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	3/27/2018-4/3/2018*
	FEI NUMBER 3008386908

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Simon W. Buensch, Site Leader

FIRM NAME	STREET ADDRESS
Hospira Healthcare India Pvt. Ltd.	B11 - B18 B21 - B23 B - 31 - 33 Plots B3 - B6
CITY, STATE, ZIP CODE, COUNTRY Sriperumbudur, Tamil Nadu, 602105 India	TYPE ESTABLISHMENT INSPECTED 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:

QUALITY SYSTEM

OBSERVATION 1

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

Specifically,

Your Quality Unit failed to ensure that all production and laboratory control operations are cGMP adopted. All the deficiencies found during current FDA inspection are indicative that your Quality Unit has not taken the necessary steps to fully ensure the adequacy of the analytical method validation/transfer, the accuracy of the analytical test results and that each event reported during manufacturing or testing are appropriately investigated. Moreover, many of the objectionable conditions noted below document that personnel may not have the necessary understanding about the importance of ensuring the integrity of the cGMP data.

This is a recurrent observation for this site from previous FDA inspection conducted on 07/01/2016.

LABORATORY SYSTEM

OBSERVATION 2

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Jose E Melendez, Investigator - Dedicated Drug Cadre Ademola O Daramola, Generic Drug User Fee Amendments (GDUFA) Drug Specialist	X Ademola O Daramola Generic Drug User Fee Amendments (GDUFA) Drug Specialist Signed By: Ademola O. Daramola -S Date Signed: 04-03-2018 23:51:37	4/3/2018

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

Specifically,

A. Microbiology laboratory data is unreliable. For example, the following discrepancies were observed between the individual microbial growth counts recorded in your laboratory controlled records and the actual counts observed in your growth media plates, which had been read by your microbiologists and stored in trash bags inside the microbiology laboratory prior to destruction. According to your QC microbiology management (PM), your firm uses two levels of review to ensure that media plates are accurately reconciled:

1. Total Aerobic Microbial Count (TAMC) and Pathogen Testing results for Purified Water USP sample points (b) (4), (b) (4), and (b) (4) for (b) (4) line, (b) (4) line, and (b) (4) product lines reported on March 27, 2018 were manipulated as follows:

Media ID	Incubation Date	Record Date	Reported	Recount/Actual
(b) (4) Purified water (PW) Point (b) (4)	03/21/2018	03/27/2018	01 cfu	**TNTC***
(b) (4) Point	03/21/2018	03/27/2018	05 cfu	**TNTC***
(b) (4) Purified Water Point (b) (4)	03/21/2017	03/27/2018	06 cfu	**TNTC***

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Note: TNTC = Too Numerous to Count

2. Total Aerobic Microbial Count (TAMC) test results for bacterial and fungal limits for personnel monitoring on (b) (4) facility Line (b) (4) reported on March 27,2018 were manipulated as follows:

Media ID (Employee name/reason/location)	Incubation Date	Record Date	Reported	Recount/Actual
(b) (6) /Vendor/Smoke study. Forehead (FH)	3/20/2018	3/27/2018	Nil	**5**
(b) (6) 80083995	3/21/2018	3/27/2018	Nil	**1**
(b) (6) 80106598 Forehead (FH)	3/20/2018	3/21/2018	Nil	**6**
(b) (6) 80106598 Forehead (CH)	03/20/2018	3/21/2018	Nil	**1**
(b) (6) 80106598 (b) (4)	03/20/2018	3/21/2018	Nil	**2**
(b) (6) 80106598 (b) (4)	03/20/2018	3/21/2018	Nil	**4**
Unlabeled				**3**
(b) (6) /Vendor/Smoke Study RHFT	03/20/2018	3/27/2018	Nil	**4**
(b) (6) /vendor LHFT (b) (4) (b) (4)	03/20/2018	3/27/2018	Nil	**Growth observed. Unable to determine total number of cfu**

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Sriperumbudur, Tamil Nadu, 602105 India	Drug Manufacturer

				due to partially destroyed plate
(b) (6) (b) (4) 80106598	03/20/2018	03/27/2018	Nil	**10**
(b) (6) /Vendor LHFT	03/20/2018	03/27/2018	Nil	**Growth observed. Unable to determine total number of cfu due to partially destroyed plate**

Note: TNTC = Too Numerous to Count

OBSERVATION 3

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

Specifically,

A. Your firm's Quality control (QC) Chemistry Analysts manipulated test sample weights to obtain passing result for (b) (4) tests for several batches of (b) (4) Injection USP raw materials and finished Product.

