

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847-8738 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 01/21/2016 - 01/29/2016
	FBI NUMBER 3002875215

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Benjamin G. Boling, Managing Director

FIRM NAME Teva Pharmaceutical Works Private Limited Company	STREET ADDRESS Tancsics Mihaly ut 82
CITY, STATE, ZIP CODE, COUNTRY Godollo 2100, Hungary	TYPE ESTABLISHMENT INSPECTED Sterile 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:

OBSERVATION 1

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

1. Personnel monitoring contact plate for the right forearm from cleanroom operator "(b) (4)", collected at (b) (4) on 14 January 2016 was read by a microbiologist, a recorded result of (b) (4) CFU was made on (b) (4), and the plate was discarded. Less than one hour later the same plate was examined and observed to contain (b) (4) CFU.
2. Personnel monitoring contact plate from the (b) (4) monitoring point of cleanroom operator "(b) (4)" collected at 13:45 on 13 January 2016 was read by a microbiologist, a recorded result of (b) (4) CFU was made on (b) (4), and the plate was discarded. Less than one hour later the same plate was examined and observed to contain (b) (4) CFU.
3. Surface contact sample from point (b) (4) in room (b) (4), a Grade C area, collected on 13 January 2016 was read by a microbiologist, a recorded result of (b) (4) CFU was made on (b) (4), and the plate was discarded. Less than one hour later the same plate was examined and observed to contain (b) (4) CFU.
4. Surface contact sample from point (b) (4) in room (b) (4), a Grade C area, collected on 13 January 2016 was read by a microbiologist, a recorded result of (b) (4) CFU was made on 21 January 2016, and the plate was discarded. Less than one hour later the same plate was examined and observed to contain (b) (4) CFU.
5. Volumetric air sample from point (b) (4) in room (b) (4), a Grade D area, collected on 13 January 2016 was read by a microbiologist, a recorded result of (b) (4) CFU was made on (b) (4), and the plate was discarded. Less than one hour later the same plate was examined and observed to contain (b) (4) CFU.
6. On 21 January 2016, four discarded sealed personnel monitoring contact slides were observed. Three contact slides had (b) (4) CFU and one contact slide had (b) (4) CFU. These were all read by analysts on 19 January 2016, and the associated data sheets reported all counts as (b) (4). In one instance, an operator was monitored (b) (4) on the (b) (4) on the left arm using (b) (4) different contact slides. The colonies on (b) (4) of the (b) (4) slides appeared to share the same size, color, and morphology.

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7. Records for microbial (b)(4) monitoring samples fail to identify the number of colonies counted on the plate and report accurate counts. For example:
- a. (b)(4) sample # (b)(4) from 14 January 2016 on (b)(4). It was reported to have (b)(4) CFU. However, the plate contained microbial growth spread over the entire surface of the (b)(4).
 - b. (b)(4) sample # (b)(4) from 14 January 2016 on (b)(4). The microbiologist did not record the number of colonies identified, only a final result of (b)(4) CFU that included a calculation dividing the number of colonies by (b)(4) due to the sample size. The plate showed the growth of (b)(4) CFU.

OBSERVATION 2

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

1. The following investigations identified operator behavior as the likely root cause of contaminated vials during media fills:
 - a. Media fill (b)(4) on (b)(4) line with 31 turbid units. The investigation identified inappropriate behavior by an operator that brought non-sterile tape into the RABS.
 - b. Media fill (b)(4) on the ampoule line (b)(4) with 17 turbid units. The investigation identified aseptic behavior was not followed during changing of the filling tank.
 - c. Media fill (b)(4) on SVP line (b)(4) with 1 turbid unit. The investigation identified inappropriate aseptic behavior during set-up and filling.
 - d. Media fill (b)(4) on (b)(4) line (b)(4) with 1 turbid unit. The investigation identified the operators failed to follow cleaning procedures as a root cause.

In each case these root causes were identified with the aid of video recordings from the facility surveillance system. The investigations failed to evaluate and document review of video recordings from previously manufactured commercial batches to determine if similar operator behavior existed. They also failed to evaluate videos of subsequent commercial batches to verify that deficiencies in operator behavior had been corrected.
2. Investigation into a sterility test failure for the drug product (b)(4) (batch # (b)(4)) did not extend to include potential issues during manufacturing. The sterility test was not invalidated following laboratory investigation, and the batch was rejected. However, no root cause was identified in the investigation, and no official investigation was performed to evaluate potential manufacturing root causes. Rather, a manufacturing 'overview' was performed, and the corrective actions taken included designing (b)(4) racks to hold sample bags during material transfer and sterility testing, and updating the sterility testing sample preparation SOP to require operators document the (b)(4) sample quantity.

