Head Office
Mail: P.O. Box CT 2783, Cantonments-Accra, Ghana
(+233)-302-233200/235100
(+233)-551-112223/4/5 (Hotline)
Email: fda@fda.gov.gh
Digital Address: GA-237-7316

FDA/TOD/ID/MFD/DG/24/0233

1st July 2024

The Managing Director
Entrance Pharmaceutical and Research Centre
16 Okpoi Gonno, Light Industrial Area
Accra, Ghana

Tel: 030223437

Dear Sir,

SUSPENSION OF MANUFACTURING ACTIVITIES FOLLOWING 2024 ROUTINE GMP INSPECTION

Following the routine inspection of your facility located at 16 Okpoi Gonno, Light Industrial Area, Accra, by the Food and Drugs Authority from 24th to 26th June 2024 to ascertain the level of compliance to Good Manufacturing Practices (GMP), certain deficiencies were observed.

The deficiencies which have been categorized into 5 'Critical', 39 'Major' and 5 'Other' deficiencies have rendered the facility non-compliant with the WHO guidelines for Good Manufacturing Practices.

In view of this, the safety, quality, and efficacy of the general and beta-lactam pharmaceutical products manufactured at your facility are a threat to public health and safety. Find attached the deficiencies and their categorization.

You are, by this letter, directed to suspend all production activities and submit Corrective and Preventive Action Report (CAPA) within fifteen (15) days upon receipt of this letter.

Please treat as urgent and comply.

Yours faithfully,

DR. DELESE A. A. DARKO
CHIEF EXECUTIVE OFFICER

0782

cc. DCEO, Health Products and Technologies Division-FDA
Director, Centre for Import and Export Control Directorate-FDA
Director, Centre for laboratory Services and Research Directorate-FDA

M5,9,32

SUMMARY OF DEFICIENCIES

S/ No.	DEFICIENCY	AREA
CRITICAL DEFICIENCIES		
1.	A review of the high-performance liquid chromatographic (HPLC) system revealed the following: i. System suitability tests are not done as part of the sample set for HPLC analysis. ii. Column verification on initial receipt and suitability checks are not done prior to use in analysis. iii. There is no procedure for review of the audit trails and no evidence of regular review of the audit trails. iv. The chromatographic system is not linked to a network system and there are no sufficient controls in place to manage the system, evidenced by a lack of an effective data back up and data management system. v. There is no documented procedure for creating and deleting user groups. Additionally, users in each group are not qualified for the responsibilities and privileges granted to them. vi. There are no procedures for the management of the columns. vii. There is no valid agreement between the company and the supplier of the HPLC machines specifying responsibilities between the company and the supplier and necessary arrangements for after sales services.	**QUALITY CONTROL**
2.	Tests for related substances and organic impurities are not done for raw materials received and finished products released, which have this defined in their applicable specifications.	**QUALITY CONTROL**
3.	Cleaning validation has not been done for both the beta lactam and non-beta lactam manufacturing lines and premises. Existing protocol developed for the beta lactam does not provide scientific justification for the selection of	**QUALIFICATION AND VALIDATION**

	the product used and acceptance criteria is also not based on health-based exposure limit.	
4.	The following equipment for production and laboratory activities are not qualified: i. Sampling booth (WHD/SB/01) ii. Dispensing booth (NMB/DB/GF5/01) iii. Filling and Capping Machine (NMP/FC/GF24/02) iv. Manufacturing Vessel (NMP/MV/GF18/01) v. Airjet Bottle Cleaning Machine (NMP/AJC/GF23/02) vi. LAF – beta lactam microbiology laboratory vii. LAF – non-beta lactam microbiology laboratory (NQT/EQT/LAF/001). viii. Autoclave (non beta lactam microbiology lab) ix. The visual inspection process and equipment	**QUALIFICATION AND VALIDATION**
5.	A combination of several identified deficiencies present data integrity issues that compromise the accuracy, reliability and trustworthiness of data used to support GMP decisions: i. Incomplete or missing records (evidenced by deficiency numbers 9i, 2, 12, 1, 13, 18, 38) ii. Uncontrolled documents. (evidenced by deficiency numbers 42, 20) iii. Lack of audit trails (evidenced by deficiency number 1) iv. Unsecured data (evidenced by deficiency number 1) v. Inconsistent data (evidenced by deficiency numbers 25, 43)	**DOCUMENTATION**
MAJOR DEFICIENCIES		
6.	The change control management system is not functional. For example, a review of a change control (CC/23/043) raised for the installation of a new AHU and Sampling Booth for the non-beta lactam raw material warehouse revealed: i. The FDA was not notified contrary to the terms and conditions of their manufacturing license. ii. Impact analysis of the change on existing systems and facilities was not done as required. iii. Timelines and compliance dates for completion were not completed.	**PHARMACEUTICAL QUALITY SYSTEM**

