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 ORAPHARMInternational483responses@fda.hhs.gov	02/20/2023-03/02/2023 FEI NUMBER 3012323885

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Venkatesh, A.R. CEO

FIRM NAME	STREET ADDRESS
Global Pharma Healthcare Pvt. Ltd.	A-9, SIDCO Pharmaceutical Complex
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Thiruporur – 603110, Tamilnadu, India	Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.

Specifically,

A. You aseptically fill the (b) (4) mg/mL to manufacture (b) (4) for the US market. You intend to achieve the sterilization of the drug product through (b) (4) filtration on a (b) (4) filter for sterilization. There is not adequate validation data to demonstrate that the (b) (4) and the accompanying filter housing and equipment can reliably sterilize the (b) (4) solution. In addition, you have not established that the sterilization process is effective across different manufacturing conditions such as the pH and temperature of the solution, filtration pressure, flow rate, maximum filtration time, batch size (volume) and effect of (b) (4) sterilization on the filter's retention capability. You have also not established the worst-case scenario for the bioburden.

Your General Manager of the Quality Assurance stated that a controlled filling room temperature (b) (4) °C) established the filtration temperature, and the passing assay of the drug product confirms the filter compatibility.

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	Eileen A. Liu -S Digitally signed by Eileen A. Liu -S Date: 2023.03.02 16:54:50 +05'30' Rajiv R. Srivastava -S Digitally signed by Rajiv R. Srivastava -S Date: 2023.03.02 17:11:13 +05'30'	Eileen A. Liu, CSO Rajiv Srivastava, CSO	03/02/2023

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According to your Manufacturing process flow chart, you use (b) (4) (b) (4) filter for the manufacturing of (b) (4) for the US market. However, your (master) Batch Manufacturing Record Doc. No. BMR/CMC/001 Effective date 9/28/2020 includes a (b) (4) (b) (4) filter (this is really the (b) (4) (b) (4) filter as per your General Manager QA). You have entered SOP No. (b) (4) SOP-SFU-EEN-018-01 Filter Integrity Test for (b) (4) Filters in (b) (4) Section (Effective date 1/30/2021) and SOP No. (b) (4) SOP-SFU-EEN-019-01 Filter Integrity Test for (b) (4) Filters in (b) (4) Section (Effective date 1/30/2021) in wet ink in the executed BMRs, e.g., Batch No's (b) (4) The BMRs for the batches noted use of (b) (4) filter Lot No. (b) (4)

Your General Manager of the Quality Assurance stated that the pressure ((b) (4) psi) recorded for the (b) (4) filter was for the (b) (4) filter. You used (b) (4) (b) (4) lot of (b) (4) filters to manufacture all (b) (4) batches that were shipped to the US market. No explanation was provided for why the opening balance of (b) (4) filters for years 2021 and 2022 was (b) (4) despite documented usage. Purchase order reconciliation of filters could not account for any quantity of the (b) (4) filters Lot No. (b) (4)

Entry	Filter	Lot No.	Year	Opening balance	Closing balance	Notes
1	(b) (4)	(b) (4)	2020	(b) (4)		(b) (4) filter for (b) (4) batches
2			2021			(b) (4) filter for (b) (4) batches
3			2022			(b) (4) filter for (b) (4) batches
4			2020			(b) (4) filter for (b) (4) batches
5			2021			(b) (4) filter for (b) (4) batches
6			2022			(b) (4) filter for (b) (4) batches

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Eileen A. Liu, CSO
Rajiv Srivastava, CSO

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You did not have purchase order or any document to verify that (b) (4) filters Lot No. (b) (4) was procured at your facility. Your QA manager stated that filters are considered consumable items and are not recorded in the warehouse entry register.

B. You conducted filter integrity test (FIT) for the (b) (4) filter by pressure hold method: (b) (4) The pressure and hold time used for FIT are not validated and are not documented in a procedure. You have not recorded the equipment IDs of the pressure gauges used for the FIT in the BMRs. Your General Manager of Quality Assurance stated that the SOP No. (b) (4) SOP-SFU-EEN-018-01 Filter Integrity Test for (b) (4) Filters in (b) (4) Section (Effective date 1/30/2021) noted in the (b) (4) BMRs is not actually for the FIT for the (b) (4) This procedure describes FIT for (b) (4) filter at (b) (4) psi of the test pressure and (b) (4) of hold time.

C. You do not perform container closure integrity test (CCIT) for the (b) (4) drug products. Your General Manager QA stated that the (b) (4) mg/mL is filed in an (b) (4) bottle and solution is not visible. Because of this, a manual visual inspection is the only test to detect any leak. There is no assurance or documentation that this visual inspection can detect aseptic barrier issues with the container or closure.