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3. Complaint investigation 204883 has not been performed in a timely manner consistent with established investigation timeframes. The complaint was received 11 October 2015 for a report of abnormally colored (b) (4) vials in lot (b) (4). Retain samples were examined 19 October 2015 and found to confirm the appearance of vials with (b) (4) product. These vials with (b) (4) product were analytically tested on 04 November 2014 and found to contain OOS levels of impurities and OOS results for the color test of this distributed batch.

The original due date of (b) (4) for the investigation was extended until (b) (4) without thoroughly describing the justification for the extension. The investigation was not completed by this date and no further extension was requested until after the record was requested during the inspection on 28 January 2016. At the time of the inspection no root causes had been identified and no thorough evaluation of other lots of (b) (4) or other products that could be impacted had been performed.

Previous complaints for (b) (4) had been received, including 136121 dated 06 April 2015. The investigation for 136121 failed to include a thorough investigation of potential root causes for (b) (4) vials.

4. Breaches in alert limit levels for WFI do not include thorough investigation into microbial isolates, such as strain identification. For example, action levels were exceeded on 17 November 2014 and 24 November 2015, with (b) (4) CFU/100 ml and (b) (4) CFU/100 ml, respectively, from a tool washing station; the organisms were identified as *Pseudomonas fluorescens* and *Ralstonia pickettii*. Although the previous (b) (4) of (b) (4) sampling time points (September 2014 - November 2014) were at, or above, the alert limit ((b) (4) CFU/100 ml), none of the isolates were identified. As such, it is unclear whether the same gram-negative bacterial contamination was present. Water from this WFI point in the SVP (small volume parenteral) plant is used to wash stopper bowls, cap bowls, (b) (4) for stoppers and caps, filling (b) (4) cleaning brushes, scissors, pistons, manifolds, connectors, forceps, and glassware. The investigation into the action limit breach did not include the impact of washing these materials with water potentially contaminated with gram-negative bacteria, or increased endotoxin levels.

OBSERVATION 3

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

1. Integral units are rejected during media fills without adequate justification.
 - a. During media fill batch (b) (4) on the (b) (4) line, there were a total of (b) (4) vials processed. The machine data report identified 10 vials rejected for vial tare weight out of range, 325 vials rejected for net weight out of range, 3830 rejected for vials without (b) (4), and 57 good vials rejected. This is a total of 4222 (b) (4)% of the filled vials. These rejected vials included (b) (4) units that were filled with media and were integral.
 - b. During media fill batch (b) (4) on the (b) (4) line, there were a total of (b) (4) vials processed. The

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machine data report identified 145 vials rejected for vial tare weight out of range, 291 vials rejected for net weight out of range, 1799 rejected for vials without (b) (4), and 39 good vials rejected. This is a total of 2274 (b) (4) % of the filled vials. These rejected vials included units that were filled with media and were integral.

2. Media fills are invalidated without adequate justification:

- a. During media fill batch (b) (4) on the SVP line, the media fill was aborted due to a mechanical failure of the conveyor between the (b) (4) and the filling machine. At the time of the mechanical failure 3696 integral vials had been filled. These vials were not incubated and the media fill was invalidated. During routine production the portion filled prior to a mechanical failure would be released as a sub lot.
- b. During media fill batch (b) (4) on the LVP line, the media fill was aborted due to a leak at the (b) (4) connection of the (b) (4) line. The investigation stated "The dripping was not intensive, it was weak and slow" and it was unknown when the leak had started. At the time the leak was identified there had been 158 boxes each containing 30 media filled units that were already filled. None of these units were incubated and the media fill was invalidated without further evaluating the impact of this leak.

