DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, CDER Inspection Assessment Branch 10903 New Hampshire Avenue Bldg. 51, Room 4316 Silver Spring, MD 20993 Phone: 1-301-796-3254 Industry Information: www.fda.gov/oc/industry	February 27-28, March 1-3 and 6-8, 2017
	FEI NUMBER 3006549835

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vikramkumar B Shukla, Vice President Operations

FIRM NAME	STREET ADDRESS
Dr. Reddy's Laboratories Ltd.	Plot No. P1 to P9, Phase III Duvvada, VSEZ
CITY, STATE AND ZIP CODE Visakhapatnam - 530 046, A.P., India	TYPE OF ESTABLISHMENT INSPECTED Sterile Injectable Drug and Oral Solid Dosage

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

OBSERVATION #1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has already been distributed.

1. On 27 February 2017, during the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) product was observed to have leaked onto the (b) (4) below the (b) (4) This was pointed out to firm management by the FDA investigators. A thorough investigation of the source of this leakage was not performed before dismantling the (b) (4) An investigation was performed and then approved on 02 March 2017. It concluded the observed leakage was from (b) (4) before filling started.

This conclusion did not consider that the spilled product was observed at the end of the batch and product from the (b) (4) would have likely evaporated during the filling. Follow-up studies were then conducted as part of the investigation that showed intentionally spilled product evaporated in approximately 50 minutes. The amount of time between (b) (4) and the observation of unevaporated spilled product was approximately 112 minutes. The updated investigation had been reviewed and signed by Manufacturing and Science Technology, Production, and Quality Assurance concluded "there was no subsequent leakage after (b) (4) and the spill was most likely from the (b) (4), even though the evaporation data did not support this conclusion.

Previous investigations into leakage incidents that occurred during manufacturing have not been thoroughly investigated to ensure true root causes have been identified and appropriate corrective actions are implemented. Despite repeated investigations, these incidents continue to occur. This was noted during the review of the following quality impacting incident reports:

a. Incident 200168017 was initiated due to product leakage observed on the (b) (4) on the manufacturing vessel before the (b) (4) during filling and (b) (4) loading of (b) (4) Injection, (b) (4) mg/vial, batch (b) (4) The incident report indicated that the (b) (4) was not tightened properly. The loss or

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product resulted into the batch yield not conforming to specification. The procedure was revised to add precautionary steps during connection as preventive action.

b. Incident 200168685 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) prior to (b) (4) during filling of (b) (4) Injection, (b) (4) mg/vial, batch (b) (4) The incident report indicated that improper connection as the root cause and the SOP was revised to incorporate instructions and precautions on (b) (4) connections.

c. Incident 200193210 was initiated due to product leakage observed on the (b) (4) gasket of the (b) (4) vessel during filling of (b) (4) Injection, batch (b) (4) The loss of product resulted into batch yield not conforming to specification. Preventive Maintenance Plan (PMP) task checklist was revised to verify all (b) (4) gaskets during scheduled maintenance as preventive action.

d. Incident 200225061 was initiated due to product leakage observed on the (b) (4) during filling of (b) (4) Injection, USP (b) (4) mL, batch (b) (4) No assignable root cause has been identified.

e. Incident 200198319 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) prior to (b) (4) during filling of (b) (4) Injection, batch (b) (4) The incident report indicated that improper connection as the root cause. Due to the loss of product, the batch did not conform to yield specification.

f. Incident 200215055 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) prior to (b) (4) during filling of (b) (4) Injection, batch (b) (4) The incident report indicated that the (b) (4) dislodged from the (b) (4) causing the product to leak. Awareness training was provided for the operator involved, and line clearance procedure was revised to incorporate (b) (4) verification in the batch record.

2. Collection of trending data for documentation errors, such as GDP errors, calculation errors, missing signatures, or incomplete documentation, began in May of 2016. It identified 314 errors in 22 Batch Manufacturing Records reviewed in May 2016. No critical evaluation of this data was performed to evaluate root causes these errors. These errors repeated in subsequent months. For example:

June 2016 there were 258 errors identified in 15 Batch Manufacturing Records

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July 2016 there were 224 errors identified in 17 Batch Manufacturing Records
August 2016 there were 128 errors identified in 21 Batch Manufacturing Records
September 2016 there were 143 errors identified in 22 Batch Manufacturing Records
October 2016 there were 200 errors identified in 21 Batch Manufacturing Records

No evaluation was performed to determine root causes or evaluate why localized training of the affected personnel was ineffective in eliminating errors.

