DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
466 Fernandez Juncos Avenue San Juan, PR 00901-3223 (787)729-8500 Fax:(787)729-6809	2/21/2019-3/6/2019* FEI NUMBER 3008171790

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
David Fuster, Plant Manager

FIRM NAME	STREET ADDRESS
Caribe Holdings (Cayman) Co. Ltd dba PuraCap Caribe	State Rd 698 Km 0.8, Bo. Mameyal
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dorado, PR 00646	Drug 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:
Facilities and Equipment System

OBSERVATION 1

Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

A. During our review of your firm's Cleaning Validation Program, we observed that times frames for protocol executions, Final Summary Reports (FSR) and Corrective and Preventive Actions (CAPAs) completion were not achieved in a timely manner. There are three (3) open protocols approved in 2016, two (2) open protocols and two (2) protocols closed, one (1) closed after the start of our current inspection approved in 2017 and two (2) open protocols approved in 2018. Your firm does not have a sound justification for tardiness on the cleaning validation program. Details for open and closed cleaning validations protocols are summarized in table below.

Document Identification	Title	Protocol Approved On	CAPA# /Status	Protocol Last Execution	Protocol Status
PR-16CL-001	Dirty and Clean Hold Time for Simvastatin	4/7/2017	Not Applicable	5/30/2018	Open

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	Jose F Velez, Investigator Marian E Ramirez, Investigator	X Jose F Velez Investigator Signed By 2000547088 Date Signed 03-06-2019 08:37:25	3/6/2019

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Document Identification	Title	Protocol Approved On	CAPA# /Status	Protocol Last Execution	Protocol Status
PR-16CL-002	Cleaning Validation Protocol for Utensils	11/10/2016	Not Applicable	4/25/2018	Open
PR-16CL-003	Cleaning Validation Protocol for Plastic Bins	2/15/2017	Not Applicable	7/24/2018	Open
PR-17CL-001	Cleaning Verification Protocol for the (b) (4) Tablet Press and Peripherals after the Compression of Gemfibrozil product	8/29/2017	CAPA-19-0009 / Open CAPA-19-0009 / Open CAPA-19-0009 / Open	9/15/2017	Closed on 2-26-19 after inspection initiated
PR-17CL-002	Cleaning Verification Protocol for the Tablet Press Machines and Peripheral Equipment after the Compression of Amlodipine Besylate	8/31/2017	Not Applicable	6/6/2018	Closed
PR-17CL-005	Cleaning Verification Protocol for the (b) (4) and Peripheral Equipment after the	11/10/2017	CAPA-18-0066 / Open	9/6/2018	Open

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Document Identification	Title	Protocol Approved On	CAPA# /Status	Protocol Last Execution	Protocol Status
	Compression of Doxycycline Hyclate Tablets 100 mg.				
PR-17CL-006	Cleaning Verification for the (b) (4) Bin Hopper for Scale-Up Amolodipine Besylate	1/9/2018	Not Applicable	1/31/2018	Open
PR-18CL-001	Cleaning Verification Protocol for the Packaging Line (b) (4) after the completion of the Packaging Process of Simvastatin Products	3/26/2018	Not Applicable	9/12/2018	Open
PR-18CL-002	Cleaning Verification Protocol for the Campaign Length Expansion of Gemfibrozil Granulation and Coating Equipment Train	3/14/2018	Not Applicable	6/29/2018	Open

Additionally, on 3/4/2019, your firm's Cleaning Specialist indicated that there are no cleaning validation exercises performed for the packaging equipment trains. A Risk Assessment, TA-17-003 "Equipment Cleaning Procedure Risk Assessment for the Packaging Area at PuraCap Caribe, Dorado Facility in Puerto Rico" that initiated in 2017, is still routing for approval as of 3/4/2019.

B. Furthermore, during our initial walkthrough of your firm's facility on 2/21/2019, we observed a dirty utensil, not place in a polyethylene bag nor labeled as "clean" in the Clean Equipment Room (b) (4) The utensil was identified by the Manufacturing Supervisor as a (b) (4) used only for an excipient of Gemfibrozil. On 3/4/2019, Manufacturing Supervisor explained that the cleaning of the (b) (4) is not documented anywhere, and there are no specific instructions provided for the cleaning process of utensils. The only instructions available for the cleaning of utensils are on SOP 20-21- 05 stating: "(b) (4) " and on the cleaning checklist: Form 00824 Rev 07 stating "Utensils/ portable equipment available in the room are clean, covered with or in polyethylene bag and identified with a label of "Clean" and the expiration date".