- 3. Not all personnel with access to the cleanrooms participate in media fills. For example, a plant engineer, compounding operator, production expert, and monitoring technicians have access to the (b) (4) cleanroom. However, these individuals did not participate in any of the 2015 media fills.
- 4. Smoke studies for the (b) (4) filling line fail to include evaluation of defined interventions. For example, fixing and setting of (b) (4), fixing of the (b) (4), and cleaning of the (b) (4) are not included in the smoke study evaluations.
- 5. Smoke studies for the (b) (4) filling line do not represent the activity of making sterile connections when the maximum size filling tank is present.
- 6. Validated loading patterns for the (b) (4) are not utilized. Operators were observed to add cleanroom goggles, (b) (4) containers, or other additional items to validated loads that did not include these items. The validated pattern of items included in the load "Eszkoz 3" was not followed for loads used in preparation of materials for (b) (4) and (b) (4). During November of 2015 there were (b) (4) loads identified to contain goggles. In 16 of the (b) (4) loads, the goggles were added to a load that had not been validated to include goggles.

OBSERVATION 4

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

- 1. Restricted Access Barrier System (RABS) (b) (4) are used to perform interventions inside of the aseptic filling areas.

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The (b) (4) were observed to pass over exposed product contact surfaces and sterile components during manufacturing.

- a. RABS (b) (4) are only replaced after they have failed a visual or automated integrity test. For example, a review of the RABS (b) (4) integrity log book for the RABS in (b) (4) covering the previous (b) (4) integrity testing results from 17 September 2015 to 18 January 2016, revealed that at least two and up to eight (b) (4) failed integrity testing during each testing time point. No investigations or deviations were initiated following the detection of (b) (4) failures to determine the potential impact on batches produced during the period prior to (b) (4) integrity failure detection. For example, the following sterile drug batches were manufactured immediately prior to the failing RABS (b) (4) integrity tests:

Product:	Plant:	Batch:	Production Date:
(b) (4) Injection, (b) (4) mg/ml	LVP	(b) (4)	03/26/2015
(b) (4) Injection, (b) (4) U	(b) (4)		09/16/2014
(b) (4) Injection (b) (4) mg/ml	(b) (4)		11/24/2014

- b. On 18 January 2016, integrity testing of RABS (b) (4) was performed without (b) (4) the (b) (4) portions of several (b) (4). An operator failed to (b) (4) several RABS (b) (4) during (b) (4) wherein the (b) (4) portion of 5 different (b) (4) did not (b) (4), and did not appear to be under (b) (4). These (b) (4) were all reported as passing the integrity test.
- c. On 18 January 2016, the removal and replacement of several tested (b) (4) for the RABS located in the (b) (4) (b) (4) plant was not documented on the (b) (4) integrity testing log book. Although the log book entry identified a single RABS (b) (4) as failing the integrity test (b) (4) #1-2), and identified it as being replaced, the (b) (4) was not actually observed to be replaced during the time specified in the log.
- d. Supervisory review of the RABS (b) (4) integrity log books failed to identify several discrepancies related to (b) (4) integrity test failure and subsequent replacement. For example:
- On 17 December 2015, the (b) (4) numbered 6, 8, and 10 were identified as both passing and failing the integrity test. This log entry was reviewed and approved on the same day.
 - On 17 November 2015, (b) (4) number 12 was identified as both passing and failing the automated integrity test. This log entry was reviewed and approved on the same day.
 - On 08 December 2015, the (b) (4) integrity test result log entry for (b) (4) number 12 contains 2 checks and a single minus symbol. As the result of the test should be either a check (pass) or a minus (fail), the result of the integrity test were unclear. This log entry was reviewed and approved on 09 December 2015.
 - On 20 January 2016, the SVP (small volume parenteral) (b) (4) integrity test result log sheet contained only

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X's in the field to indicate that testing had taken place, but did not contain information about the outcome, and was not signed. As of 26 January 2016, this (b) (4) integrity test log entry was not reviewed by a supervisor.


2. Deficiencies in aseptic behavior were observed:

- a. On 08-09 September 2015, during the set-up and filling of (b) (4) Injection the following behavior was observed:
 - i. An operator passed a pen directly over the stopper bowl to another operator.
 - ii. An operator performed an undocumented intervention after the vial filling machine stopped. The operator briefly sprayed their (b) (4) with (b) (4) and placed it into the RABS (b) (4) to perform the intervention without waiting for the disinfectant to dry. This method of disinfectant application is inconsistent with established procedures.
 - iii. Operators were observed leaning against the cleanroom wall.
 - iv. During the setting of the line, an operator was seen to sit on the floor of the clean room. The gown was not changed.
 - v. During the setting of the line the operator left the RABS (b) (4) open for extended periods of time, even when not working in the immediate area.
- b. On 20 November 2015, during the filling of (b) (4) on the (b) (4) aseptic filling line, an operator performed numerous undocumented interventions. In several instances, prior to placing their (b) (4) into the RABS (b) (4), the operator either failed to wait for the disinfectant (b) (4) to dry, or didn't spray it on their (b) (4) at all. Additionally, after performing the interventions and removing their (b) (4) from the RABS (b) (4), the operator appeared to spray a mist of (b) (4) into the air above the RABS (b) (4), but did not spray the (b) (4) directly with the disinfectant. This method of disinfectant application is inconsistent with established procedures.