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	Jose E Melendez, Investigator - Dedicated Drug Cadre Ademola O Daramola, Generic Drug User Fee Amendments (GDUFA) Drug Specialist	X Ademola O Daramola Generic Drug User Fee Amendments (GDUFA) Drug Specialist Signed By: Ademola O. Daramola -S Date Signed: 04-03-2018 23:51:37	4/3/2018

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For example, five (5) batches of (b) (4) API and one (1) batch of (b) (4) Injection USP that were tested by your analysts, and released with purported passing results of (b) (4) were retested during this inspection, under the monitoring of your firm's Management and Subject matter experts on 3/27/2018. All six (6) batches failed to meet the specification. Results from further investigation conducted by the site during this inspection and extended to several batches that were tested and released from January 2017 to March 2018 indicated that the historical data does not have the expected level of variability between sample weights and their associated (b) (4) percentages between (b) (4) samples ((b) (4)) tested from the same individual batches. Results are tabulated as follows:

Product and Batch Number	Initial Test Date	% result (b) (4)	Status	Retest during Inspection	% result (b) (4)	Status
(b) (4) (b) (4) Batch #(b) (4)	02/16/2018	(b) (4)	PASSED	03/28/2018	(b) (4)	FAILED
(b) (4) Batch #(b) (4)	02/16/2018		PASSED	03/28/2018		FAILED
(b) (4) Batch #(b) (4)	02/16/2018		PASSED	03/28/2018		FAILED

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X Ademola O Daramola
Generic Drug User Fee Amendments (GDUFA) Drug Specialist
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(b) (4) Batch #(b) (4)	03/20/2018	(b) (4)	PASSED	03/28/2018	(b) (4) FAILED
(b) (4) Batch #(b) (4)	03/20/2018		PASSED	03/28/2018	FAILED
(b) (4) Finished Product Batch #(b) (4)	05/25/2017		PASSED	03/28/2018	FAILED

(b) (4) FP Batch #(b) (4) was again retested on the instructions of the firm's management on 3/31/2017 and the retest result confirmed the failed status of the batch.

OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

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A. Failure to complete laboratory and customer complaint investigations thoroughly and within a reasonable period to prevent the distribution of products not meeting required safety and effectiveness.

For example,

1. Your firm opened an investigation PR #231167 on 11/23/2017 to find the root cause of OOS failures in unknown impurities of several (b) (4) Injection USP batches. Your investigation PR ID#231167 showed the root cause was because the existing HPLC analytical Method was not stability indicating due to the method's inability to accurately separate the known and unknown impurities.

   An alternate UPLC method (Method No. MCD-06473) was validated by your analytical development group in 2015 and used to analyze and release (b) (4) batches of (b) (4) finished products. At the time that the UPLC method was used for analysis of the batches, the UPLC method had not been submitted or filed with the FDA for approval. Further investigation (PR ID #231167) revealed that during the comparative analysis of the existing HPLC gradient (HPLC method MCD-06473) and new UPLC Method (UPLC MCD-06473), you failed to include a critical Impurity (b) (4) correction factor in your initial calculation. Recalculation of all (b) (4) batches of (b) (4) when including the Impurity (b) (4) correction factor led to high out of release specification (OOS) results for twelve (12) of the (b) (4) batches. Your firm filed an initial (b) (4) Field Alert Report (FAR #090940) on November 29, 2017 in respect of the twelve (12) OOS batches of (b) (4) Injection with a remark that investigations were ongoing and a CAPA will be determined upon completion of investigation. The investigation was generated on 11/23/2017, and since that time, no market action was taken against the 12 distributed OOS batches of (b) (4) Injection.

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On March 27, 2018, your DGM R&D Quality Pharma stated that the investigation is still open and no decision has been made over the12 distributed OOS batches. As of today, (approximately 5 months after this issue was discovered), seven (7) of the twelve (12) batches had expired in the market. The twelve affected batches are as follows:

S.No	Product and Batch Number	Expiration Date
1	(b) (4) (b) (4) injection batch	**11/2017**
2	(b) (4) (b) (4) injection batch	**12/2017**
3	(b) (4) (b) (4) injection batch	**12/2017**
4	(b) (4) (b) (4) injection batch	**12/2017**
5	(b) (4) (b) (4) injection batch	**12/2017**
6	(b) (4) (b) (4) injection batch	**12/2017**
7	(b) (4) (b) (4) injection batch	**01/2018**
8	(b) (4) (b) (4) injection batch	**11/2018**
9	(b) (4) (b) (4) injection batch	**11/2018**
10	(b) (4) (b) (4) injection batch	**11/2018**
11	(b) (4) injection batch	**11/2018**

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12	(b) (4) injection batch	**01/2019**

2. On 3/28/2017, your firm received one (1) customer complaint (PR #1793803) related to presence of particulates in (b) (4) Injection (b) (4) g finished product; Lot (b) (4). The investigation was initiated to evaluate the case same day.

   Your QC/AD department evaluated the reserve samples and did not confirm the customer's complaint. Between March 2015 and March 2017, your firm had received 49 additional complaints for (b) (4) Injection (b) (4) g reporting similar condition. Per Investigation PR #1793803, previous similar complaints (49) revealed the particles are pieces of (b) (4) (coring) that could be due to handling of (b) (4) stopper by the patient. (b) (4) vials of reserve samples were visually inspected with respect to the nature of complaint and all the vials were found to be intact with no particles observed.

   Complaint sample – one (b) (4) vial was received at the site on 04/19/2017 for evaluation. The photographs of complaint sample received from customers showed that the vial contained a (b) (4) particle in (b) (4) solution and a wider pierce mark on the (b) (4) stopper of the vial.

   The investigation and follow up activities were found inadequate because:

a. Per your investigation, the probable root cause for 'black particle' observed by the customer is a piece of (b) (4) stopper which might have been introduced into the vial due to handling of stoppers during (b) (4). Your firm could not rule out other causes with scientific justification because the retain samples that were evaluated during the investigation were not (b) (4). To confirm this statement, I interviewed Mr. (b) (6), QA.

