DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738	11/6/2017-11/11/2017* FEI NUMBER 3005757050

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Darshan Makhey, President - Global Quality

FIRM NAME	STREET ADDRESS
Glenmark Pharmaceuticals Limited	Village Kishanpura, Baddi Nalagarh Road, Baddi
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Solan, Himachal Pradesh, 173205India	Finished Dosage 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

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,

Deficiencies noted during review of Out-of-Specification (OOS) Investigations deemed invalid by the firm between January 2015 and October 2017 include the following, but not limited to:

(A) OOS Investigation number 05/OOS15004 was initiated on January 23, 2015 to probe the Assay and (b) (4) failures associated with (b) (4) Ointment USP, (b) (4) % batch number (b) (4) The initial results ranged from (b) (4) % to (b) (4) % against a specification limit of (b) (4) % to (b) (4) %. A similar range of passing and failing results were obtained during re-injection of the same sample vial and re-sonication of freshly prepared samples from the same (b) (4) dilution. You did not investigate reasons for obtaining failing (b) (4) results ((b) (4) %) from the re-sonicated sample for (b) (4) location while the same location yielded passing results during the initial analysis ((b) (4) %) and re-injection ((b) (4) %). Additionally, you attributed the failure to sample preparation error by providing photographs of sample vials indicating the purported anomalous sample preparations. The photographs included in the investigation did not include a date stamp and your QA manager stated that copies of the photographs are not saved in electronic QA archives. Authenticity of

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the supporting photographs could not be verified by the FDA investigators. You invalidated the initial results through re-testing and reported passing results for Assay and (b) (4).

(B) You attributed the root cause for a number of stability-related OOS investigations to ruptured/damaged septa during analyses. However, the photographs indicating the purported ruptured/damaged septa do not include a date stamp and your QA manager stated that copies of the photographs are not saved in electronic QA archives. Authenticity of the supporting photographs could not be verified by the FDA investigators. Ruptured or damaged Septa is purported to be root cause only for stability-related tests that were invalidated. You invalidated the initial results through re-testing and reported passing results during each of the following OOS investigations:

Sr. No.	OOS No.	Product	Sample Stage	Batch No.	Test
1.	05/OOS15016	(b) (4) and (b) (4) (b) (4) Cream USP (b) (4) %	12 Month 30°C/65% RH	(b) (4) (b) (4) g (b) (4)	Assay and Tube Uniformity
2.	05/OOS16069	(b) (4) cream USP (b) (4) %	18 Month 25°C/60%RH	(b) (4) (b) (4) g (b) (4)	Related Substances
3.	OOSI10017014	(b) (4) Cream (b) (4) %, (b) (4) g	1 Month 40°C/75%RH	(b) (4) (b) (4) g (b) (4)	Tube Uniformity
4.	OOSI10017018	(b) (4) Cream (b) (4) % (b) (4) g	1 Month 40°C/75%RH	(b) (4) (b) (4) g (b) (4) Assay (b) (4) (b) (4) g (b) (4) (b) (4) Uniformity	Assay and Tube Uniformity
5.	OOSI10017029	(b) (4) Ointment (b) (4) %, (b) (4) g and (b) (4) g	9 Month 30°C/(b) (4) % RH	(b) (4) (b) (4) g (b) (4) (b) (4) g	Assay and Tube Uniformity
6.	OOSI10017061	(b) (4) Ointment	12 Month	(b) (4) (b) (4) g	Assay

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		(b) (4) %	30°C/(b) (4) % RH		
7.	OOSI10017086	(b) (4) (b) (4) ((b) (4) (b) (4) %)	9 Month 25°C/60% RH	(b) (4) (b) (4)	(b) (4) Content
8.	OOSI10017091	(b) (4) (b) (4) Solution	Photo stability	(b) (4) (b) (4) ml	Assay
9.	OOSI10017107	(b) (4) cream (b) (4) %	2 Month 30°C/65% RH	(b) (4) (b) (4) g (b) (4) (b) (4)	Tube Uniformity

(C) Interview conducted by QA personnel during OOS investigations include questions and answers that are not contemporaneously recorded. Several examples were uncovered wherein the questions asked (by QA) to analysts are forwarding questions in that the question itself contained information of answers to the questions.

OBSERVATION 2

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.