OBSERVATION 5

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

1. On 21 January 2016 bioburden monitoring plates under incubation in the 20-25° C incubator were observed with (b) (4) that were peeling off of the (b) (4) and containing (b) (4) that prevented the (b) (4) from being in contact with the (b) (4) surface. Of the (b) (4) product, product contact (b) (4), and product contact (b) (4) samples collected on 15 January 2016, 7 of (b) (4) had (b) (4) that were not in complete contact with the (b) (4) surface.

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Additionally, (b) (4) testing samples collected 14 January 2016 and tested using (b) (4) filtration were inspected on 21 January 2016. Approximately 15 of (b) (4) contained (b) (4) between the (b) (4) and the (b) (4) surface.

2. Techniques for collection of swab sampling of critical surfaces were not performed as described in procedure SOP W000449/3 "Surface Sampling During Microbiological Environmental Monitoring".
 - a. On 21 January 2016 after the filling of lot (b) (4) of (b) (4) on the (b) (4) line, the operator collected swab samples of the (b) (4) and the (b) (4) by only briefly touching the surface with a single stroke. The same operator failed to swab (b) (4) of the RAB (b) (4).
 - b. On 22 January 2016 after the filling of lot (b) (4) of (b) (4) on the SVP line, the operator failed to perform swab samples using (b) (4) strokes and failed to adequately reach contact surfaces when sampling the (b) (4) because the (b) (4) were not moved to allow for the surface to be sampled.
 - c. On 10 September 2015, following the production of (b) (4) Injection on the (b) (4) filling line, in (b) (4) instances, the operator rapidly swabbed their palm, while holding the swab sample container in the same hand being swabbed, but did not include swab sampling of the RABS (b) (4). In another instance, the operator only swabbed (b) (4) of the (b) (4). The (b) (4) were located (b) (4) vial dosing area (2) or (b) (4) the vial capping area (1) inside the RABS.
 - d. On 20 November 2015, following the production of (b) (4) on the (b) (4) filling line, in (b) (4) instances, an operator performed swab sampling of RABS (b) (4) by swabbing the (b) (4).
3. On (b) (4), a plate for personnel finger monitoring that occurred on 13 January 2016, was seen in a waste bin. The plate had been read within the previous hour and had cracked (b) (4). This was not documented by the analyst reading the plate and the plate had not been saved for further investigation.
4. At the end of incubation on (b) (4), the volumetric air monitoring strips that had been utilized for monitoring on 13 January 2016 were observed to have dried and shriveled media. This was not documented in the records and no investigation was initiated. The analyst reading the plates stated this dried appearance has been seen in the past when reading samples. It has not been documented or investigated by the quality unit.
5. Validation of the (b) (4) (b) (4) maximum hold time does not reflect the actual time and temperature for samples obtained during normal operation. The established maximum hold time for (b) (4) samples simulates a (b) (4) period at 2-8°C. However, the actual collected (b) (4) samples are held at room temperature for approximately (b) (4) for processing following receipt in the microbiology laboratory, after which they are refrigerated. Additionally, records are not always made to document refrigeration of (b) (4) samples following collection and holding during times when the microbiology laboratory is not in operation.
6. Reading of microbiology plates was not performed to ensure accuracy of readings:

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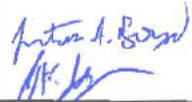

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- a. Analysts do not routinely open the lids of any plates to read samples. (b) (4) samples that had been read on 21 January 2016 contained (b) (4) that prevented the surface of the (b) (4) from being clearly viewed.
- b. Plates were kept in (b) (4) bags during readings. The bags were observed to contain (b) (4) plates and labels that obscured the reading of the entire (b) (4) surface.
- 7. There is a failure to justify allowing (b) (4) CFU on an operator hand (b) (4) performing critical interventions in the Grade A aseptic area without the need for an investigation.
- 8. There is a failure to justify the use of Grade B limits for personnel performing activities with their hands in Grade A areas for monitoring or cleaning when there is exposed product contact surfaces or when transferring materials into the Grade A areas.