PR #1793803 investigation concluded the reported particulate after (b) (4) could be a piece of (b) (4) stopper, which would have resulted due to coring, yet no attempt was made to (b) (4) the reserve samples used in the confirmatory testing prior to being evaluated. This is critical because the complaint sample was presented in the (b) (4) form. There is no assurance the (b) (4) product would have shown evidence of particulates.

b. The investigation failed to note that your firm's analytical tests for (b) (4) stoppers, including fragmentation, self-sealing, and penetrability tests for the (b) (4) stopper is performed under a reduced testing program. For (b) (4) lot or batch of (b) (4) stoppers received by the firm, (b) (4) batch per (b) (4) is tested under the full testing program including tests for fragmentation, self-sealing, and penetrability. All other lots or batches received (b) (4) are only tested for description, Identification by IR, Dimensions, and Bacterial endotoxins tests. The (b) (4) stoppers on the customer complaint samples were not tested as part of the investigation.

c. The investigation failed to suggest a CAPA to address the issue, although, the presence of particulates in sterile solutions can be life-impacting to patients.

This is a recurrent Observation from previous inspection conducted on 07/01/2016.

OBSERVATION 5

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Specifically,

There is no assurance that investigations conducted by your firm always include a thorough evaluation of the discrepancy and that appropriate scientific analytical methods are employed to find a probable root cause. Corrective and preventive actions proposed by such investigations are not always adequate or appropriate to address identified discrepancies and follow ups are not completed in a timely manner.

A. Investigation PR ID 225709

On 05/20/2015, the firm initiated PR #225709 to investigate potential data manipulation of a weigh balance slip with unreliable date and time printout. The discrepancy was observed on one (1) of two (2) weighing balance print slips printed minutes apart on the same date, but with one showing the accurate date of 12/24/2012 and the other showing questionable date 12/24/2013; that was one (1) year into the future. The discrepancy occurred in the analytical development laboratory during the validation of analytical method specificity experiment for validation of (b) (4) Injection on 12/24/2012. The discrepancy was not discovered until 3 years later during an internal audit. The specificity experiment for validation of (b) (4) Injection was performed on 12/24/2012 in preparation for submission of (b) (4) for FDA approval per protocol HVP-0233-00 using semi micro balance with ID# ADE525. The stress condition test for method specificity was performed to demonstrate effective separation of degradants from (b) (4) Injection.

PR #225709 investigation and follow-up actions were found inadequate in that,

1. The investigation identified analyst documentation error as the root cause for failing to identify the incorrect date printed on the weighing slip. The investigation's root cause was not supported by rigorous critical scientific investigation process such that it failed to consider data manipulation by laboratory analysts as a potential root cause, since the instrument performance was checked prior to use through (b) (4) and (b) (4) performance calibration checks. It also failed to consider the equipment did not have any controls in place that could prevent laboratory

personnel from physically manipulating the date and time printed out by the microbalance.

2. The investigation concluded the incorrect date recorded for the stress study had no impact on the Assay method validation of (b) (4) Injection – Protocol HVP-0233-00 and the overall objective and result of the method validation and the protocol and was thus considered valid. Non-disclosure of a material fact at the time of the (b) (4) submission should be considered impactful.

3. A CAPA for need-based training on procedure PDP-21-018-R03 (Bound laboratory note books and documentation) and QA004-10 (Good documentation Practices) were provided to the analyst on 06/02/2015 and 06/18/2015 respectively; three (3) years after the event. The corrective action of good documentation training is inadequate to address the potential data manipulation of a critical laboratory data and equipment. Notably, the same microbalance is still in use at the firm.

B. Investigation PR 214989

On 02/23/2015, your Quality Unit initiated PR #214989 to investigate an incident where an analyst in the QC Chemistry laboratory claimed to have conducted identification tests by infra-red (IR) and loss on drying (LOD) for (b) (4) raw material with vendor lot (b) (4) and item code (b) (4) using non-existent samples.

(b) (4) sterile raw material identification by IR analysis and loss on drying for sample container number 5 of (b) (4) and 6 of (b) (4) on 02/20/2015. Both tests were apparently completed and reported the results in the analysis report.[4] During secondary review of the data by the team lead, as part of the entire result data packet the team lead reviewed the pre-sampling inspection copy and sampling of raw materials provided by the receiving warehouse, and detected that pre-delivery representative samples of canister 5 of (b) (4) and canister 6 of (b) (4) for this (b) (4) raw material batch were

not received from the Supplier. He observed the pre-sampling inspection report was marked with "Container No. 05 of (b)(4) and 06 of (b)(4) are not available."

Per Investigation report PR #214989, "Based on the interview report, it was confirmed that analyst '(b)(6)' committed the mistake without crosschecking all the container labeling. Since he wasn't aware of the sampling pre-inspection report ER, he didn't recognize the shortage of sample containers and performed the analysis." The investigation and follow-up actions were found inadequate because:

1. The investigation identified the root cause as due to "analyst error only and not due to any other reason" with correction type as "None Required." The investigation failed to consider data manipulation by the analyst as a potential root cause since he could obtain and record 'valid' test results that were obtained from testing of non-existent samples.