	iv. Change implementation requirements were not adequately captured	
7.	Risk assessment for the presence of nitrosating agents in treated water and nitrosamines in finished products has not been done.	**PHARMACEUTICAL QUALITY SYSTEM**
8.	Product quality reviews does not cover all the basic requirements as prescribed by WHO guidelines for an effective product quality review. This is evidenced by the 2022 and 2023 product quality review reports done for Ciprofloxacillin.	**PHARMACEUTICAL QUALITY SYSTEM**
9.	The CAPA management system is not functional, evidenced by: i. CAPAs not registered to facilitate their evaluation and management's monitoring of their effectiveness. ii. Root cause analysis for CAPA investigations is not formally documented. iii. CAPA extensions are not done.	**PHARMACEUTICAL QUALITY SYSTEM**
10.	Deviation management system is not functional, evidenced by: i. Only three deviations have been registered in 2024 despite numerous unplanned deviations encountered during the inspection. ii. Impact analysis of unplanned deviations is not done. iii. Evaluation forms for the deviations registered were not fully completed.	**PHARMACEUTICAL QUALITY SYSTEM**
11.	The culture medium MacConkey Broth Purple w/ BCP used for tests for E. coli was observed to be expired but was still in use without any scientific justification to support its continuous use.	**QUALITY CONTROL**
12.	No OOS was registered and investigated from 2021 to 2023.	**QUALITY CONTROL**
13.	The environmental monitoring of the facility is ineffective as evidenced by: i. The type of environmental monitoring methods adopted and the frequency of monitoring of the various production areas is not based on any risk assessments or scientific justification.	**QUALITY CONTROL**

	ii. Non-viable particle monitoring is not done for the LAFs at the microbiology laboratories. iii. Surface monitoring for viable particles by contact plates, swabs or surface rinses are not done.	
14.	Autoclaves at both microbiology laboratories are being used for both media preparation and destruction which poses a significant risk of cross contamination and may compromise the integrity and sterility of media preparations.	**QUALITY CONTROL**
15.	The UV light in the pass box of the microbiology lab of the non-beta lactam unit for material movement to the LAF is not functioning which may compromise the sterility and integrity of the materials being transferred.	**QUALITY CONTROL**
16.	The storage condition of the refrigerators with freezer compartments at the microbiology laboratories of both manufacturing units for storing media and micro-organism strains is not monitored.	**QUALITY CONTROL**
17.	The pressure gauge on the autoclave at the microbiology laboratory of the non-beta lactam plant is not calibrated.	**QUALITY CONTROL**
18.	A register for both primary and secondary reference standards is not maintained.	**QUALITY CONTROL**
19.	There is no defined procedure that clearly defines the criteria of the responsible person that counter signs or verifies the work of the analysts in laboratory logbooks.	**QUALITY CONTROL**
20.	The raw material register in use at the quality control laboratory is not controlled, it is not referenced to any procedure and does not have a control number.	**QUALITY CONTROL**
21.	There is no trend analysis done for change controls.	**PHARMACEUTICAL QUALITY SYSTEM**
22.	The pressure differentials between the class D areas and the non-classified areas such as the corridors and other surrounding areas at both the beta lactam and non-beta lactam manufacturing units are not monitored to ensure the class D areas obtain and maintain an acceptable level of positive pressure relative to the surrounding areas.	**PREMISES**