OBSERVATION 6

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

- 1. FTIR is used for identity testing of raw materials. Prior to 11 January 2016 no electronic data was saved of the dynamic FTIR records. Access controls for operators permit deletion of FTIR data. The data is now stored on the hard drive of a stand-alone computer with no controls to prevent analysts from deleting data. The software lacks audit trails to document creation, modification, or deletion of files.
- 2. GC is used for (b) (4) testing of raw materials. The GC utilizing ChemStation software stores data on the hard drive of a stand-alone computer with no controls to prevent analysts from deleting data. The software lacks audit trails to document creation, modification, or deletion of files. Access controls were still in the process of being configured at the time of the inspection. Historically, no electronic data review has been required for chromatography systems.
- 3. The raw electronic data files generated during kinetic/chromogenic endotoxin testing are accessible on the computer's local hard drive, and analysts have the ability to select and delete files associated with each test performed. Additionally, the audit trails generated for each instrument have never been reviewed.
- 4. UV is used for assay testing of finished products. The data is stored on the hard drive of a stand-alone computer with no controls to prevent analysts from deleting data. Analysts can run an analysis, see the results, and choose not to save the data.
- 5. The atomic absorption spectrometer is used for analysis of raw materials. The data is stored on the hard drive of a stand-alone computer with no controls to prevent analysts from deleting data. The software lacks audit trails to document creation, modification, or deletion of files.

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	FEI NUMBER 3002875215

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Benjamin G. Boling, Managing Director

FIRM NAME Teva Pharmaceutical Works Private Limited Company	STREET ADDRESS Tancsics Mihaly ut 82
QTY, STATE, ZIP CODE, COUNTRY Godollo 2100, Hungary	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer

6. Data from the (b) (4) analyzer is used for (b) (4) testing. The software uses a shared login password, there are no audit trails, after generating results it is optional for the analyst to save the readings, and electronic data can be deleted off the hard drive of the associated standalone computer.
7. The HPLC Empower software lacks adequate procedures for audit trail reviews. The audit trail review procedure was implemented 11 January 2016 and had not yet been performed at the time of the inspection. Prior to this date, audit trails for already released batches had not been reviewed. The new procedure requires the audit trail review to cover only the project audit trail of (b) (4) randomly chosen product (b) (4).
8. Manual integration of chromatograms is permitted. Until 11 January 2016 there was no requirement to review manual integration electronically or evaluate the original chromatograms to verify the appropriateness of manual integration.
9. Review of the Empower system audit trail identified numerous examples of projects that were deleted. There was no documentation to explain why any of these projects were deleted.

OBSERVATION 7

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

1. There is no effective document control system to track and reconcile the use of GMP documents. QC Analysts, QA Personnel, and Production Personnel are permitted to print forms used to record raw GMP data from blank master copies. There is no control on how many are printed and no way to reconcile what was printed and what is ultimately reported. It was observed that more copies were printed than necessary and the forms were left in general areas for use as needed. Further, it was observed that the printed working copies could be photocopied and used to record GMP data. Examples of uncontrolled forms include, but are not limited to, environmental monitoring forms, (b) (4) testing sheets, Gas Chromatography sample preparation forms, and visual inspection records.
2. On 21 January 2016, numerous uncontrolled filled and unfilled GMP documents were observed as refuse in several closed biological waste containers. These documents included, but were not limited to, a sterility test data sheet, a form used to track the movement of (b) (4) samples, and a media fill incubation card. The sterility test data sheet had been partially filled to track information about a (b) (4) sterility check. After a typographical error was observed on the original data sheet, it was torn up, discarded, and re-written.
3. On the LVP line (b) (4) GMP forms are used for documenting activities in aseptic areas, including settle plate monitoring and (b) (4) checklists. The data on these forms can be erased. The original records are photocopied and then erased to be used again for the next batch.
4. In the (b) (4) line, the batch records are not documented contemporaneously by the personnel performing activities. Personnel outside of the filling room fill out the batch record. Not all activities occurring can be seen and the personnel in the room must tell the personnel filling out the batch record what to record.