2. The investigation concluded that there was no product impact due to the analyst's action. This conclusion assumed the discrepancy was caused by the analyst's inadvertent error and the analyst had no history of data manipulation. A claim that was not substantiated through thorough investigative process.

3. A Preventive Action was initiated for repeating analysis of the valid samples (b)(4) (b)(4)) by the same analyst in addition to being trained on "precautions to be taken before initiating an analysis." Retesting of the valid samples was assigned to the same analyst as part of the corrective action and the test results were adopted as the valid, final product result.

C. Investigation PR ID 208158

On 01/02/2015, Investigation PR #208158 was initiated to find the root cause of high OOS Impurity (b)(4) and unknown impurity observed during analysis of (b)(4) Raw Material PR # 140595. Retesting

found that initial OOS result was not representative and the root cause was described as "Personal contamination." The investigation and root cause were found inadequate because:

1. The review of test chromatograms of samples and standards and the review of instrument method and processing method revealed the retest results were processed using HPLC integration parameters that allows the Empower software to under-estimate the area counts of the various impurities. The investigation failed to consider the use of two different processing methods as a possible contributing factor to the OOS.

   For example,

Initial test with OOS results on 12/30/2014: Sample Set # (b) (4)

Instrument method – (b) (4) _RMCP_2 0_Inst
Processing Method – Method Id- 2198, Integration; (b) (4)
Processing Method – Method Id-2259, integration; (b) (4)
Standard injection processed with **2198**; Blank and sample injections (PR140595 CP T-1 and T-2) processed with **2259**

Retested with 5 new preparations with passing results on 01/06/2015: Sample set # (b) (4)

Instrument method – (b) (4) _RMCP_2 1_Inst
Processing Method – Method Id- **1150**, Integration; (b) (4).
Processing Method – Method Id-**1372,** integration; (b) (4) ? Yes (Retention time ranges (b) (4) – (b) (4), (b) (4) – (b) (4), (b) (4) – (b) (4))
Standard injection processed with 1150
Blank and sample injections (PR140595 CP T-1 and T-2) proc with **1372**

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Since retest chromatograms of sample were processed with new processing method incorporating (b) (4) (b) (4) integration factor, the area count of Impurity (b) (4), unknown impurities were under- estimated, making all 5 retests to pass within specification.

PRODUCTION SYSTEM

OBSERVATION 6

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

Specifically,

There is no assurance that your firm has adequate in-process controls to prevent critical/major product defects such as product (b) (4) (e.g. (b) (4), (b) (4) and (b) (4) adhered at the bottom of the vial) during the manufacturing process of (b) (4) Injection products.

The events detailed below revealed that your firm lack understanding of what constitutes adequate process controls, including the identification and characterization of critical process parameters necessary to assure final product quality and raise the concern related to the consistency of the (b) (4) Injection manufacturing process.

The established action limit for critical defects in (b) (4) Injection USP drug products is Not More Than (NMT) (b) (4) %.

Specifically,

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- On 08/14/2017, your packing supervisor of (b) (4) Line (b) identified a high percentage of critical defects for (b) (4) Injection USP (b) (4) g, Lot (b) (4). The % of vials showing critical defects was approximately (b) (4) %. The total number of vials showing critical defects were 2,017 vials, out of which 1,839 vials showed product (b) (4) defect.

- On 10/30/2017, your packing supervisor of (b) (4) Line (b) identified approximately (b) (4) % of (b) (4) Injection USP (b) (4) g; Lot (b) (4) vials with critical defects. The total number of vials showing critical defects were 678 vials, out of which 546 vials showed product (b) (4) defect.

- On 11/01/2017, your packing supervisor of (b) (4) Line (b) identified approximately (b) (4) % of (b) (4) Injection USP (b) (4) g; Lot (b) (4) vials with critical defects. The total number of vials showing critical defects were 637 vials, out of which 492 vials showed product (b) (4) defect.

Because of the aforesaid, your firm initiated the Quality Alert Report # 1967773 (QAR). This investigation disclosed that (b) (4) is the most common critical defect in the affected lots. The most probable cause was due to frequent (b) (4) trip during the (b) (4) cycles of the Lots (b) (4), (b) (4) & (b) (4).

QAR #1967773 states that due to power failure or power change, (b) (4) gets tripped leading to delay in reaching set (b) (4) and impact the (b) (4) of (b) (4). Nonetheless, your Quality Unit concluded that there is no impact to process and product quality due to this event.

While QAR #1967773, out-of-specification (OOS) and questionable results were observed in three (3) other lots of (b) (4) Injection USP (b) (4) g. Specifically,

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Simon W. Buensch, Site Leader

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- Lot (b) (4) (Sample prep (b) (4)) showed initial OOS results for Impurity (b) (4) and Total impurities
- Lot (b) (4) (Sample prep (b) (4)) showed questionable results for Impurity (b) (4), Impurity (b) (4), Impurity (b) (4) and Total impurities
- Lot (b) (4) (Sample prep (b) (4)) showed questionable results for Impurity (b) (4), Impurity (b) (4) & Total impurities.

No laboratory cause was identified. The investigation was extended to Global Technical Support (GTS) team.

Technical Study No. HI-364-R-277-17 was initiated. The reserve samples of the impacted Lots (b) (4), (b) (4) & (b) (4), along with other lots manufactured in the same period were visually examined.