Specifically,

(A) The batch sizes used for the establishment of (b) (4) Hold times do not represent the commercial batch size of the products marketed in the U.S. The (b) (4) stage sample quantity requirement ranged from (b) (4) to (b) (4) regardless of product batch sizes. To date, you have conducted (b) (4) hold time studies utilizing this approach for approximately (b) (4) products intended for the U.S. market. Selection of your sample size do not accurately represent the impact of (b) (4) holding times on your actual commercial batch sizes that generally varied from (b) (4) (b) (4) to (b) (4) The percent active content in your commercial products range from (b) (4) % to (b) (4) % as summarized below:

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(b) (4)

(b) (4)

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(b) (4)

(b) (4)

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(b) (4)

[redacted]

(B) On November 10, 2017 several Hold Time study samples ((b) (4) containers x (b) (4) grams) were found in the Balance room of Unit (b) (4) QC Instrument Lab-(b) Samples pertained to (b) (4) Hold Time studies representing (b) (4) (b) (4) and (b) (4) for (b) (4) Cream USP (b) (4)% batch number (b) (4) The samples were pulled in August 2017 and received in your QC lab shortly thereafter. Testing of the samples commenced more than 2 months after receipt of samples on November 7, 2017 and there is no assurance that the results generated will accurately represent the intended objective of the Hold Time studies. Your General Manager for QA stated that the batch is intended to be filed as an exhibit batch for submission under an (b) (4)

(C) Your Batch Production Records for commercial products do not specifically include the (b) (4) Hold Time calculations for all products marketed in the U.S. Your Sr. Manager for QA stated that material management controls in SAP will prevent exceeding of established (b) (4) Hold times. You do not have procedural controls in

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the Batch Production Records for all commercially distributed products to ensure compliance to established (b) (4) Hold times during SAP downtimes.

(D) You have not conducted Stage III Continuous Process Verification (CPV) to ensure that commercial products remain in a state of control. The requirement to implement continuous process verification was introduced in SOP No. 05/QA1023 revision 00 (effective: May 15, 2015). You have only conducted Stage III Continuous Process Verification on (b) (4) Ointment USP (b) (4)% as of November 2017. The rationale for selecting this product for CPV is not documented and you do not have any documented plans to conduct the CPV activities on other products commercially distributed in the U.S. market.

OBSERVATION 3

Complaint records are deficient in that they do not include the findings of the investigation and follow-up.

Specifically,

(A) You received approximately 34 consumer complaints (for product grittiness) on batch (b) (4) of (b) (4) Cream USP (b) (4)% that was released to the U.S. market in April 2017. This represented approximately 50% of all consumer complaints received from the U.S. market for the subject product in 2017. Your resulting investigation acknowledged a relatively longer Bulk Hold Time of (b) (4) and (b) (4) for the subject batch. The typical hold time for the bulk is approximately NMT (b) (4) for this product as per the General Manager of QA. You failed to conduct a comprehensive investigation to determine whether the hold time had an impact on the quality of the product. The bulk hold time studies are not conducted at commercial batch sizes to draw any meaningful comparison between the available bulk hold time data and the quality attributes of the subject product during bulk hold times.

(B) Complaints investigation for batch (b) (4) of (b) (4) Cream USP (b) (4)% did not include review of all retain samples. On November 10, 2017, FDA investigators noted that the retain storage area

included approximately (b)(4) retain samples and only (b)(4) were verified during complaint investigation. Your QA unit could not provide a rationale for selecting only (b)(4) samples for verification despite the notable number of complaints received for batch (b)(4) Returned complaint samples were not considered for any chemical evaluation by the quality unit.

(C) You introduced a data logger to understand the shipping conditions associated with (b)(4) and (b)(4) Cream USP (b)(4)% (b)(4)% intended for the U.S. market. Temperature data gleaned from the data loggers indicate that the batch numbers (b)(4) and (b)(4) were exposed to conditions outside the (b)(4) °C to (b)(4) °C limits permitted during storage. The total duration of exposure was recorded to be approximately 34 hours and 30 minutes and the maximum exposure temperature was 44.5°C. You have not conducted any evaluation to determine the impact of elevated temperatures on the quality and integrity of product. Approximately 21 consumer complaints were received in 2016 and 2017 for this product appearing to be "watery". Your General Manager for Quality stated that phase separation occurs at elevated temperatures. Returned complaint samples were not considered for any chemical evaluation by the quality unit.