You used a manufacturing process that lacked assurance of product sterility. You used this deficient manufacturing process to manufacture (b) (4) batches of (b) (4) between December 2020 and April 2022 and shipped these batches to the US customer. The batches shipped to the US customers include: Batch No's (b) (4) _(b) (4) (b) (4) units for (b) (4) batches, Expiry date (b) (4) Batch No's (b) (4) _(b) (4) (b) (4) units for (b) (4) batches, Expiry date (b) (4) Batch No's (b) (4) _(b) (4) (b) (4) units for (b) (4) batches, Expiry date (b) (4)

D. Deficiency in formulation of (b) (4) drug products was observed. Specifically,

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Sterile (b) (4) and (b) (4) Ointment did not contain preservatives to prevent microbial contamination.

E. Your firm's aseptic process simulation or media fill (MF) for Unit (b) (4) Fill Line used for (b) (4) production and Unit (b) Ointment Fill Lines for (b) (4) Ointment lacked sterility assurance. These products were distributed to the US market. Deficiencies included but were not limited to the following:

a. Three consecutive MFs were not conducted to qualify each fill line.

b. Duration and size of MF run did not simulate routine production conditions. Specifically,

i. For commercial (b) (4) production in Unit (b) (4) Line, approximately (b) (4) bottles were compounded, filtered, and filled in (b) (4) whereas during MF only (b) (4) bottles were compounded, filtered, and filled in (b) (4)

ii. For commercial (b) (4) Ointment production in Unit (b) Ointment Line, approximately (b) (4) tubes were (b) (4) and filled in (b) (4) whereas during MF only (b) (4) tubes were (b) (4) and filled in (b) (4)

c. Your firm lacked a clear and specific written procedure for aseptic interventions performed. Only (b) (4) interventions for the (b) (4) Line and (b) (4) interventions for the (b) (4) Line were conducted during each MF.

d. Not all filled units completed the (b) (4) incubation.

e. Examination of filled units after incubation was conducted by visual inspectors that were not qualified. Your firm did not require visual inspector qualification.

f. Media growth promotion (GP) tests were not conducted for media used in MF.

F. Your firm's airflow pattern evaluations (smoke studies) were deficient.

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Specifically, aseptic processing areas are deficient in that airflow pattern evaluations (smoke studies) under dynamic conditions were not performed to visualize and demonstrate unidirectional air flow in your firm's Unit (b) (4) Fill Line and Unit (b) Ointment Fill Line where sterile (b) (4) (b) (4) and sterile (b) (4) Ointment were filled and shipped to the U.S. market, respectively.

G. Aseptic processing areas are deficient in that floors, walls, or ceilings, are not smooth and/or hard surfaces that are easily cleanable. For example,

a. Unsmooth wall panel joints, soft, unsmooth, and cracked sealant, protruding nails, and nail holes were observed in the classified Grade B surfaces of your firm's Unit (b) (4) Filling Room (b) (4) All batches of Sterile (b) (4) were aseptically filled in this room from 12/2020 to 4/2022 and distributed to the U.S. market.

b, Cracks and scratches were observed in Room (b) (4) on the Grade A Fill Line RABS enclosure (b) (4) surface. All batches of Sterile (b) (4) were aseptically filled using this filling line from 12/2020 to 4/2022 and distributed to the U.S. market.

H. Cleanroom operators who conduct aseptic filling of sterile (b) (4) in Unit (b) (4) (b) (4) Fill Line were not adequately qualified. For example,

a. Cleanroom operators were qualified after completing (b) (4) gowning validation of (b) cfu (alert limit) and (b) cfu (action limit) per (b) (4) SOP-MBD-030-01, rev 01.

b. Cleanroom operators who perform aseptic fills were not qualified through MF. No (b) (4) requalification through MF was required.

c. There were no written procedures regarding aseptic techniques and aseptic behaviors. The firm's management stated verbal instructions were given to operators.

d. There was no clear and specific written procedure for aseptic gowning. Only a gowning process check list was provided per (b) (4) SOP-MBD-030-01, rev 01.

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e. Sterile cleanroom garbs were reused by washing and (b) (4) The firm did not track or have studies to show how many times garbs could be re-used. Discolored overall, discolored, and worn-out booties were observed being used in the cleanrooms.