- Lot (b) (4) - (2 vials showed the defect of (b) (4) adhered at the bottom of the vial);
- Lot (b) (4) - (5 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (2 vials showed the new defect of (b) (4))
- Lot (b) (4) - (2 vials showed the defect of (b) (4) adhered at the bottom of the vial; 1 vial showed (b) (4) defect & 1 vial showed the new defect of (b) (4))
- Lot (b) (4) - (24 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (7 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (15 vials showed the defect of (b) (4) adhered at the bottom of the vial & 6 vials

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showed the new defect of (b) (4))

- (b) (4) - (9 vials showed the defect of (b) (4) adhered at the bottom of the vial & 1 vial showed (b) (4) defect)

Technical Study No. HI-364-R-277-17, concluded "The probable root cause can be inferred that a defect product i.e. (b) (4) vial or (b) (4) vial with high (b) (4) may have taken up for testing, which was apparently overlooked during the visual inspection practices led to labeling & packaging as observed with some reserve samples mentioned caused reporting with high impurity trends (OOS and questionable results with respective preparation)".

QAR #2055990 was initiated on 11/01/2017 to evaluate each of the manufacturing stages of (b) (4) Injection USP (b) (4) g; Lots (b) (4), (b) (4), (b) (4), (b) (4), (b) (4), (b) (4) & (b) (4). The review of the manufacturing records, including the (b) (4) cycles and the alarm summary reports disclosed the following:

- Lot (b) (4) – (b) (4) cycle completed satisfactory
- Lot (b) (4) – Issue of (b) (4) tripping
- Lot (b) (4) – (b) (4) cycle completed satisfactory
- Lot (b) (4) – (b) (4) cycle completed satisfactory
- Lot (b) (4) – Issue of (b) (4) tripping, (b) (4) alarm
- Lot (b) (4) – (b) (4) cycle completed satisfactory
- Lot (b) (4) – (b) (4) cycle completed satisfactory

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QAR #2055990 investigation concluded the initial OOS and OOT impurities results in Lots (b) (4), (b) (4) & (b) (4), was due to high (b) (4) after (b) (4) resulted into (b) (4) (b) (4) inside the vials. However, no process/procedures deviations were identified throughout the investigation process that might cause such defect. The in-process quality checks were found within batch record specifications.

Your Quality Unit also initiated the QAR #2067512 on 11/13/2017, to investigate the new defect identified as (b) (4) inside the vials that was detected in reserve samples of Lots (b) (4), (b) (4), (b) (4) & (b) (4). But, Lot (b) (4) that also showed vials (2) with the same defect was not part of this evaluation.

(b) (4) % re-inspection was performed for Lots (b) (4), (b) (4), (b) (4) & (b) (4) along with the reserve samples, in which (b) (4) vials were removed and rejected. Satisfactory results were obtained. No additional (b) (4) vials were identified. However, the investigation is silent in relation to Lots (b) (4), (b) (4) & (b) (4) that showed vials with product (b) (4) defect i.e. drug product adhered at the bottom of the vials.

QAR #2067512 disclosed the (b) (4) inside the vials can be caused due to (b) (4) above critical product (b) (4) and as such is not product quality attribute impacting. This defect was categorized as major defect by your Quality Unit. At that time, no assessment of the process was conducted to prevent reoccurrence and mitigate the number of filled vials with such new major defect.

Your firm initiated Technical Study HI-364-R-328-17 to evaluate the quality attributes of (b) (4) Injection USP reserve samples that showed the defect of (b) (4) (b) (4) inside the vials. The drug product lots selected for analyses were: (b) (4). However, the quality attributes of the lots that showed the defect of drug product adhered at the bottom of the vial were not evaluated. In addition, the technical study is silent regarding the rationale used for sampling the test vials and the sample preparations procedure.

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On 12/27/2017, your laboratory (GTS) analyzed the lots for appearance, assay, (b) (4) and related substances. The analytical results obtained are as follow:

- Lot (b) (4) – one (1) (b) (4) vial failed to meet the (b) (4) specification. The result obtained was (b) (4) %. The established limit is NMT (b) (4).
- Lot (b) (4) – Four (4) (b) (4) vials showed OOS or questionable results for related substances (i.e. Impurity (b) (4) and Total impurities).
- Lot (b) (4) – Three (3) (b) (4) vials showed OOS results for assay, (b) (4) and related substances.

Technical Study HI-364-R-328-17 is still in progress since 12/27/2017. No action has been taken against at least four (4) released lots that showed product (b) (4) defect during the reserve sample examination. For example,

- Lot (b) (4) - (b) (4) adhered at the bottom of the vial
- Lot (b) (4) - (b) (4) adhered at the bottom of the vial
- Lot (b) (4) - (b) (4) inside the vial
- Lot (b) (4) - (b) (4) adhered at the bottom of the vial & (b) (4)

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B. Your Quality Unit fails to approve scientifically sound test procedures to prevent potential defects that would alter the quality attributes of your finished products distributed in USA market.

