DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Zhihao Peter Qiu, Division Director CDER/OPQ/OPMA/DBM, WO Bldg 51 10903 New Hampshire Ave, Silver Spring, MD 20993 Phone: 301-796-2627 / OPFBLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	08/10/2020-08/14/2020
	FEI NUMBER 1018495

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Michelle P. Logan, Vice President and General Manager

FIRM NAME	STREET ADDRESS
Patheon Manufacturing Services, LLC.	5900 Martin Luther King, Jr. Hwy.
CITY, STATE AND ZIP CODE Greenville, NC 27834	TYPE OF ESTABLISHMENT INSPECTED Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. The responsibilities of the quality control unit are not in writing and fully followed.

Specifically,

1.1. CPS-50: Quality Systems Policy, effective 12/09/2018, section 1.2.3.14, requires the assessment of risk and management of change in a compliant manner.

a. SOP-QA-324: Site Change Request (SCR) Process Using TrackWise, effective 02/21/200, requires quality risk assessment information for changes. Change Control Report (SCR) # 576968, approved by quality assurance on 04/25/2020, proposes an upgrade to Pharmaceutical Development Services (PDS) Suite (b) (4) including structural changes and HEPA filter installations. The rationale for the tasks created as part of the change and risk assessment of the impact on the environmental monitoring program and air flow patterns in PDS Suite (b) (4) was not documented.

b. VAL-15259, IQ/OQ/PQ Protocol for (b) (4) Vial Washer, 132522, in Building (b) (4) PDS Suite (b) (4) approved 01/25/2016, Risk Analysis section (page 9), categorizes the vial washer as high-risk equipment and requires a periodic in-depth individual review. On 08/14/2020, Staff Validation Engineers with initials (b) (6) provided VAL-13517, Greenville Site Washer Validation/Revalidation Rationale, approved 03/15/2018, which recategorized the vial washer as low risk equipment and only requires a holistic review of washing process. The quality unit failed to manage the change in a compliant manner and assess impact to the equipment qualification program.

1.2 CPS-50: Quality Systems Policy, effective 12/09/2018, section 1.2.3.11, requires the implementation of a system to assure vendors/suppliers are providing materials of the required quality.

a. SOP-QA-134: Supplier Qualification Program, effective 08/15/2019, the supplier evaluation (b) (4) fails to assign risk according to the supplier type. Suppliers of product contact sterile materials may be approved based on

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a questionnaire without further assessment.

b. Certificates of Analysis data for product contact sterile materials including filling (b) (4) assemblies, pumps and bags are not validated.

1.3. CPS-50: Quality Systems Policy, effective 12/09/2018, section 1.2.3.9 requires a system in place for the traceability of actives, excipients, packaging components and finished product. The quantity of tailgate samples for actives placed in the freezers (Equip ID (b) (4) (b) (4) are not documented in the respective equipment logbooks.

1.4. CPS-50: Quality Systems Policy, effective 12/09/2018, section 1.2.3.7 requires procedures are properly followed.

a. SOP-QA-179: Laboratory Sample Transport, Receipt, Storage, Shipping, and Destruction Processes, effective 03/01/19, requires proper handling and storage of laboratory samples. On 08/13/2020, while touring the QC Microbiology Lab, the (b) (4) incubators, with equipment ID (b) (4) utilized for in-process bioburden samples were unlocked. In addition, the key for refrigerator with equipment ID 132459, used for storage of QC Microbiology and commercial QC Chemistry samples, was placed in the key hole of the refrigerator door. The QC Microbiology Manager with initials (b) (6) stated that, except the Sterility Lab and the Controlled Substance Lab, anyone who has badge access to the building will have access to the QC Microbiology and QC Chemistry Lab.

b. SOP-ENG-93: Certification of HEPA Supply/Return and Exhaust Air Filters, effective 12/14/17, requires evaluation of work height air velocity data by the quality unit; nonetheless, air velocity is not tested at the work height level.

c. According to SOP-ENG-90, Certification of Laminar Clean Air Work Stations and Rooms, effective 09/06/2018, HEPA filter patch repairs may be performed for any leak with a reading of (b) (4) % or greater in the integrity test. A (b) (4) reading equivalent to (b) (4) % of the (b) (4) challenge is indicative of a significant leak and may call for replacement of the HEPA filter. The reading limit for patch repair should be defined.