This is a recurrent observation from previous FDA inspection in March 2018.

Quality System

OBSERVATION 2

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

Your Quality Unit failed to approve documents such as Annual Product Review, Laboratory Investigation Reports, Corrective and Preventive Actions and disposition of rejected material in a timely manner.

For example,

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A. Procedure #10-17-02, Annual Product Review (APR), and effective date, 09/21/2016, establishes that the APR should be completed and approved within 90 days of the reporting period stated on the APR schedule. Upon our request, we found the Quality Unit failed to approve the following APRs within the required time frame:

Product	Review Period	APR due date	APR completed
Doxycyline Hyclate Tablets, USP	11/08/2016 to 11/07/2017	02/07/2018	03/04/2019, after the inspection was initiated
Doxycycline Hyclate, USP	11/09/2015 to 11/08/2016	02/08/2017	05/19/2017
Amlodipine Besylate Tablets, USP	04/08/2017 to 04/07/2018	07/07/2018	02/26/2019, after the inspection was initiated
Gemfibrozil 600mg Tablets, USP	03/27/2017 to 03/26/2018	06/26/2018	09/18/2018

Your firm failed to annually evaluate the performance of manufactured products and compare results with the approved specifications to determine the need for changes in specifications, manufacturing or control procedures.

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B. Procedure #70-14-02, Laboratory Investigation, effective date: 12/01/2016, establishes "a time frame of NMT (b) (4) is allowed for the laboratory to complete each investigation. Any exceptions must be justified by the department supervisor and authorized by the department manager, QA manager or designee". During our review of Form 00485 Rev01, Assignment of Laboratory Investigation Report (LIR) Number, effective date: 01/09/2017, we found 23 out of (b) (4) LIRs not completed in 2018. Out of 23 LIRs not completed, seven (7) LIRs were related to commercial products and 16 LIRs related to pilot batches of non-commercial products.

Additionally, for the seven (7) LIRs, all Justification and Authorization to Extend LIRs, Form 00487, were approved on 02/23/2019, after we initiated our current inspection. The reason for these extensions were "Additional time is required for the approval process by QC and QA departments". The following table summarizes the LIRs not completed in 2018:

LIR Number	Reason	LIR initiated	Original Completion date	Extension Approved
18-0002	Amlodipine Besylate API, USP, last bracketing standard injection contains no data on (b) (4), lots RBC02950 and	01/16/2018	02/25/2018	1st extension: 09/27/2018 2nd extension: 02/23/2019

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	RBC02951			
18-0057	(b) (4) water port (b) (4) OOS for Total Plate Count	06/26/2018	07/25/2018	02/23/2019
18-0059	Amlodipine Besylate 5 mg Tablets, USP, Stability lot 16A0004F2P9V atypical water result	06/27/2018	07/27/2018	02/23/2019
18-0063	Gemfibrozil 600 mg Tablets, USP, Stability Lot 16M0005FB-600 Assay OOS	07/02/2018	08/01/2018	02/23/2019
18-0100	Simvastatin 20 mg Core Tablets, USP, lots 18S0120T3 and 18S0121T3 Assay OOS	11/12/2018	12/12/2018	02/23/2019
18-103	Simvastatin 20 mg Coated Tablets, USP lot 18S0120C3, (b) (4) (b) (4) Assay OOS	11/15/2018	12/15/2018	02/23/2019

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Jose F Velez, Investigator
Marian E Ramirez, Investigator

X Jose F Velez Investigator Signed By: 2000547088 Date Signed: 03-06-2019 08:37:25

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18-104	Simvastatin 20 mg Coated Tablets, USP lot 18S0120C3, (b) (4) (b) (4) (b) (4) (b) (4) Assay OOS	11/16/2018	12/15/2018	02/23/2019

Your Quality Unit failed to follow the requirements for procedure 70-14-02 related to the closing in a timely manner LIRs and providing reasonable justification to issue LIR extensions.