Technical Study No. HI-364-R-277-17 was initiated to investigate the OOS and questionable results obtained during the related substance release testing for (b) (4) Injection USP (b) (4) g; Lots (b) (4), (b) (4) & (b) (4). As part of the investigation, reserve samples of the impacted lots along with other lots manufactured in the same period were visually examined. The visual inspection disclosed product (b) (4) defects in the following reserve sample lots:

- Lot (b) (4) - (2 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (5 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (2 vials showed the new defect of (b) (4))
- Lot (b) (4) - (2 vials showed the defect of (b) (4) adhered at the bottom of the vial; 1 vial showed (b) (4) defect & 1 vial showed the new defect of (b) (4))
- Lot (b) (4) - (24 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (7 vials showed the defect of (b) (4) adhered at the bottom of the vial)
- Lot (b) (4) - (15 vials showed the defect of (b) (4) adhered at the bottom of the vial & 6 vials showed the new defect of (b) (4))
- (b) (4) - (9 vials showed the defect of (b) (4) adhered at the bottom of the vial & 1 vial showed (b) (4) defect)

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Your Study No. HI-364-R-277-17, concluded "The probable root cause can be inferred that a defect product i.e. (b) (4) vial or (b) (4) vial with high (b) (4) may have taken up for testing, which was apparently overlooked during visual inspection practices led to labeling & packaging as observed with some reserve samples mentioned caused reporting with high impurity trends (OOS and questionable results with respective preparation)".

This discrepancy confirms that your in-process controls for visual inspection of filled vials, including the examinations by operators, quality representatives and the in-process sampling plan are not sufficiently robust and reproducible to prevent that vials showing critical/major/minor defects are not released for distribution in USA market.

C. Control procedure SOP-89448 Operation and alarm handling procedure of (b) (4) ((b) (4) Cycle) of (b) (4) facility defines Level I alarm as "An alarming condition, which directly impacts on the safety, identity, strength, purity or quality attributes of the product or CPP of the process and wherein the machine or the system does not perform an action or control to mitigate or avoid the impacting on SISPQ". Nonetheless, your firm does not establish before February 2018 a formal mechanism to perform a comprehensive periodic evaluation of the alarm events that occurred in (b) (4) #LSME 008 & (b) (4) #LSME 971 during production activities for (b) (4) Injection USP drug product distributed in USA market.

OBSERVATION 7

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

Specifically,

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A. There is no assurance that your process simulation studies (media fills) performed in the (b) (4) Lines (b) & (b); (b) (4) Line (b) and (b) (4) Line (b) are truly representative of the conditions observed and/or that might occur during routine aseptic filling operations of vials. This is evidenced in that, although corrective and inherent operator's interventions are simulated during the media fills, the frequency and the duration at which these interventions are simulated are not accurately established.

There is no documented evidence in the commercial batch records about the end time of the interventions (inherent/corrective) and not all the corrective interventions performed during the aseptic filling process are documented in the commercial batch records.

During my review of the data for (b) (4) Line (b) commercial filled batches (b) (4) lots) that were selected to justify the process simulation for (b) (4) mL (b) (4) in 10/2017, I observed the following.

- (b) (4) Injection USP (b) (4) g; Lot (b) (4) – Corrective interventions were performed (b) (4) times; (b) (4) times were identified; (b) (4) time (b) (4) missing
- (b) (4) Injection (b) g; Lot (b) (4) - Corrective interventions were performed (b) (4) times; no identification
- (b) (4) Injection USP (b) (4) g; Lot (b) (4) - Corrective interventions were performed (b) (4) times; (b) (4) time was identified; (b) (4) times (b) (4) missing
- (b) (4) g; Lot (b) (4) - Corrective interventions were performed (b) (4) times; all of them were not identified
- (b) (4) Injection USP (b) (4) g; Lot (b) (4) - Corrective interventions was performed (b) (4) time; no identification

None of these discrepancies related to lack of continuously documenting corrective interventions in the manufacturing batch records were identified by your QA unit during the batch record review process. Similar deficiencies might be observed in (b) (4) Line (b), (b) (4) Line (b) and (b) (4) Line (b) commercial production, since same documentation and review practices are followed.

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B. Your firm lacks a written control procedure that describes in sufficient details the instructions the manufacturing operators must follow when unusual frequency of corrective interventions is observed during routine aseptic filling process.

Control procedure SOP-89368 Monitoring and trending of Interventions during batch manufacturing, Section 4.1.5 defines corrective intervention as "an intervention that is required to correct or adjust an aseptic process during its execution. Interventions observed during the normal production on a much lesser frequency as compared to the routine intervention". The corrective interventions are performed either through open (b) (4), access port or (b) (4).

SOP-89368 categorized "Removal of jammed (b) (4) stopper in the (b) (4) bowl from front side" as a corrective intervention. Section 6.1.3.2 of this procedure states "Performing corrective interventions repeatedly at a frequency more than what occurs in commercial manufacturing poses an unnecessary risk of contamination to the aseptic process".