23.	Defined limits of the pressure differentials for the classified areas are not stated on numerous magnehellic gauges at both the beta lactam and non-beta lactam manufacturing units to facilitate monitoring.	
24.	The colloid mill (NMP/CM/GF18/01) in the suspension preparation room of the non-beta lactam unit is installed in a way that blocks access to a return air grill of the room and does not permit effective cleaning and maintenance of the filters of the air grill and its immediate surrounding area leading to a build-up of dirt and risk of contamination.	**PREMISES**
25.	Humidity records at the raw material warehouse of the non-beta-lactam unit were observed to be out of range for extended periods. However, no deviation has ever been raised to address this.	**PREMISES**
26.	The level cleanliness at the packaging materials warehouse is not adequate. Dust and dirt were observed on boxes.	**PREMISES**
27	Raw materials are stacked closely to the dynamic pass box, making it impossible to open the pass box for materials entry into the sampling booth at the Beta-lactam warehouse.	**PREMISES**
28	There is poor stacking discipline, improper storage, and segregation of the primary and secondary packaging materials at the non-beta lactam warehouse. Additionally, a location chart is available to allow orderly storage of the various categories of materials.	**PREMISES**
29	Sections of the walls and ceilings of the following areas has developed dampness or water intrusion which can lead to contamination: i. Raw material warehouse (non-beta lactam) ii. Bottle store (beta lactam manufacturing unit, first floor) iii. Sugar store (non-beta lactam manufacturing unit, ground floor)	**PREMISES**
30	Floor pitting was observed on portions of the floor at the non-beta lactam's PVC packaging materials storage area.	**PREMISES**

31	Recesses that are difficult to clean were observed on the ceilings of the two manufacturing units and the laboratories due to the improper hermetical sealing of light fittings and poor installation and maintenance of ventilation points and the light fittings.	**PREMISES**
32.	The following instruments and measurement systems were either past their due dates for re-calibration or not calibrated: i. Thermometers of the sugar dissolving vessels (NMP/SDV/GF17/01 and NMP/SDV/GF17/02) on the oral liquid non beta lactam lines (Dec 2023). ii. Analytical balance (BQC/EQT/BAL/001) located at the beta-lactam sampling booth (May 2020). iii. Magnehellic gauges used to monitor the laminar air flow of the dispensing booths and sampling booths are not calibrated.	**EQUIPMENT**
33.	Routine maintenance and calibration records (where appropriate) were unavailable for the following equipment. i. Fume chamber at the wet chemistry laboratory ii. Dispensing booth (NMB/DB/GFS/01 non-beta lactam oral liquid) iii. Sampling booth (WHD/SD/01 - non-beta lactam raw material warehouse) iv. Dispensing booth (beta- lactam manufacturing unit) v. Sampling booth (beta lactam raw material warehouse vi. Sampling booth (packaging material warehouse vii. LAF – beta lactam microbiology laboratory viii. LAF – non-beta lactam microbiology laboratory (NQC/EQT/LAF/OO1).	**EQUIPMENT**
34.	Hold time studies have not been completed for intermediate storage, in-process hold times and cleaning and sanitisation.	**GOOD PRACTICES IN PRODUCTION**
35.	There is no defined procedure to follow to ensure product safety and prevent contamination in the event of bottle burst, explosion or breakage during bottle filling and capping operation.	**GOOD PRACTICES IN PRODUCTION**
36.	The visual inspection stations at the non-beta lactam oral liquid packaging room (NMP/IT/GF33/04) and the dry	**GOOD PRACTICES IN PRODUCTION**