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5. Sample information and paper records for environmental monitoring are not made contemporaneously. Environmental monitoring records, to cover active air and settle plates are made outside of the cleanroom, once the operator performing the monitoring exits. This could be (b) (4) after the samples are actually collected. The sample information written directly on to the plates is not written at the time the samples are collected. At the (b) (4) of the (b) (4) the unlabeled samples are removed from the filling line and then documented.

For example, settle plates were recorded to be exposed in the RABS of the (b) (4) line at (b) (4) on 21 January 2016. The plates were exposed unlabeled and came out of the filling line at the end of filling at approximately (b) (4). The operator must remember which sample is which by the order in which they have been stacked. The paper records were made after the operator exits. The operator recorded the first settle plate was (b) (4) at (b) (4), when it actually occurred at (b) (4).

6. The listed sampling time for (b) (4) active air sampling strips collected during lot (b) (4) of (b) (4) was written on a sheet of paper attached to a bag containing the strips, but not to the individual strips. As such, the time of sampling for each strip could not be identified.

Additionally, the volumetric samples utilize varying volumes of air samples. The records fail to identify the volume of the sample that was collected.

OBSERVATION 8

An (b) (4) -Field Alert Report was not submitted within three working days of receipt of information concerning bacteriological contamination in a distributed drug product.

Complaint 129076 was received 05 March 2015 for a report of a non-integral bag of (b) (4) lot (b) (4) due to leaking at the (b) (4). The batch was manufactured in May of 2014. The initial evaluation of whether a field alert was required concluded no field alert would be filed. However, this assessment failed to thoroughly evaluate historical data that showed three batches manufactured November-December of 2013 were rejected related to the same defect as described in investigation 243506. This ultimately required the (b) (4) of the (b) (4) to be replaced in August of 2014, which did not occur until after lot (b) (4) was manufactured in May 2014. The previous investigation had also identified the leak as difficult to detect due to very slow appearance of leaks that are not readily apparent during the 100% offline visual inspection. Investigation into rejected lots (b) (4) and (b) (4) found leaking units when a second 100% inspection was performed that were not detected during the initial 100% visual inspection. Two other batches manufactured in October of 2014 were aborted related to a similar defect as described in investigation 312784.

The complaint sample was received on 19 March 2015 and the investigation confirmed the non-integral unit was due to a bad (b) (4) at the (b) (4) related to the manufacturing process, consistent with previously observed failures. No field alert was filed.

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OBSERVATION 9

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

1. Growth promotion testing for (b) (4) used in media fills and sterility testing does not include gram-negative bacteria. (b) (4) is prepared using (b) (4) for (b) (4), and is purchased as a pre-made (b) (4) for (b) (4). No documented scientific justification was provided to explain the exclusion of gram-negative bacteria in the different (b) (4) batches during growth promotion testing.
2. The 2012 (b) (4) mg/ml solution (b) (4) sterility testing method validation was not found to be reproducible during a re-test performed in (b) (4). During the initial validation and suitability test performed in March of 2012, (b) (4) was observed to grow after approximately 2 days of incubation. Inexplicably, tests attempting to reproduce these results in (b) (4) were not able to demonstrate growth for (b) (4) using the same conditions. No investigation was performed to determine the cause of this discrepancy.
3. Sterility testing of (b) (4) components is not performed with bottles that are large enough or filled with enough media to ensure the components can remain (b) (4) in the media.

OBSERVATION 10

Buildings used in the manufacturing of a drug product are not maintained in a good state of repair.

1. There were apparent openings in the seams between (b) (4) panels of flooring material in the areas below the SVP filling line, inside of the aseptic filling area.
2. Cracks were observed in the (b) (4) floor panels at the junction of the (b) (4) separating the (b) (4) and the SVP aseptic filling area. Additionally, the seams between (b) (4) panels of flooring material were not adequately maintained in the areas below the (b) (4). On 22 January 2016 and 26 January 2016 standing water was observed on the floor under and around the (b) (4) due to leaks from the (b) (4).
3. There were apparent white residues and (b) (4) stains on the surfaces above the barrier (b) (4) in the SVP line.
4. On the SVP line a (b) (4) shield for a light was observed with a piece missing. Another light shield was observed to be cracked.

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OBSERVATION 11

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Spore strip D-values are not periodically verified. The D-value for spore strips, used in (b) (4) validation, are accepted based on the manufacturer's Certificate of Analysis, however this value has not been validated.

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