For the period from May 2017 to September 2017, (b) (4) commercial batches were aseptically filled in (b) (4) Line (b). These batches were retrospective evaluated and trended to identify the determined frequency for simulating the inherent and corrective interventions in the media fill. The aforesaid corrective intervention was only observed in seven (7) batches with a maximum of (b) (4) occurrences in two (2) of the batches. The frequency of this intervention per batch is as follow:

- (b) (4) Injection USP (b) (4) mg; Lot (b) (4) – (b) (4) times
- (b) (4) Injection USP (b) (4) mg; Lot (b) (4) – (b) (4) time
- (b) (4) Injection (b) g; Lot (b) (4) - (b) (4) time
- (b) (4) Injection (b) g; Lot (b) (4) - (b) (4) time
- (b) (4) Injection (b) g; Lot (b) (4) - (b) (4) times
- (b) (4) Injection (b) g; Lot (b) (4) - (b) (4) time

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- (b) (4) Injection USP (b) (4) mg; Lot (b) (4) – (b) (4) time

On 03/30/2018, I witnessed the aseptic filling process of (b) (4) ((b) (4) Injection USP) (b) g; Lot (b) (4). This product was aseptically filled in (b) (4) Line (b). During the time from (b) (4) to (b) (4), I observed the operator working in the aseptic filling area doing the same closed (b) (4) corrective intervention (Removal of jammed (b) (4) stopper in the (b) (4) bowl from front side of the filling line) (b) (4) times. Nonetheless, the filling operation continued as a routine process. No assessment of the stoppering operation was performed at that time to identify the cause that may be responsible for increasing the unusual frequency of such corrective intervention. Subject intervention was performed a total of (b) (4) times during the entire filling process.

This is a recurrent observation for this site from inspections conducted on 03/30/2011; WL 320-13-18 dated 05/28/2013; 02/04/2015 & 07/01/2016.

OBSERVATION 8

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically,

On 03/30/2018, I witnessed the aseptic filling process of (b) (4) ((b) (4) Injection USP) (b) g; Lot (b) (4). This product was filled in (b) (4) Line (b). Around (b) (4), I observed the operator working in the aseptic filling area doing the corrective intervention (Removal of toppled vials from (b) (4) conveyor). Per manufacturing batch records, this corrective intervention must be performed from the front side of the filling line through the (b) (4). However, the operator did the intervention opening the rear side (b) (4) of the filling line. After this discrepancy was brought to the attention of your manufacturing operator, he decided to include a comment in the manufacturing batch records of how the referenced intervention was accurately performed.

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LABORATORY SYSTEM

OBSERVATION 9

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

Specifically,

Your firm lacks stability-indicating methods for the following finished drug products, therefore, there is no assurance of the reliability of the data and the results generated with the use of the following test methods:

A. The method validation performed for (b) (4) Injection USP (b) (4) mg, per Validation Protocol Study Number HI-377-116-16 titled "Revalidation for the Determination of Related Substances in (b) (4) Injection by HPLC" and as specified in Test Method, STP #MCD-064726, titled "(b) (4) Injection USP (b) (4) mg" with approval date 12/11/2017, is inadequate in that:

1. The method precision demonstrated for assay and impurity during method validation was inadequate. The validation used expired samples for demonstration of method precision.
2. The method's stability-indicating properties were not demonstrated during validation. No sample stress testing was performed.

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3. For the accuracy determination, no impurity standard was quantitatively evaluated during method validation. Accuracy was not demonstrated for all known impurities. Spiked impurity was not injected to demonstrate the accuracy and robustness of the method
4. The method does not always separate the Related Compounds, Impurity (b) (4) from the main peak.

B. The method validation performed for (b) (4) Injection assay and impurity by UPLC per Validation Protocol Study Number HI-368-R-086-15 titled "Co-validation for determination of chromatographic purity in (b) (4) sterile and (b) (4) Injection by UPLC" and as specified in Test Method, STP #MCD-064733, titled "(b) (4) Injection USP (b) (4) mg" with approval date 11/08/2017 and DTP #MCD-064734, titled (b) (4) Injection USP (b) (4) g" is inadequate in that,

1. Method precision was not demonstrated for assay and impurity during method validation. The method used expired sample for demonstration of method precision.
2. The method's stability-indicating properties were not demonstrated during validation. No sample stress testing was performed.
3. For the accuracy determination, no impurity standard was quantitatively evaluated during method validation. Spiked impurity samples were not injected to demonstrate the accuracy of the method
4. The method does not always separate the Related Compounds, Impurity (b) (4) from the main peak.

C. Method validation of (b) (4) Injection is inadequate and may be non-stability indicating because:

1. The method does not always separate the Related Compounds, Unknown Impurity from Impurity (b) (4). Several cases of OOS were recorded for Impurity-(b) (4) within the QC laboratory.

2. During assay, an unspecified peak elutes on the shoulder of the main (b) (4) peak in standard which is not fully resolved by the method.

In addition to the aforesaid, the analytical method development unit provided me with a list of problematic QC methods as follows:

S. No	Product	Test Method	Issues
1	(b) (4) Injection	Chromatographic Purity (HPLC/UPLC)	Specificity determination in Isocratic HPLC method; Non-equivalency of UPLC and registered gradient methods
2	(b) (4) Injection	Assay by HPLC	Unspecified peak elutes on the shoulder of (b) (4) peak in standard which leads to failure of analysis
	(b) (4) Injection	Related Substances by HPLC	Unknown impurity and impurity (b) (4) are not separated
3	(b) (4) Injection	Related Substances HPLC	Separation issues with impurity (b) (4) and (b) (4) isomer
4	(b) (4) Injection	Assay by HPLC	Peak tailing not met during system suitability
5	(b) (4) Injection	(b) (4)	Difficulty in meeting

		assay by IC	%RSD during system suitability test
6	(b) (4) Injection	Related Substances by HPLC	Unknown impurity increases due to inadequate system wash

OBSERVATION 10

The calibration of instruments is not done at suitable intervals in accordance with an established written program and with provisions for remedial action in the event accuracy and/or precision limits are not met.