OBSERVATION 2

The accuracy, sensitivity, specificity, reproducibility, of test methods have not been established. Specifically,

A. The sterility method suitability testing for your firm's (b) (4) and (b) (4) Ointment did not meet the protocol acceptance criteria. Your firm lacked sterility assurance for the above drug products distributed to the U.S. market. Specifically,

a. Analytical Method Verification Protocol for Sterility Test – (b) (4) Protocol No. STVP/2019/004, requires that for product positive control, clear visible growth of microorganisms should be obtained after incubation. However, the positive product control test was not performed during method suitability validation.

b. Analytical Method Verification Protocol for Sterility Test – Sterile (b) (4) Ointment, Protocol No. STVP/2020/002, requires that for product positive control, clear visible growth of microorganisms should be obtained after incubation. However, the positive product control test was not performed during method suitability validation.

B. The sterilization of (b) (4) Ointment batch (b) (4) by (b) (4) method was not validated. Batch (b) (4) was manufactured in December 2020 for the U.S. market. Your firm lacked sterility assurance for the above drug product distributed to the U.S. market.

OBSERVATION 3

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

Specifically,

Filling Machine ID # (b) (4) FLM/113 is used for the manufacturing of (b) (4) for the US customers. The machine fills (b) mL of (b) (4) mg/mL in an (b) (4) (b) (4) Grade bottle of (b) (4) mm diameter and (b) (4) mm height. The (master) Batch Packing Record Doc. No. BPR/CMC/001 Effective date 9/28/2020 does not have filling speed.

The design qualification confirmed that the machine is designed to fill (b) mL, (b) mL, (b) (4) mL at (b) (4) bottles (b) (4) speed in a bottle of (b) (4) mm to (b) (4) mm height; outside the specification of the bottle used for (b) (4) ((b) (4) mm height) and the fill volume. The performance qualification was determined to be acceptable, however, no data for the batches that were used for test runs was included in the PQ Report.

OBSERVATION 4

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions.

Specifically,

A. On 2/23/2023, Assistant Manager of Quality Assurance stated the (b) (4) effectiveness study has not been carried out for the Unit (b) Sterile Manufacturing Block where (b) (4) is manufactured for the US market. As per your procedure SOP No. (b) (4) SOP/SFU/EEN-008-0 Procedure for (b) (4) for in (b) (4) Plant (Effective date 1/29/2021), you carry out (b) (4) of clean area (including filling room) before resuming the production and after a (b) (4) or air handling unit is not under operation for more than (b) (4) In addition, you have not established the (b) (4) (b) (4) phase times for the (b) (4) Hence, there is no assurance that (b) (4) with (b) (4) does not cross contaminate aseptically filled products. E.g., according to the filling machine equipment use log, you carried out (b) (4) on 4/10/2022 from (b) (4) – (b) (4) and after (b) (4) you started filling for (b) (4) Batch No. (b) (4) (filling on 4/10/2022 (b) (4) – (b) (4). However, in the batch record you have noted filling

timing 4/11/2022 (b) (4) – (b) (4) Your production manager did not have any explanation for the discrepancy between the equipment use logbook and the batch packing record.

On 2/28/2023, your Microbiologist shared Validation Protocol to Determine the Duration of (b) (4) Effectiveness No. (b) (4) DFEP/001/00-23 Effective date 1/11/2023 and corresponding report No. (b) (4) DFER/001/00-23 to verify the conducted (b) (4) effectiveness study. The report lacks the location/rooms of the study, number, and locations of the microbial indicators, and missing the signature dates for the reviewers and approvers. Your Microbiologist who carried out the (b) (4) study could not remember the room number where he carried out the (b) (4) study.

B. Your cleaning process for the Unit (b) Sterile manufacturing area is deficient such that the cleaning record does not include cleaning of several areas of the room including but not limited to; doors, handles, and HEPA filter grills. The cleaning is documented on Format No. (b) (4) PRD-GEN-002-F-001-00 but this corresponds to procedure (b) (4) SOP-PRD-GEN-002-0 Procedure for Cleaning and Maintenance of the Manufacturing Areas (Tablets, Capsules, (b) (4) Liquid, and (b) (4) Preparations) (Effective date 4/15/2021), which is not for the Sterile Unit (b) Your General Manger QA stated that the cleaning of the Unit (b) Sterile area is carried out as described in procedure (b) (4) SOP-SFU-FFS-005-02 General Cleaning Procedure for Sterile Formulation Plant (Effective date 2/3/2021). This procedure uses a (b) (4) system for cleaning and does not include (b) (4) The procedure lacks instruction for cleaning and sanitizing the surfaces. You have also not validated the effectiveness, contact times for the cleaning agents for various surfaces.

C. Surfaces that contact (b) (4) container-closures were not cleaned, sanitized, decontaminated, or sterilized, and there were no written procedures indicating any such activities should be performed.