3. Investigations into observations of objectionable organisms in the (b) (4) system were not thorough.

a. (b) (4) identification of isolates from the (b) (4) system identified the objectionable organism Burkholderia cepacia from point (b) (4) for sampling performed 01 August 2014. No root cause was determined and no corrective actions were performed. No additional identification was conducted to determine if other recovered organisms in subsequent samples were also Burkholderia cepacia.

b. Subsequent (b) (4) identification from samples collected on 30 August 2014 (points (b) (4) and samples collected 21 September 2014 (point (b) (4) identified the objectionable organism Acenitobacter baumanii. No root cause was determined and no corrective actions were performed. No additional identification was conducted to determine if other recovered organisms were also Acenitobacter baumanii.

c. Incident 200135364 was opened when (b) (4) identifications of isolates from the (b) (4) system identified the objectionable organism Burkholderia cepacia from point (b) (4) for sampling performed 29 May 2015. No definitive root cause was determined. The report did not describe historical data, which had previously identified this organism. A potential root cause was identified to be the sampling hose touching a nearby drain. No sampling of the drain was performed to further confirm this root cause. No expanded identification of recovered microbial growth from (b) (4) sampling was conducted to verify if this organism was present in subsequent sampling.

d. Incident 200142186 was opened when (b) (4) identifications of isolates from the (b) (4) system identified the objectionable organism Vibrio vulnificus from point (b) (4) for sampling performed 23 July 2015. The result was reported 30 July 2015. On 31 July 2015 use of the system was suspended and the system was

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sanitized. Sampling was repeated on 01 August 2015 and identifications were performed. Vibrio vulnificus was not identified, but other objectionable microorganisms were found: Burkholderia cepacia (4 use points) and Acinetobacter haemolyticus (1 use point).

Sanitization was again repeated on 11 August 2015 followed by sampling and isolate identification. This follow-up sampling again identified the objectionable organisms Burkholderia cepacia (2 use points) as well as Pseudomonas and Acinetobacter organisms.

Sanitization was again repeated on 20 August 2015 and 21 August 2015 followed by sampling and isolate identification. Follow-up sampling again identified the objectionable organisms Burkholderia cepacia (1 use point) on 07 September 2015 from a sample collected 28 August 2015. The (b) (4) system had already been cleared for use on 04 September 2015. This is prior to implementation of corrective actions identified in the investigation. No additional actions were specified after the additional finding on 07 September 2015.

The report justified release of (b) (4) Tablets batch (b) (4) manufactured at the time the original Vibrio vulnificus was detected, based on microbial limits and specified organisms testing. No studies were performed to show the objectionable organisms identified in the (b) (4) system during this investigation and previous investigations identified in 3a, 3b, and 3c could be reliably detected by the existing microbial test methods.

The final investigation report evaluated historical trending of objectionable organisms in the (b) (4) system. Those instances described in points 3a, 3b, and 3c of this observation were not included in the historical evaluation.

4. Incident 200166175 was opened when Staphylococcus aureus was identified during active air monitoring of the (b) (4) Block (b) (4) laminar flow hood point (b) (4) on 25 January 2016. The investigation identified the likely root cause as improper gowning and hygiene of employees. The corrective action was identified to be training of personnel when the investigation was closed on 16 February 2016. The first training was not held until 22 March 2016 and some personnel were not trained until 20 April 2016. Additionally, there was no expanded follow-up sampling or identification of isolates to evaluate whether training had been effective.

