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	5/12/2022-5/20/2022*
	FEI NUMBER 3004672766

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Pareen Dashottar, Vice President & Site Head

FIRM NAME	STREET ADDRESS
Glenmark Pharmaceuticals Limited	Plot No S - 7, Colvale Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY Colvale, Goa, 403513 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

1. Investigations that confirmed leakage near the (b) (4) of (b) (4) dosage products were not thoroughly investigated to identify a root cause and extended to all relevant products packaged into (b) (4) tubes that are distributed to the US market. For example:

    a. Investigation INI103211322 dated November 23, 2021, was opened when a tube of (b) (4) Gel (b) % from exhibit batch (b) (4) for the European market was found to be leaking near the (b) (4) prior to testing for the six-month accelerated study timepoint. The product, tubes, equipment, and manufacturing process are the same as the already commercialized product for the US market.

    The investigation was closed without thoroughly investigating and did not identify a root cause for the leakage near the (b) (4) of the tube.

    Further, the investigation stated there were no related market complaints for commercialized (b) (4) Gel (b) % product. However, US market complaints for leaking tubes were received for (b) (4) Gel and other products manufactured on the same (b) (4) filling machine.

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	Justin A Boyd, Investigator Jose M Cayuela, Investigator - Dedicated Drug Cadre	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 05-20-2022 13:29:45	5/20/2022

b. Complaint GOMC20401 received September 4, 2020, for (b) (4) Ointment (b) (4) % batch (b) (4) (Expiry December 2021) from a distributor identified approximately 784 tubes with product leaking from the (b) (4) and discoloration due to leaking from the (b) (4). The complaint was closed as substantiated. The investigation was not extended to US market batches of (b) (4) Ointment (b) (4) % that were manufactured on the same (b) (4) filling machine or any other product manufactured on the (b) (4) filling machine.

c. Complaint GOMC21115 received March 19, 2021, for (b) (4) Ointment (b) (4) % batch (b) (4) (Expiry September 2022) from a distributor that identified approximately 45 tubes with discoloration near the (b) (4) end and leaking product from the (b) (4). The complaint was closed as substantiated, but the investigation did not identify a root cause and was not extended to US market batches of (b) (4) Ointment (b) (4) % that were manufactured on the same (b) (4) filling machine or any other product manufactured on the (b) (4) filling machine.

d. US market complaint GOMC18362 received on October 24, 2018, for (b) (4) Cream (b) (4) % batch number (b) (4) (Expiry August 2020). The complainant described the (b) (4) of the tube was leaking. The product was manufactured on the (b) (4) filling machine. The complaint was closed as substantiated with no market action taken.

e. US market compliant GOMC18371 received on October 30, 2018, for (b) (4) Cream (b) (4) % batch number (b) (4) (Expiry August 2020). The complainant described leakage from the (b) (4). The product was manufactured on the (b) (4) filling machine. The complaint was closed as substantiated with no market action taken.

The following US market leaking product complaints were received for products manufactured

into (b) (4) tubes on the (b) (4) or (b) (4) filling machines and were closed as unsubstantiated:

- Complaint GOMC19044 received on February 4, 2019, for (b) (4) Gel (b) % batch (b) (4) (Expiry August 2020). The complaint described a severe leak at the bottom of the tube. The product was manufactured on the (b) (4) filling machine.
- Complaint GOMC19055 received on February 13, 2019, for (b) (4) Gel (b) (4) % batch (b) (4) (Expiry May 2020). The complainant described the (b) (4) was incompletely sealed and leaking. The product was manufactured on the (b) (4) filling machine.
- Complaint GOMC19484 received on December 16, 2019, for (b) (4) Cream (b) (4) % unknown batch number. The complainant described the tube was splitting open and leaking out. The product was manufactured on the (b) (4) filling machine.
- Complaint GOMC20145 received on March 23, 2020, for (b) (4) Gel (b) (4) % batch (b) (4) (Expiry August 2021). The complainant described the (b) (4) at the bottom was leaking. The product was manufactured on the (b) (4) filling machine.
- Complaint GOMC20511 received November 13, 2020, for (b) (4) Gel (b) % batch (b) (4) (Expiry June 2022). The complaint described a hole in the bottom of the folded part. The product was manufactured on the (b) (4) filling machine.
- GOMC21313 received on August 2, 2021, for (b) (4) Ointment USP (b) % batch (b) (4) (Expiry February 2023). The complainant described the tube leaks all through the tube due to cracks. The product was manufactured on the (b) (4) filling machine.
- GOMC22044 received on February 6, 2022, for (b) (4) Gel (b) (4) % batch (b) (4) (Expiry April 2023). The complainant described the tube had leaks with product oozing out in several places other than the top. The product was manufactured on the (b) (4) filling

machine.