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d. Batch Production Record for (b) (4) MWOCOM-1977, v. 3.0, requires visual integrity of bags is verified; nonetheless, there is no documented description of visual integrity verification requirements.

1.5. CPS-50: Quality Systems Policy, effective 12/09/2018, section 1.2.3.13 requires quality review and approval of deviations and corrective and preventive actions.

a. Turbulence in Class B air flow was identified in PDS (b) (4) during the 2017 Air Flow Pattern Study and no deviation or discrepancy was opened. The same turbulence issue was captured in the 2019 Air Flow Pattern Study and deemed to cause an effect in ISO 5 air flow patterns under Deviation # 560788, approved by the quality unit 12/12/2019. Nonetheless, PDS (b) (4) continued to be in commercial operation under the aforementioned conditions.

The deviation fails to evaluate any potential impact to lots manufactured under the aforementioned conditions and incidence of environmental monitoring action and alert level excursions that might have been alerts of an airflow pattern disruption. The incidence of non-viable air excursions in the Grade A area potentially affected by disruption of laminar air flow were identified to be 12 out of 47 alert level excursions and 17 out of 38 action level excursions in Grade A area of PDS (b) (4) according to the Environmental Monitoring Trend Reports for PDS (b) (2019/00421/00, Reviewed 6/21/2019 for Q1 2019, 2019/00767/00, reviewed 9/24/2019 for Q2 2019, 2019/01073/00, reviewed 12/16/2019 for Q3 2019, 2019/01073/00, reviewed 03/26/2020 for Q4 2019, and 2020/00610/00, reviewed 06/24/2020 for Q1 2020),

b. According to Deviation 540656, created on 06/11/2019 and canceled on 11/27/2019, on 5/9/2019 during set up operations for (b) (4) batch (b) (4) a settle plate for sample location (b) (4) near the fill (b) (4) showed (b) (4) CFU. The investigation states that the plate was dropped after exchanging the sample and that the sample is invalid. Nonetheless, the root cause analysis states the production operators were working close to the plate and not moving at a slow pace, causing air turbulence that disrupted unilateral air flow. The EM Manager with initials Q.F. stated that client requested additional discussion and at that time they identified the settle plate had been dropped. The supervisor was not notified per SOP-QC-463, Environmental Control: Test Type Instructions, v 37.0, approved 05/01/2020. An investigation assessment was not conducted with this new information.

2. The system for cleaning and disinfecting the room and equipment to produce aseptic conditions is not adequate.

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Specifically,

As per SOP-194, Environmental Cleaning for (b) (4) Lines (b) (4) and PDS Suites (b) (4) Filling and Manufacturing, effective 4/1/2020, disinfectants used in the PDS (b) (4) aseptic processing area are (b) (4) As per document 2017/00031/02, Disinfectant Efficacy Study, conducted in 2016 and approved by the quality unit on 01/17/2020 (Quality Assurance Engineer III, QA Audits with the initials (b) (6) stated that the issuance date for the original report was 11/01/2018), house environmental isolate Acinetobacter lwoffii was resistant to (b) (4) on (b) (4) Paint and (b) (4) Floor surfaces and resistant to (b) (4) on Glass, (b) (4) and (b) (4) Glove surfaces with the approved (b) (4) contact time. House isolate Staphylococcus epidermidis was resistant to (b) (4) on (b) (4) Paint, and (b) (4) Floor surfaces with the approved (b) (4) contact time. The disinfectant efficacy study established (b) (4) will be efficacious against the aforementioned strains; nonetheless, the sporicidal is applied (b) (4) allowing growth of disinfectant resistant organisms in the interim.

In addition, as per internal memos, dated 6/28/2019 and 8/13/2020, in 2018 and 2019, S. epidermidis and Acinetobacter spp continue to be the most prevalent isolates recovered from the sterile areas.

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