5. The (b) (4) Integrity Test Unit (b) (4) equipment #PRE-346 is used to perform an integrity test of

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	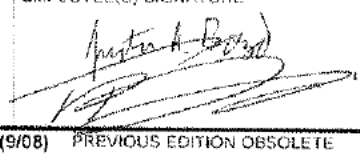	Justin A. Boyd, Investigator Toyin B. Oladimeji, Investigator	03/08/2017

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the (b) (4) that are used for the (b) (4) SOP OPR519-00, "Operation of (b) (4) Integrity Tester", states in part "In case of failure of (b) (4) integrity test, write justification for the failure and repeat the test only for that particular failed (b) (4) and if the (b) (4) integrity passes, then proceed for the next routine activity. If integrity failure is confirmed, then immediately inform the superior and replace the faulty (b) (4) with new (b) (4) and perform the (b) (4) integrity test before the start of the (b) (4) eak test". A (b) (4) replacement was not performed after (b) (4) integrity test failed twice, superior was not notified per instructions in the SOP, and investigations were not initiated. This was evidenced on the following instances:

a. (b) (4) Number IS1 (b) (4) Batch Report 1062 for batch (b) (4)
b. Number IS1 Batch Report 1078 for batch
c. Number IS1 Batch Report 1158, not batch related
d. Number IS1 Batch Report 1158, not batch related
e. Number IS1 Batch Report 1165, for batch (b) (4)
f. Number IS1 Batch Report 1171, for batch

6. Thorough investigations with scientifically justifiable conclusions to incidents of out-of-specification (OOS) were not performed and/or failed to implement appropriate corrective actions for the root cause determination. The corrective action and preventive action (CAPA) state that training awareness should be conducted; however due to the number of repeated analyst errors identified as the root cause, there is no assurance that the CAPAs are effective in addressing the actual causes as the incidences attributed to analyst errors still continue. The deficiencies are evidenced in the following:

a. OOS 310009438 was initiated due to OOS result obtained during stability testing of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated that analyst error attributed to the failure. However, the investigation did not identify the specific analyst error even though the procedures stipulated in the test method were followed. No actual or probable root cause was identified. The samples were reanalyzed and passing result was reported.

b. OOS 310007780 was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. However, a specific analyst error was not

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	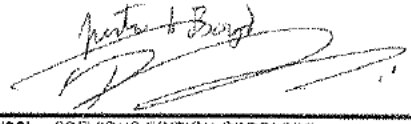	Justin A. Boyd, Investigator Toyin B. Oladimeji, Investigator	03/08/2017

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identified. The samples were reanalyzed and passing result was reported.

c. OOS 310008334 was initiated due to OOS obtained during analysis of (b) (4) Injection USP (b) (4) mg (b) (4) mL, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

d. OOS 310009250 was initiated due to OOS obtained during analysis of (b) (4) njection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

e. OOS 310009706 was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated transient equipment error was root cause and awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

f. OOS 310009622 was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated unknown analytical error attributed to the root cause – there was a delay in injecting the samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

g. OOS 310010270 was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was root cause – there was a delay in injecting the samples. Awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

h. OOS 310008552 was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The

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investigation report indicated that sampling error by the analyst was the root cause and the quality assurance manager stated that there was also a delay in receiving samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

i. OOS 310009929 was initiated due to OOS obtained during particulate matter test of stability sample of (b) (4) injection (b) (4) mg/vial, batch (b) (4) Test results obtained did not meet specification of ≥(b) (4) µ: NMT (b) (4) and ≥(b) (4) µ NMT (b) (4) Analyst error was identified as the root cause and no corrective action was initiated. The samples were reanalyzed and passing result was reported.

j. OOS 310010238 was initiated due to OOS obtained during particulate matter test of (b) (4) Injection (b) (4) ng, batch (b) (4) Test results obtained did not meet specification of ≥(b) (4) : NMT (b) (4) and ≥(b) (4) µ NMT (b) (4) No assignable root cause was identified. The analyst involved was trained as a corrective action. The samples were reanalyzed and passing result was reported.

7. There was a failure to identify the characteristics of the fiber/particle rejects, or determine the source of the fibers/particulates in injectable products. SOP OPR012-15, Procedure for Visual Inspection of Filled, Sealed and Over Coded Vials by Using Visual Inspection Hood, describes evaluation of the particulate matter observed during visual inspection for its color, size, and shape. The drug products listed below had rejected vials with (b) (4) fibers that were not characterized or evaluated for a source:

a. (b) (4) Injection, batch (b) (4)

b. (b) (4) Injection, batch (b) (4)

c (b) (4) Injection, USP (b) (4) mg/vial, batch (b) (4)

Failure to perform thorough investigations is a REPEAT OBSERVATION from the 05 November 2015 FDA WARNING LETTER.