- MC/I103/2022/0004 received on March 2, 2022, for (b) (4) Ointment USP (b) % batch (b) (4) (Expiry April 2023). The complainant described how the (b) (4) end hissed and it seemed like the seal was not very good. The product was manufactured on the (b) (4) filling machine. This complaint was not yet closed as of May 17, 2022.

Further, multiple US market complaints for (b) (4) Ointment USP (b) % including, but not limited to GOMC22053, GOMC21432, GOMC21408 have been received for product that was dried out or difficult to remove from the tube. There has not been a thorough evaluation of whether these complaints are related to the market complaints and investigations identifying non-integral packaging.

2. OOS and Incident investigations have resulted in rejections of fourteen batches of (b) (4) (b) (4) Tablets since May of 2018 for failures of (b) (4), content uniformity, or stratified sampling. Additionally, there have been 10 valid OOT investigations since January of 2020. The investigations have not been thorough and extended to other batches, for example:

   a. Investigation INI102210272 was opened when stratified sampling of finished tablets assay in batch (b) (4) of (b) (4) Tablets (b) (4) mg did not meet specifications. The batch was rejected. The investigation identified the root cause to be use of a high (b) (4) setting for the (b) (4) on the compression machine. This caused segregation of (b) (4) powder in the (b) (4). No validated limits for the (b) (4) (b) (4) had been established.

      The investigation conducted a study to evaluate (b) (4) ratios and implemented new limits as a preventive action. This action was not extended to the other strength of this product, (b) (4) Tablets (b) (4) mg. It was not extended to ensure appropriate

(b) (4) limits were established for every tablet product produced for the US market.

Operators can change the (b) (4) during a batch, meaning a portion of the batch may use a higher (b) (4) and be more susceptible to (b) (4) segregation than other parts of the batch. The investigation did not evaluate compression machine PLC data to determine the (b) (4) used for previous batches of (b) (4) Tablets (b) (4) mg, for batches of (b) (4) Tablets (b) (4) mg, or for any other tablet product distributed to the US market that could have been impacted by segregation due to excessive (b) (4) for a portion or all of the batch.

b. Investigation OOSI10221029 was opened when batches (b) (4) and (b) (4) of (b) (4) Tablets (b) (4) mg failed (b) (4). The batches were rejected. The investigation identified the root cause to be a higher (b) (4) that led to the possibility of improper (b) (4) due to higher (b) (4).

The investigation implemented new, lower targets in the batch records for in-process (b) (4) of the (b) (4), but the specification was not changed. The final specification for (b) (4) of the (b) (4) of not more than (b) (4) % remained unchanged. Subsequent batches were found to have similar (b) (4) as the OOS batches, for example batches (b) (4). Additionally, the investigation recommended additional controls on the (b) (4) of the excipients, including (b) (4), but no changes have been made.

3. (b) (4) Gel (b) % batches manufactured October-November of 2020 resulted in OOS investigations OOSI10320189 (batch (b) (4)), OOSI10320200 (batch (b) (4)), and OOSI10320206 (batch (b) (4)) due to low viscosity. All three batches were rejected. The investigations identified the root cause as low intrinsic viscosity of an excipient, (b) (4) (b) (4), from the vendor (b) (4). All excipient batches had met the

established specification of (b) (4) - (b) (4) m^3/kg. The investigation did not implement new specifications for (b) (4) or thoroughly evaluate the impact of (b) (4) viscosity on the finished product before continuing production.

The investigation proposed using (b) (4) from a different vendor, (b) (4), which had the same specifications for (b) (4) viscosity of (b) (4) - (b) (4) m^3/kg as (b) (4) Subsequently, (b) (4) batches were manufactured in January of 2021 with (b) (4). Batches (b) (4) (OOTI10321007) and (b) (4) (OOSI10321009) were rejected due to high viscosity. The additional batches (b) (4) used (b) (4) with the same incoming viscosity value from the supplier of (b) (4) m^3/kg and internal testing of (b) (4) - (b) (4) m^3/kg that was observed for the rejected batches. Although they were within specifications results, they had higher viscosity than historical batches. The investigation did not thoroughly investigate these batches or ensure the testing of (b) (4) tube at random for finished product viscosity is supported by validation data demonstrating uniformity of viscosity throughout a batch. The investigation recommended going back to (b) (4) as the supplier.

Commercial production resumed with (b) (4), but no changes to the specification for (b) (4) viscosity have been implemented. (b) (4) that was found outside the range of (b) (4) - (b) (4) m^3/kg during internal testing has been approved and used in released batches. For example, batches (b) (4) and (b) (4).

4. Investigation OOSI10322011 was opened when (b) (4) Capsules (b) (4) mg batch (b) (4) failed specifications for content uniformity on January 20, 2022. The batch was rejected. The investigation identified the root cause to be too large of particle size of the API, even though it was within the existing specifications. The investigation was not extended to other strengths of the same product that used the same API to determine the impact of the API particle size on those strengths.