C. Your firm issued CAPA 19-0009 on 02/24/2019 under Cleaning Verification Protocol for the (b) (4) Tablet Press and Peripherals after the Compression of Gemfibrozil product, PR-17CL-001 approved on 02/26/2019, after we initiated the current inspection. The last cleaning execution under this protocol was 09/15/2017. CAPA 19-0009 was initiated due to out of specifications found during the determination of Gemfibrozil Residue in Cleaning Swabs on (b) (4)) Equipment ID# 011256 on 05/04/2018 and 11/08/2018 and Metal Detector Equipment ID# 041497. According to the Preventive Action Description in this CAPA, a technical assessment will be initiated by the Engineering Department to evaluate the affected equipment parts. Quality unit approved CAPA 19-0009 on 02/26/2019. However, (b) (4)) Equipment ID# 011256 and Metal Detector Equipment ID# 041497 have been used to manufacture Gemfibrozil Tablets up to date. Your Quality Unit failed to initiate CAPA 19-0009 in a timely manner to take actions to prevent Gemfibrozil residues on the (b) (4) and metal detector.

Furthermore, CAPA 18-0066 was issued and approved by the Quality Unit on 10/11/2018 under PR-

17CL-002 (Cleaning Verification Protocol for the Tablet Press Machines and Peripheral Equipment after the Compression of Amlodipine Besylate) and PR-17CL-005 (Cleaning Verification Protocol for the (b) (4) and Peripheral Equipment after the Compression of Doxycycline Hyclate Tablets 100 mg). PR-17CL-002 was approved by the Quality Unit on 12/19/2018 and PR-17CL-005 is still open since last cleaning execution on 09/06/2018. According to the Preventive Action Description in this CAPA, SOP 20-03-08, Use, Documentation and Handling of Logbooks in the Manufacturing, Pilot Plant and Packaging Areas will be updated to include the new campaign length recommended for Amlodipine Besylate and Doxycycline Hyclate. Upon our request, we found that this procedure is still on draft and there is no sound justification for keeping this CAPA open since 10/11/2018.

D. On 2/21/2019, during our initial walkthrough of your firm's facility, we observed bins for Doxycycline Hyclate Tablet Blend, item: B10032, lot# 18D0162B1, labeled as: "IMPORTANT Do not use". This lot #18D0162B1 is associated to NOE-18-0123DC2 due to yield specification found out of specifications. On 12/28/18, NOE-18-0123DC2 was closed with lots 18D0162B1 and 18D0215B1 recommended for rejection. Materials Handling SOP, 30-01-07, states the following: "Any lot or material that is assigned the rejection disposition by the Quality Assurance Department will be promptly informed to the warehouse and Inventory Analyst immediately and shall be labeled Material Rejected in accordance with the Quality Assurance Department's "Preparation, Use and Disposition of Labels" 10-33 current version". "(b) (4) " However, the "Rejected" label for lot 18D0162B1 was placed on 2/21/2019 and for lot 18D0215B1 on 2/28/2019, after we initiated current inspection. Furthermore, both lots were moved from the "Staging Area" in the warehouse to the "Reject Cage" on 3/1/2019.

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Production System

OBSERVATION 3

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

Procedure #40-108-03, General Validation and Qualification Procedure: Requirement and Control, effective date 05/03/2018 does not include manufacturing sampling size, testing requirements and acceptance criteria for blending during validation exercises. During our revision of Validation Protocol No. PR-18P-005 for Doxycycline Hyclate 50 MG tablets using API sourced from (b) (4) (b) (4) dated 04/04/2018, we found that there are no instructions on the sampling size and amount of sample tested during blending operations other than required tests ((b) (4) (b) (4)) and acceptance criteria. Your firm has not determined if the variability of the sample location is significant for Doxycycline Hyclate API from (b) (4) during blending operations.

***DATES OF INSPECTION**

2/21/2019(Thu), 2/22/2019(Fri), 2/25/2019(Mon), 2/28/2019(Thu), 3/01/2019(Fri), 3/04/2019(Mon), 3/06/2019(Wed)

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X Marian E Ramirez
Investigator
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