OBSERVATION #2

Written procedures for production and process controls designed to assure that drug products have the identity,

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strength, quality, and purity they purport or are represented to possess have not been established and followed.

1. The defect library used to train the visual inspectors did not include any examples of "black particles" for (b) (4) products until 09 February 2017. During qualification of the operators vials with "black vials" were not included in any of the (b) (4) products in clear vial challenge kits. Review of trending for (b) (4) batches manufactured in 2016 of the (b) (4) product (b) (4) Injection showed that 18 batches had at least one vial rejected for black particles.

2. Of the (b) (4) challenge kits for (b) (4) product in clear vials, there is only one example of the critical defect "glass particle". This vial was prepared in-house. The size of the glass particle was not measured and no criteria were established when creating the challenge vial.

Unacceptable procedures for qualification of visual inspectors is a REPEAT OBSERVATION from the 05 November 2015 FDA WARNING LETTER.

OBSERVATION #3
Failure to maintain complete data to ensure compliance with established specifications and standards.

1. Reported analysis of (b) (4) API lot (b) (4) was conducted on 18 April 2014. On 17 April 2014 there was an unreported sequence of the same method and analytical reference number. The injections included samples identified as "Blank" and "Systemsuitability". The "Systemsuitability" chromatograms on 17 April 2014 had a similar peak profile to the samples injected in the reported analysis on 18 April 2014, but a different peak profile than the "Systemsuitability" injections from 18 April 2014.

There was no incident investigation initiated for this test and there is no explanation in the analytical records for the unreported sequence. At the time there was no requirement for review of the sequence audit trails from the Chromeleon software and no retrospective review of previously generated data was performed when review of the sequence audit trails was started in April of 2015.

The corporate FDA Warning Letter issued to Dr. Reddy's on 05 November 2015 identified similar data integrity concerns at another site. Investigation and retrospective review for data integrity was not extended to the

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Chromeleon chromatography data generated at this site.

2. Video recordings of the media fill are required to be made per the media fill protocols and must be reviewed by QA. These video recordings for media fill batches (b) (4) have since been destroyed.

OBSERVATION #4

Production records do not contain complete and accurate information.

1. Review of Biometric entry data, which uses fingerprints to track and grant employee access to the facility, indicated that personnel signing for steps in production records were not actually present at the time of the steps indicated in the records.

a. During the filling of media fill batch (b) (4), (b) (6) signed for the "checked by" portions of the batch record when biometric and card reading entries indicate he was in other areas of the facility. Examples include, but are not limited to:

i. Page #36, documentation of differential (b) (4) of the (b) (4) at (b) (4) Page #34, in-process checks for the (b) (4) performed at (b) (4) However, the biometric entry data showed the employee entering the (4) block from outside at (b) (4)

ii. Page #66, intervention for fallen/rejected vial removal from 16:39 to 16:40. Biometric entry shows the operator entering the changing room at 16:41:56.

iii. Page #65, sterilized seals addition at 16:49 to 16:50, however this employee was entering the Block (b) (4) building from the outside at 16:54:35.

iv. The biometric entry data does not show the employee entering the change room to enter the "Filling Area (b) (4) Block" until 08:34:43 on 25 October 2016. However, the employee performs many activities from approximately (b) (4) on 24 October 2016 until 08:30 on 26 October 2016.

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Additionally, when this employee was asked questions about what had occurred, he provided false and misleading statements before later admitting he may not always present at the time the activity occurs.

b. Review of (b) (4) Injection, batch (b) (4) manufacturing batch record showed that the operator who verified and signed the "Checked by" column for completion of process step (b) (4) of the batch record (process instructions) was not present at the time of performance. Step (b) (4) was performed between 14:00 to 14:10. However, according to the Biometric Access System, the operator was at the exterior entrance to the (b) (4) block at 14:04, and entered the change room for the critical area at 14:21. The operator (b) (6) was interviewed and confirmed he did not witness the operation. He signed the batch record after the process step was completed.

2. In media fill batch record (b) (4) page #14 includes the step # (b) (4) for cleaning of LAF and step # (b) (4) for switching the LAF on and recording the reading on the magnehelic gauge. These steps were documented to done by (b) (6) and then checked by (b) (6) on 23 October 2016. Neither of these operators were present in the facility at that time. Further investigation found that these entries had been copied out of a LAF logbook. The entry was then signed and backdated by these individuals that had not performed or been present for these steps.