OBSERVATION 4

Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.

Specifically,

Data compiled by QA personnel intended for filing of Annual Product Quality Review (APQR) for commercial products is not reviewed for accuracy. For example, the 2016 APQRs for (b)(4) and (b)(4) (b)(4) Cream USP, (b)(4)% (b)(4)% and (b)(4) Cream USP, (b)(4)% included statistical evaluation of data compiled in an Excel file. However, the data residing on the Excel file is not documented to have undergone any review for completeness and accuracy by the Quality Unit. In addition, statistical evaluation of the data reported in the APQR utilizing Minitab is not saved in any electronic QA archives. You General

Manager for QA stated that Minitab files are deleted after the statistical evaluation is printed for reporting in APQRs. Minitab electronic files were not available for FDA investigators for review during the current inspection.

OBSERVATION 5

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically,

(A) Your firm failed to fully investigate change control notification # 100020293. That change control pertained to, "It is proposed to remove BUG from the respective program in SAP system as identified by IT department during investigation of Incident No. INI1 00170300 to correct the batch size quantity in raw material issue slip (picking sheet) generated through SAP using transaction ZPP0054." Where after printing of picking sheet of product (b) (4) Tablets, (b) (4) (SFG Code: - (b) (4) , (b) (4) Tablets, (b) (4) mg (SFG Code: - (b) (4)), (b) (4) Tablets, (b) (4) mg (SFG Code:- (b) (4) and (b) (4) Tablets, (b) (4) mg (SFG Code:- (b) (4)), we observed that IT activities were not documented as to how the "BUG" was removed. Additionally, after the "BUG" was removed, only (b) (4) batches ((b) (4)) were assessed to verify if the SAP system was functioning properly.

(B) On November 6, 2017, it was stated that the firm has (b) (4) shredders. Upon our review of shredder ID: SH/04 located in the Regulatory Affairs staff room, we found quality documents shredded in the teeth and surrounding internal moving parts of the shredder. The documents appeared to be eight (8) pieces of chromatographs and more than five (5) forms with document number F05/QC102/**. These apparent quality documents were also not listed on the logbook for shredding as required by section 5.6 of the firms Standard Operating Procedure (SOP) CM/QA 0-49 which states, "The record for disposal of GMP documents shall be maintained as per Annexure – I "Document Disposal Record."

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OBSERVATION 6

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,

On November 6, 2017, we observed that a warehouse employee was able to access quality folder/documents as well as create/delete documents/ folders on Quality Department network drives. For example, the warehouse employee was able to access/delete documents and folders that included, but not limited to:

- IPQA Data Donot Delete
- Addendum to Operational Qualification Protocol Blister Packing Machine ((b) (4)
- Qualifications
- (b) (4)
- other quality documents

If documents are deleted from any drives, documents are not moved to the recycling bin. Your IT Executive stated that "any files deleted from the server will be permanently flushed" and further stated that "the file will be permanently deleted from server with no traceability." Additionally, your firm does not have any written procedures to handle computer data integrity issues outside the Quality Laboratories.

OBSERVATION 7

Employees are not given training in the particular operations they perform as part of their function.

Specifically,

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On November 6, 2017 it was observed that in the course of an approximately (b) (4) work day, training for employees who work in Production Department are documented with reading, understanding and taking written exams of more than (b) (4) Standard Operating Procedures (SOP).

For example:

Senior Officer (Packaging) with employee # 90027116: On August 16, 2017 the employee is documented to have read, understood and took written exams of (b) (4) Standard Operating Procedures (SOP) which totaled over (b) (4)

Production Department with employee # 90027112: On August 12, 2017 employee is documented to have read, understood and took written exams of (b) (4) Standard Operating Procedures (SOP) which totaled over (b) (4) pages.

***DATES OF INSPECTION**
11/06/2017(Mon), 11/07/2017(Tue), 11/08/2017(Wed), 11/10/2017(Fri), 11/11/2017(Sat)

X Dipesh K Shah
Office of International Programs Employee
Signed By: 1300184065
Date Signed: 11-11-2017 18:05:10

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