Specifically,

Your Quality Unit failed to perform Performance Qualification (PQ) of a critical equipment.

For example,

Your Microbiology department personnel utilizes an isolate Identification system; (b) (4) with serial number (b) (4), and the (b) (4) software to identify microbes that are isolated from the incubated (b) (4) media plates to the species level.

During my review of this critical equipment, I inquired from Microbiology management, including Director, Aseptic Sterility, whether the equipment's IQ, OQ, and PQ were performed, to which they answered in the affirmative. I then requested to review the records for these tests to verify the qualifications were adequately performed. I found the equipment's performance qualification (PQ) folder was missing. The Director stated the performance verification (PV) was performed in lieu of the

PQ. She also stated that this is the firm's usual practice in accordance with relevant SOPs. She also stated the SOP allows completion of IOQ (Installation and Operational Qualification) in place of PQ.

When I was reviewed the "Facility, Utility and Equipment Qualification procedure (SOP-89640, valid 02/02/2018), Page 11 of 34, under Section 6.3.8, the SOP specifically required IQ, OQ and PQ determinations for critical equipment. The SOP stated that prior to initiation of PQ, IQ/OQ shall be completed including certification of IQ/OQ/IOQ reports (Page 19 of 34, Section 6.6.9. In other words, PQ is a requirement in addition to IQ and OQ per the company's procedure.

OBSERVATION 11

An (b) (4) -Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Specifically,

During the period from 07/07/2017 to 08/21/2017, your Quality Control laboratory initiated PR #1925966, 1960797 & 1972092 to investigate OOS and questionable results observed in three (3) lots of (b) (4) Injection USP (b) (4) g. No laboratory root cause was identified for the referenced events. Therefore, the investigation was extended to Global Technical Support (GTS) team.

Technical Study No. HI-364-R-277-17 was initiated and reserve samples of the impacted lots along with other lots manufactured in the same period were visually examined. The visual inspection disclosed product (b) (4) defects in the following reserve samples released lots: (b) (4), (b) (4) & (b) (4).

Your Study No. HI-364-R-277-17, concluded "The probable root cause can be inferred that a defect product i.e. (b) (4) vial or (b) (4) vial with high (b) (4) may have taken up for testing, which was

apparently overlooked during visual inspection practices led to labeling & packaging as observed with some reserve samples mentioned caused reporting with high impurity trends (OOS and questionable results with respective preparation)".

In addition,

Your firm initiated the Technical Study HI-364-R-328-17 to evaluate the quality attributes of (b) (4) Injection USP reserve samples that showed the new defect of (b) (4) inside the vials. The drug product lots for analyses were: (b) (4), (b) (4) & (b) (4). However, the quality attributes of lots that showed the defect of drug product adhered at the bottom of the vials were not evaluated in this study. The lots were analyzed for appearance, assay, (b) (4) and related substances. The analytical results obtained are as follow:

- Lot (b) (4) – one (1) (b) (4) vial failed to meet the (b) (4) specification. The result obtained was (b) (4) %. The established limit is NMT (b) (4).
- Lot (b) (4) – Four (4) (b) (4) vials showed OOS or questionable results for related substances (i.e. Impurity (b) and Total impurities).
- Lot (b) (4) – Three (3) (b) (4) vials showed OOS results for assay, (b) (4) and related substances.

This discrepancy confirms that your in-process controls for visual inspection of filled vials, including the examinations by operators, quality representatives and the in-process sampling plan are not sufficiently robust and reproducible to prevent that vials of commercial lots (see table) showing product (b) (4) defects are not released for distribution in USA market.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	3/27/2018-4/3/2018*
	FEI NUMBER 3008386908

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Simon W. Buensch, Site Leader

FIRM NAME	STREET ADDRESS
Hospira Healthcare India Pvt. Ltd.	B11 - B18 B21 - B23 B - 31 - 33 Plots B3 - B6
CITY, STATE, ZIP CODE, COUNTRY Sriperumbudur, Tamil Nadu, 602105 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

S. No	Batch No	Manufacture Date	Expiry
1	(b) (4)	May 2017	(b) (4)
2	(b) (4)	May 2017	
3	(b) (4)	June 2017	
4	(b) (4)	August 2017	

***DATES OF INSPECTION**
3/27/2018(Tue), 3/28/2018(Wed), 3/29/2018(Thu), 3/30/2018(Fri), 4/02/2018(Mon), 4/03/2018(Tue)

X Jose E Melendez
Investigator - Dedicated Drug Cadre
Signed By: Jose E. Melendez -S
Date Signed: 04-03-2018 23:53:22

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Jose E Melendez, Investigator - Dedicated Drug Cadre Ademola O Daramola, Generic Drug User Fee Amendments (GDUFA) Drug Specialist X Ademola O Daramola Generic Drug User Fee Amendments (GDUFA) Drug Specialist Signed By: Ademola O. Daramola -S Date Signed: 04-03-2018 23:53:37	4/3/2018