	powder packaging room (BMP/FIT/FF82/01) is deficient in the following ways: i. The visual inspectors are not properly trained. ii. The lux intensity of the inspection light is not known. iii. The lightbulbs on the inspection station of the non-beta lactam oral liquid packaging room 2, were not functional at the time of the inspection.	
37.	The deduster at the capsule filling room of the beta-lactam was not functioning properly exposing the room and the immediate surroundings to dust.	**GOOD PRACTICES IN PRODUCTION**
38.	Batch manufacturing records reviewed were observed not to be completed concurrently with production activities	**GOOD PRACTICES IN PRODUCTION**
39.	There is no metal detector attached to the encapsulation machine.	**GOOD PRACTICES IN PRODUCTION**
40.	QA did not authorise and clear the line and area for the commencement of the filling and capping operation for X'feron Syrup with Batch number LO21HO93 that was ongoing at the time of the inspection.	**GOOD PRACTICES IN PRODUCTION**
41.	A review of the HVAC system revealed the following: i. The drying process of the AHU filters is inadequate, filters supposed to be fully dried were found to be moist which may lead to the risk of microbial growth. ii. Various pressure gauges on the AHUs are not calibrated. The pressure gauge (MG/N115) for AHU/SF/3A/1500CFM was not functional Some were also without equipment ID numbers. iii. The procedure for monitoring of the filter cleaning, inspection and replacement of the AHUs was ineffective in that the frequency of the filter (riser and fine filters) visual inspection was not indicated, filters are changed by routine visual inspection which is unscheduled and there was procedure for handling damaged filters.	**UTILITIES**
42.	The labelling policy of the facility is deficient, evidenced by: i. Status and/or equipment identification labels were unavailable on several equipment and rooms such as the sampling booths WH/SD/O3 and WH/SB/02 at the beata-lactam warehouse and the sampling booth of the non-beta lactam warehouse.	**DOCUMENTATION**

	ii. Available status labels on various production equipment and production rooms are not controlled, do not have a title and are not traceable to the equipment and room/area. This was observed for example for status labels affixed on the real time stability chambers. iii. There is no proper identification for areas indicated as quarantine at the packaging materials warehouse.	
43.	Complete vendor/supplier qualification records could not be established for vendors. (e.g. Prudence Pharmaceuticals manufacturer of Amlodipine).	**SUPPLIER AUDITS AND APPROVAL**
44.	Various operators and supervisors interviewed were unable to fully demonstrate appreciable knowledge of GMP as well as competency in their areas of operation.	**PERSONNEL**
OTHER DEFICIENCIES		
45.	i. The layout of the current microbiology laboratories for both beta and non-beta lactam does not support effective gowning and changing procedures, as evidenced by a lack of designated areas for primary gowning and changing.	**QUALITY CONTROL**
46.	The schematic diagrams for the placement of data loggers for the temperature and humidity mapping studies report and the rodent bait stations are not available.	**PREMISES**
47.	Numerous fixed pipeworks connecting raw materials including water and dissolved sugar through the mixing rooms and preparation rooms to the filling rooms of the non-beta lactam unit are not clearly labelled to indicate content and direction of flow.	**PREMISES**
48.	There are no equipment identification numbers for the electric flycatchers installed at the entry points of the various warehouses. The same are also not monitored.	**EQUIPMENT**
	A review of the water treatment and purification system revealed the following: i. The HMI control panel monitor of the purified water distribution system is not functional. ii. Maintenance of the various components of the water treatment and purification system were not fully captured on the maintenance records and logbooks.	**UTILITIES**
49.	The complaint sample of Ancigel Antacid Suspension was not received for testing against the retained sample,	**COMPLAINT HANDLING PROCEDURE**

	contrary to the provisions of the SOP for Handling of Market Complaint QAD/SOP/016.	

REFERENCES

1. WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles (WHO TRS 986, 2014, Annex 2).

2. WHO Good Manufacturing Practices: Water for Pharmaceutical Use (WHO TRS 970, 2012, Annex 2).

3. WHO Good Practices for Pharmaceutical Quality Control Laboratories (WHO TRS 957, 2010, Annex 1).

4. WHO Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products (WHO TRS 1019, 2018, Annex 8)