3. Gown inspection records show that (b) (4) critical area gown #10012017-07 was inspected and found acceptable on 27 February 2017 and 28 February 2017. On 27 February 2017 a gown with this number was observed in the (b) (4) waste area in a bag that identified these (b) (4) critical area gowns had been rejected on 23 February 2017.

4. Visual inspection records for (b) (4) show that there were only two vials rejected for "Black Particles". However, the defect library identifies one vial from batch (b) (4) with black particles is part of the library and analytical request records show two additional vials from batch (b) (4) were submitted for identification of black particles.

OBSERVATION #5

Written procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed, including validation of all aseptic process.

1. Requirements of what activities need to be performed during a media fill to qualify a person to perform aseptic activities have not been established. For example, document FT 7PR155/A07 "Media Fill Participation List of

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	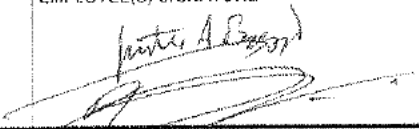	Justin A. Boyd, Investigator Toyin B. Oladimeji, Investigator	03/08/2017

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Food and Drug Administration, CDER Inspection Assessment Branch 10903 New Hampshire Avenue Bldg. 51, Room 4316 Silver Spring, MD 20993 Phone: 1-301-796-3254 Industry Information: www.fda.gov/oc/industry	February 27-28, March 1-3 and 6-8, 2017
	FEI NUMBER 3006549835

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vikramkumar B Shukla, Vice President Operations

FIRM NAME	STREET ADDRESS
Dr. Reddy's Laboratories Ltd.	Plot No. P1 to P9, Phase III Duvvada, VSEZ
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Personnel for Performing Aseptic Activities" identifies that operator "(b) (6) , "(b) (6) , and "(b) (6) are "qualified for performing aseptic activities" based on the media fill conducted 12 January 2017. The corresponding media fill batch record does not document these personnel performing aseptic operations.

2. There are no entrance or exit logs to show which operators were present and when they were present in the filling room. The intervention of maximum (b) (4) people in the room during media fill batch (b) (4) does not document which (b) (4) operators were in the room. The biometric access data for this time period does not show the entrance of (b) (4) people into the filling area.

3. On 07 March 2017, upon entering the line (b) (4) filling area, (b) (4) operators were already in the room, exceeding the limit of (b) (4) which was qualified during media fills.

4. On 27 February 2017, during the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) sample bags, plastic wrappers from environmental monitoring media, and packaged materials that included (b) (4) (b) (4) were observed to be partially blocking the air returns inside of the (b) (4)

5. Procedure OPR518-00 "Operation of Online Continuous Particle Monitoring System (Line (b) (4) " does not describe actions to take when non-viable particle counts are exceeded during set-up. On 07 March 2017 an alarm for action level of the non-viable particle counts occurred just prior to performing aseptic connections. The personnel performing activities did not stop working when the alarm occurred.

OBSERVATION #6
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

1. Surface monitoring inside of the (b) (4) performed using (b) (4) plates was observed on 27 February 2017. After sampling, (b) (4) was sprayed onto wipes held with the (b) (4) in order to wipe the sampled (b) (4) surfaces. In spraying the wipe, the operators were observed to get (b) (4) on the (b) (4) This is prior to performing subsequent monitoring of the (b) (4)

2. The microbiology media used for settle plates, active air samples, and touch plate monitoring of the (b) (4) gloves do not contain neutralizing agents. (b) (4) is sprayed in the areas where the monitoring occurs.

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3. (b) (4) contact plates are used for surfaces that are not flat, such as (b) (4) (b) (4)

4. On 27 February 2017 the person performing monitoring of the inside of the stopper bowl did not first move the stoppers. This prevented the plate from contacting the flat surface of the stopper bowl and the stoppers caused damage to the (b) (4) surface of the plate.

OBSERVATION #7

Procedures for the preparation of master production and control records are not followed.

1. Master copies of raw data forms are available on a shared computer drive in the microbiology laboratory. These can be modified with batch information and printed. For example, raw data sheets for sterility testing or performing microbial limits tests.

2. Blank GMP forms can be copied by laboratory of production personnel. For example, batch record pages or analytical testing raw data forms. There is no process to uniquely identify the original document.