Additionally, OOTI10322008 was opened when (b) (4) Capsules (b) (4) mg batch (b) (4) was out of trend for content uniformity on January 24, 2022. The investigation attributed the higher variability to the same larger API particle size distribution described in OOSI10322011. The batch was released.

Subsequently, OOS I103/2022/0013 was opened when (b) (4) Capsules (b) (4) mg batch (b) (4) failed content uniformity on March 17, 2022. The same root cause related to particle size distribution of the API was assigned.

5. Investigation INI103211301 was opened when (b) (4) Tablet (b) (4) mg batch (b) (4) was found to have broken tablets during a hold time study prior packaging on November 16, 2021. The batch was rejected. The investigation did not thoroughly investigate and identify a root cause for why the tablets were broken.

   The investigation did not address market complaint GOMC21160 for batch (b) (4) of (b) (4) Tabs (b) (4) mg on April 8, 2021, which reported broken tablets and was closed as unsubstantiated.

   From batch (b) (4), there were 224 broken tablets and 2532 chipped/capped tablets rejected during in-process inspections. From batch (b) (4), there were 186 broken tablets and 3403 chipped/capped tablets rejected during in-process inspections. There are no established limits that would require further investigation based on the type and number of rejects observed during in-process inspection.

6. Investigation OOSI10321012 was opened when (b) (4) Capsules USP (b) (4) mg batch (b) (4) did not meet specifications for assay or organic impurities on January 21, 2021. The batch was rejected. The root cause described that remnants of (b) (4) from the (b) (4)

previously used in the equipment might not have been removed properly from the hosepipes and interacted with the API, causing the formation of the impurity. However, a hypothesis study was completed to apply (b) (4) directly to the tablet (b) (4) and the impurity peak was not generated. The data from the hypothesis study does not scientifically support the stated root cause.

7. Investigation OOSI10320163 was opened when (b) (4) Tablets USP (b) (4) mg batch (b) (4) was OOS for unknown impurities. The manufacturing investigation correlated the impurity peak to a disinfectant used in the (b) (4) area and the root cause identified that disinfectant solution may have been added to (b) (4) instead of (b) (4). Batch (b) (4) was rejected.

   Another batch, (b) (4) was observed to contain a peak at the same location and was included in the OOSI10320163 investigation. No phase 1a laboratory error was observed with the peak in (b) (4). Repeat testing and testing of packaged tablets did not identify the same peak as the original analysis, although the associated manufacturing investigation identified the disinfectant as a source of the peak at this retention time. The original analysis was invalidated and attributed to other laboratory contamination, without further identifying the source of that contamination. Batch (b) (4) was released.

8. Investigation INI103210468 was opened when a cleaning verification swab collected from the discharge valve of (b) (4) after batch (b) (4) of (b) (4) Ointment USP (b) % failed. Batches (b) (4) of (b) (4) Cream USP (b) % had already been manufactured in (b) (4) and was rejected. There was no cleaning verification swab taken after batch (b) (4). The next batch was (b) (4) of (b) (4) and (b) (4) gel (b) (4) %/(b) (4) % and cleaning verification was conducted following this batch and passed.

   No further additional cleaning verification samples were taken as part of the investigation to

determine if the cleaning process was still in a validated state. Routine cleaning verifications are taken only after batches of (b) (4) Ointment of (b) (4) Cream, based on their worst case PDE values, however these products are considered "very slightly soluble" and not the most difficult products manufactured on this equipment to clean.

9. INI103210838 was opened when (b) (4) in-process checks for tablet hardness for core (b) (4) (b) (4) Tablets USP, batch (b) (4), were above the established limit. The container the tablets were taken from was rejected. The root cause was attributed to leaving the tablet bag open to allow for sampling by IPQA after compression had been completed. The investigation included a hypothesis study that found if the tablets are left open to the environment for (b) (4) (b) (4) or more, their hardness will increase above the specification limit.

   As a result of the investigation, instructions were put into the batch record regarding protecting tablets during sampling, but no evaluation was made of how this impacted tablets. Including, how long the bags can remain open during normal operations or when there are stoppages for breaks or machine breakdowns. Additionally, this investigation was not extended to determine if other products were sensitive to the environment and required additional batch record instructions.

10. Investigation OOSI10320040 was opened when (b) (4) / (b) (4) tablets (b) (4) mg batch (b) (4) did not meet specifications for content uniformity. The batch was rejected. The root cause identified a lack of instructions for properly setting the compression machine including established ranges for (b) (4). As a preventive action, (b) (4) ranges were established for this product. The investigation was not extended to ensure appropriate (b) (4) ranges were established for all US market tablet products.

