Engineer is assigned the same rights and privileges as the System Administrator at Lupin (Page where under “Admin and Security”, the system administrator and service provider/vendor is able to set security profile, register new role, Set Global Profile, Register New User, Activate New User Account, Set User Account Status, Register Standard Reason, temporary password reset, etc.

B. In general, you do not document alarms in the batch records, review, investigate, assess, and trends alarms recorded in the data acquisition software during manufacturing and packaging operations at the facility. We observed on March 22, 2021, the HMI screens for and located in (Room a message displayed on the screen occurred March 17, 2023. According to your production management, these alarms are not documented and reviewed by your firm. In addition, alarms for vision systems in the packaging areas are not being recorded in the batch packaging record and investigate.
Laboratory Control System

**OBSERVATION 9**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, or followed. Specifically,

Your firm lacks sterility assurance for drug products already distributed to the U.S. market. Specifically, your sampling conducted in the filling line Room is deficient in that bottles instead of bottles are being used for. Specifically, and bottles are being used to conduct operations. During, these bottles are filled with growth media then incubated for 14 days. However, these bottles do not allow for visualization of microbial growth that may be present after incubation. Your firm lacks appropriately designed visual inspector qualification program that demonstrates visual inspectors can accurately identify different degree (including low level) of microbial contamination in these bottles. This deficient practice of using bottles for operation has been used since the commercial distribution of drug product in 2012.

**OBSERVATION 10**

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, test procedures designed to assure that components, drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,
Your failed to test [redacted] received from your supplier according to [redacted] Monograph as exemplified below.

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Acceptance Criteria</th>
<th>Lupin Acceptance Criteria</th>
</tr>
</thead>
</table>

Eileen A. Liu, Investigator

Yvins Dezan, Investigator

SEE REVERSE OF THIS PAGE

DATE ISSUED
03/29/2023