3. There is no effective process to ensure reconciliation of documents. QA does not reconcile the forms issued and the forms returned if no additional pages are re-issued. Reconciliation when additional pages were issued was found to be ineffective in detecting discrepancies. For example, 5 pages issued for Analytical Record 890000853527 could not be found in the archived data on 01 March 2017. The reconciliation of this batch had noted no discrepancies at the time it was archived. The 5 extra pages were later found filed with Analytical Record 890000853752. This record had also been reconciled, but the five extra pages were not detected.

OBSERVATION #8

Appropriate controls are not exercised over computer or related systems to assure that changes to master production records and control records or other records are instituted only by authorized personnel.

1. General computers are used in the laboratories and production areas. The personnel can create and delete files on these systems without oversight or specific procedures to describe how the computers are to be used. During

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the inspection recent files were observed to have been deleted off these computers, the computer "Recycle Bins" were emptied, and in some cases the personnel had deleted the "Recent" document list in programs such as Microsoft Word and Excel.

Further, when asked about these activities during the inspection, an employee from the chemistry laboratory, two employees from the microbiology laboratory, and two employees from the production department provided repeated false and misleading statements before later admitting they had recently deleted files from the computers.

2. Filter integrity test results can be deleted from the Sartorius tester. A demonstration of the deletion process was performed by a production employee on 02 March 2017.

3. Glove integrity test results can be deleted. A demonstration of the deletion process was demonstrated by a production employee.

4. The production supervisor has access to change date/time on the (b) (4) PLC (Programmable Logic Controller).

OBSERVATION #9
Data is not documented contemporaneously.

1. (b) (4) sampling records and environmental monitoring records are not made at the time of sampling. The records are made at a later time when the samples are delivered to the laboratory. Additionally, the person collecting the samples does not sign or date the record, which is a REPEAT OBSERVATION from the 06 March 2015 FDA 483.

2. (b) (4) plates, glove touch plates, and swabs used for surface monitoring are not labeled at the time the samples are collected. The media is left in place unlabeled until all samples are collected.

3. A missing entry in the batch record for batch (b) (4) was made at a later time without any indication that it had not been made contemporaneously.

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OBSERVATION #10

Thorough review of documents is not performed.

Documentation of settle plates in logbook FT7QC228/F13-00 was done two different ways. Some analysts recorded the start time and end time of the exposure. More commonly the analyst recorded only the amount of time it took to open the plate and did not record the end time of exposure in the record. The person reviewing the documentation signed both ways as being approved.

OBSERVATION #11

Procedures for maintenance of equipment had not been established and followed.

1. The (b) (4) used to (b) (4) the (b) (4) area of the (b) (4) used for filling line # (b) (4) appears to be cracking.

2. The (b) (4) covering the HEPA filters inside of the (b) (4) of filling line # (b) (4) had tears with exposed fibers above the incoming (b) (4)

3. Approved procedures for preventative maintenance did not include maintenance recommended by the equipment manufacturer. For example, the supplier manual for the (b) (4) Equipment recommends (b) (4) inspection of the air ducts for dust. This is not performed as part of the routine cleaning or maintenance. When the (b) (4) air duct of the "Clean" (b) (4) equipment in block (b) (4) was inspected on 01 March 2017, dust and an unidentified black residue was observed. This piece of equipment is not product dedicated.

OBSERVATION #12

Review of process performance qualification (PPQ) for (b) (4) Injection (b) (4) mg/vial, batch (b) (4) revealed that the samples collected for finished product release testing is not statistically representative of the manufactured batch. According to the Assistant Manager, Manufacturing Science & Technology, the samples collected in the PPQ are limited to the number of samples required to conduct the testing. There is no evidence and/or documentation to support when and how the samples were collected throughout the batch manufacturing. This is a REPEAT OBSERVATION from the 06 March 2015 FDA 483.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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OBSERVATION #13

Samples collected to evaluate conformance of a batch are not representative.

Samples taken for bioburden and endotoxin monitoring of unfiltered bulk product are taken at the conclusion of compounding activities. During the subsequent testing for release of the bulk and preparation for filling (which was observed to take up to (b) (4), as well as the filling process (which can take up to (b) (4) the bulk product remains unfiltered.

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