Specifically, your firm does not have SOP(s) for the cleaning and sterilization of the Unit (b) (4) (b) (4) Fill Line bowls used for the dispensing of (b) (4) bottles, (b) (4) caps, and (b) (4) caps which were all product contact surfaces. The (b) (4) Fill Line is located in Filling Room (b) (4) and used to aseptically fill (b) (4) for the U.S. market.

D. (b) (4) Unit Preparation ID# SS/UPA/087 lacked load pattern and sterilization cycle validation. Specifically,

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The above (b) (4) was used for the sterilization of, for example, filling nozzle, (b) (4) tubing, (b) (4) containers, (b) (4) bottles, bowls for sterile container-closure, tools, other change parts, and cleanroom garments, used for Unit (b) (4) Fill Line aseptic filling activities. However, your firm lacked load pattern validation to ensure successful sterilization was achieved.

OBSERVATION 5

Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals. Specifically,

A. Active pharmaceutical ingredient (API) (b) (4) was used in the manufacturing of (b) (4) Your firm failed to test incoming (b) (4) to determine conformance to identity, purity, strength, and other appropriate specifications. Instead, you released API for use in drug production based solely on certificates of analysis (COA) from your supplier without establishing the reliability of the supplier's analysis through appropriate validation and ensuring that at least one specific identity test is conducted for each lot.

B. Your firm failed to qualify the supplier for excipient (b) (4) used in the manufacturing of (b) (4)

OBSERVATION 6

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

A. You manufacture sterile (b) (4) mg/mL) for the US market in non-dedicated equipment in Unit (b) Sterile Plant where you also manufacture (b) (4)

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(b) (4) for Myanmar and (b) (4) for Myanmar and Ethiopia. You have not validated the cleaning procedure for the manufacturing equipment including but not limited to: (b) (4) vessel (ID # (b) (4) MAV/108), filtration tank (ID# (b) (4) FLT/110), and filling machine (ID # (b) (4) FLM/113).

Instead, your QC manger stated that the firm analyzed the rinse samples collected after cleaning the manufacturing equipment to test for the last drug products against a specification for NMT (b) (4) ppm by UV method. However, it was also stated that the test method to analyze the swab sample for low levels (sub ppm level) of drug substances was not validated and LOD and LOQ were not established. As a result, there is no analytical assurance that the cleaning procedure prevents cross contamination on this non-dedicated equipment.

On 4/7/2022, you manufactured (b) (4) mg/mL Batch No. (b) (4) right after manufacturing (b) (4) Batch No. (b) (4) on 4/3/2022. However, cleaning verification of the manufacturing equipment after manufacturing (b) (4) involved testing the rinse for the (b) (4) and not for the (b) (4)

B. On 2/21/2023, during walkthrough of the filling room in Unit (b) (4) I saw a black, brown colored greasy deposit on the bottle transfer (b) (4) bowl, which is part of Filling Machine ID # (b) (4) FLM/113. The brownish material deposition on the bowl was confirmed by wiping the surface of the container with a blue lint free cloth. The portion of the lint free cloth that was rubbed against the black, brown surface of the bowl revealed brown spots. According to the equipment use logbook, the filling machine was last cleaned on 1/31/2023 after manufacturing (b) (4) Batch No. (b) (4) and has not been used since.

On 2/27/2023, your Production Manager stated that there was no procedure for cleaning the Filling Machine ID # (b) (4) FLM/113. He stated that there was no space to store dirty and clean equipment in Unit (b) (4) Sterile Plant. After completion of the batch, the filling machine accessories are taken out for cleaning. After cleaning, the accessories are re-fixed immediately to the filling machine. Before, starting the production, all the filling machine accessories are taken out and (b) (4) and re-fixed to

the filling machine. On 2/21/2023 during the walkthrough of the filling room, I saw none of the equipment on the filling machine was wrapped or covered.

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Environmental monitoring (EM) and personnel monitoring (PM) for the Unit (b) (4) Fill Line used in manufacturing (b) (4) are deficient. For example,

A. There were no written justifications based on risk assessment for selected EM locations.

B. EM alert and action limits were not based on historical data.

C. Swab used for viable surface monitoring does not contain disinfectant neutralizer. Your firm had no studies to demonstrate residual disinfectant would not interfere with test results.

D. No non-viable particle air samples were collected inside the Grade A filling zone and the Grade B surrounding areas during active filling.

E. There was no growth promotion test performed for (b) (4) plates used for personnel monitoring.

F. There were no identifications of isolates recovered from EM or PM samples.

G. EM and PM (b) (4) media incubation temperature and time were not supported by corresponding (b) (4) media growth promotion.