OBSERVATION 2

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There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

1. The initial process validation VR/PV/PD/807 for (b) (4) Gel (b) % did not thoroughly evaluate inter-batch or intra-batch variability. For example, only (b) (4) samples of filled tubes were tested for viscosity.

   To qualify a new supplier of the excipient (b) (4), one additional process validation batch was conducted and documented in VR/PV/PD/111. During this validation batch, (b) (4) tubes were sampled at each of the (b) (4) of filling. The validation report does not evaluate variability within the batch. The (b) (4) sample had the lowest viscosity with a result of (b) (4) poise and the values increased with each sampling timepoint until the (b) (4) sample, which had the highest result of (b) (4) poise.

   For (b) (4) Gel (b) %, there were three batches rejected in 2020 and two batches rejected in 2021 for failing to meet viscosity specifications.

2. Process validation studies for US market tablet products did not ensure there was data to support ranges for compression machine settings. For example:

   a. Product specific (b) (4) and (b) (4) limits have not been established for all products. The batch records list the operational capabilities of the machine, not the ranges that would ensure proper machine setting to produce tablets meeting all specifications. Investigations of rejected tablet lots have identified a lack of these parameters as a root cause.

   b. Validation reports used to support the establishment of compression machine compaction force ranges do not include raw data to support actual compression force during the

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manufacturing process. For example, process validation for (b) (4) Tablets (b) (4) mg and (b) (4) Tablets (b) (4) mg.

OBSERVATION 3

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Procedures to ensure accurate and consistent integration of chromatographic peaks have not been established.

1. Procedure CM/QC013 requires the use of the Apex Track Algorithm to be used for integrating all chromatograms. The procedure lists timed integration events that can be manually entered to modify the processing, but does not provide detail on when they should be used, how these events should be used, or how they are reviewed.

   For example, during the processing of (b) (4) Tablets (b) (4) mg batch (b) (4). The analyst manually entered events for percent liftoff and percent touchdown that applied to a single unknown impurity peak in the chromatogram. These parameters generated results of (b) (4) % and (b) (4) %, reported as (b) (4) % for this peak. This is a passing result compared to a specification of NMT (b) (4) %. If the percent liftoff and percent touchdown had been applied the same as all other impurity peaks and standard peaks the results would have been (b) (4) % and (b) (4) %, which would not have met specification.

   Even though the analyst is manually setting where the integration lines will be placed with the percent liftoff and percent touchdown, the practice is not captured in the requirements of CM/QC013 for manual integration. Manual integration requires supervisory approval and capture of the original system integrated chromatogram and the chromatogram after manual

changes for justification.

However, when the analyst manually entered the timed integration events into the processing method for (b) (4) Tablets (b) (4) mg batch (b) (4), the original Apex Track integrated chromatogram was not saved for review and justification of the changes. Only the final chromatogram is saved.

2. Procedure CM/QC013 requires a calculation for setting the minimum area for all related substances tests. The analysts are not recording this calculation and it is not being reviewed to ensure the processing method has integrated all required peaks.

   For example, during related substances testing for (b) (4) Tablets (b) (4) mg batch (b) (4) there was no documentation of the minimum area calculation. The minimum area was set in the processing method with a value of (b) (4). When calculated according to CM/QC013, the minimum area used in the processing method should have been (b) (4).

3. The chromatography procedures do not require additional evaluation of the method when there is interference with a peak of interest. For example, during testing of (b) (4) Cream batch of (b) (4) for related substances, a placebo peak was not resolved from known Impurity (b).

OBSERVATION 4

Batch production and control records do not include complete information relating to the production and control of each batch.

Procedure 19PD672 requires compression machine operators to calculate the tablet reject limits based on batch specific data from machine set-up. However, operators are using preset values without calculating the batch specific limits. If changes are made to the reject limits, these calculations are not documented in the batch record or reviewed to determine if the parameters were set correctly to reject

tablets that may not meet specifications.

During investigations into out of specification hardness limits documented in INI103210858 for batch (b) (4) of (b) (4) Tablets USP (b) (4) mg and INI103210838 for batch (b) (4) for (b) (4) (b) (4) Tablets USP (b) (4) mg, the investigations state in the impact assessment compression machines were set to reject non-conforming tablets. However, the investigations did not determine whether the rejection limits were set appropriately

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.

Specifically, three (3) dead legs with 3D values of (b) (4) were observed in the (b) (4) system that supplies (b) (4) for the (b) (4) and (b) (4) of (b) (4) dosage drugs (e.g., (b) (4) Tablets, (b) (4) Tablets, (b) (4) Tablets, (b) (4) Tablets, (b) (4) Tablets, and (b) (4) Tablets).

*DATES OF INSPECTION

5/12/2022(Thu), 5/13/2022(Fri), 5/16/2022(Mon), 5/17/2022(Tue), 5/18/2022(Wed), 5/19/2022(Thu), 5/20/2022(Fri)

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