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OBSERVATION 8

Laboratory controls do not include determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of drug product containers and closures used in the manufacture, processing, packing, or holding of drug products.

Specifically,

Primary packaging materials, including the (b) (4) ml bottle, cap, and (b) (4) for the container closure system used for (b) (4) are supplied by a vendor and released for use per your procedure, (b) (4) SOP-QCD-061-02 Procedure for Sampling and Release of Packing Materials (Effective date 11/19/2021) without a provision for testing these materials for sterility. These primary packing materials are supplied as sterile. Between 2019 and 2022, you have received (b) (4) shipments of bottles, caps and (b) (4) from your vendor.

You did not test the caps and (b) (4) for the sterility before releasing for use in the manufacturing.

The Sterility Test Reports data sheets for shipments of 2019, 2020, 2021, and 2022 are not issued in your Microbiology Document Issue and Reconciliation Form for the respective years. It is not clear how the Sterility Test Report data sheets, Format No. (b) (4) MBD-023-F-001-0, was available to the QC lab to carry out the sterility test.

OBSERVATION 9

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

A. You did not follow your procedure, (b) (4) SOP-QAD-027-04 Procedure for Approval and Release of Finished Product to Market (Effective date 1/28/2022) and released (b) (4) to the US market.

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	Eileen A. Liu -S Digitally signed by Eileen A. Liu -S Date: 2023.03.02 17:03:49 +05'30' Rajiv R. Srivastava -S Digitally signed by Rajiv R. Srivastava -S Date: 2023.03.02 17:18:46 +05'30'	Eileen A. Liu, CSO Rajiv Srivastava, CSO	03/02/2023

A number of batches released to US market without review from your quality control unit including but not limited to: Batch No's (b) (4) Your General Manager of QA stated that the batches were released based on the Certificates of Analysis.

B. On 2/21/2023, during walkthrough of your QA document room, I found prefilled Checklist for Finished Product Batch Release for sale – Production Review, Checklist for Finished Product Batch Release for sale – QC Review, and Checklist for Finished Product Batch Release for sale – QA Review. Your QA Executive stated that she forgot to attach the pages to the BMRs and could not provide the respective BMRs.

OBSERVATION 10

Established specifications, standards, sampling plans, test procedures, laboratory control mechanisms, are not followed, documented at the time of performance.

Stability samples are not stored according to your written procedure.

Specifically, (b) (4) stability batch (b) (4) (set up date 6/1/2022, for 36 months study) was observed stored in the (b) (4) position in the long-term stability chamber located in the Microbiology Laboratory. Per (b) (4) SOP-QAD-047-02, rev 02, entitled "Stability Management Procedure", section 5.10.2 states "In case of liquid, (b) (4) injection and (b) (4) the entire sample shall be charged in (b) (4) position".

OBSERVATION 11

The quality control unit lacks the responsibility and authority to approve, reject all components, drug product containers, closures, in process materials, packaging material, labeling, drug products. Specifically,

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	02/20/2023-03/02/2023 FEI NUMBER 3012323885

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Venkatesh, A.R. CEO

FIRM NAME	STREET ADDRESS
Global Pharma Healthcare Pvt. Ltd.	A-9, SIDCO Pharmaceutical Complex
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Thiruporur – 603110, Tamilnadu, India	Drug Product Manufacturer

Your firm failed to follow procedure per section 5.1.6 of the (b) (4) SOP-QAD-003-06, rev 06 entitled "Change Control Procedure", in which change requests are to be initiated for changes of specifications of raw materials, packing materials, finished products, and the manufacturing process parameters, etc. Your firm did not evaluate the potential impact of the following changes on the process, quality, safety, purity, and efficacy of the finished products. Specifically,

A. Your firm failed to initiate change control for the (b) (4) caps (b) (4) specification from "no (b) (4) to "with (b) (4) . A total of (b) (4) batches ((b) (4) to (b) (4) and (b) (4) to (b) (4) for the U.S. market were affected by this change.

B. Your firm failed to initiate change control for (b) (4) final product release pH specification from pH (b) (4) – (b) (4) to pH (b) (4) - (b) (4) A total of (b) (4) batches ((b) (4) to (b) (4)) for the U.S. market were affected by this change.

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Eileen A. Liu -S Digitally signed by Eileen A. Liu -S Date: 2023.03.02 17:05:51 +05'30'

Rajiv R. Srivastava -S Digitally signed by Rajiv R. Srivastava -S Date: 2023.03.02 17:19:59 +05'30'

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Eileen A. Liu, CSO
Rajiv Srivastava, CSO

DATE ISSUED

03/02/2023