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

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857 | 11/22/2022-12/2/2022* |
| | FEI NUMBER<br>3004011473 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kirti Maheshwari, Chief Operating Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Intas Pharmaceuticals Limited | Plot No. 5 To 14, Pharmez, Near Village Matoda, Sarkhej-Bavla National Highway No. 8-A, Taluka, Sanand |
| CITY, STATE, ZIP CODE, COUNTRY<br>Ahmedabad, Gujarat, 382213 India | TYPE ESTABLISHMENT INSPECTED<br>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. Environmental monitoring samples were not counted accurately. On November 22, 2022, review of plates from QC1 that had been counted by one analyst and checked by a second analyst, found the reported result to be less than the number of colonies on the plate. For example:

   a. Point (b) (4), swab from the (b) (4) stopper chute parenteral line #(b) (Block (b)), associated with aseptically filled batch (b) (4) of (b) (4) Injection (US market) on November 16, 2022. The reported result was "Nil", but the plate was observed to have (b) CFU. This sample was collected from a Grade A area with an action limit of (b) CFU.

   b. Point (b) (4), settle plate in the Grade C area of Manufacturing (b), associated with batch (b) (4) of (b) (4) Injection on November 16, 2022. The reported result was (b) CFU, but the plate was observed to have (b) CFU.

   c. Point (b) (4) Left Hand, personnel monitoring sample from Grade C associated with the manufacturing of aseptically filled batch (b) (4) of (b) (4) Injection on November 16, 2022. The reported result was (b) CFU, but the plate was observed to have (b) CFU.

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d.Point (b) (4), active air sample from washing and assembly Grade C area associated with the manufacturing of batch (b) (4) of (b) (4) Injection on November 16, 2022. The reported result was (b) CFU, but the plate was observed to have (b) CFU.

e.Point (b) (4), settle plate from the Grade C area of Manufacturing (b) (4) on November 16, 2022. The reported result was (b) CFU, but the plate was observed to have (b) CFU.

f.Point (b) (4), settle plate from the material (b) (4) in Grade C associated with the manufacturing of batch (b) (4) of (b) (4) Injection on November 16, 2022. The reported result was (b) (4) CFU, but the plate was observed to have (b) (4) CFU.

g.Point (b) (4), settle plate from change room one, Grade D, associated with batch (b) (4) of (b) (4) Injection on November 16, 2022. The reported result was (b) (4) CFU, but the plate was observed to have (b) (4) CFU.

h.Point (b) (4) swab sample from the Outlet of (b) (4) machine B1063. The reported result was (b) (4) CFU, but the plate was observed to have (b) (4) CFU.

2.Microbiology personnel reported the laboratory practice was to count colonies that merge together, with similar morphology, as one colony. Review of plates showed this practice resulted in under counting of colonies. For example:

a.Plate (b) (4) (Left Hand) from November 16, 2022, associated with batch (b) (4) of (b) (4) Injection, had a reported value of (b) CFU. However, it appeared two separate colonies had merged, meaning there were (b) CFU on the plate. The alert level requiring an

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investigation for this point is ≥(b) CFU.

b. Point (b) (4) swab sample from the Tablet (b) (4) of (b) (4) machine B1063. The reported result was (b) (4) CFU, however it appeared two separate colonies had merged, meaning there were (b) (4) CFU on the plate.

3. Paper printouts are used as the raw data for (b) (4) analysis. The printouts are automatically assigned a sequential sample number when printed. During reconciliation of analysis performed on January 13, 2021, for instrument SC1111, printouts could not be provided for review:

a. Printouts for sample #(b) associated with stability testing of (b) (4) Injection (b) (4) mg.

b. Printouts for sample #(b) associated with stability testing of (b) (4) mg.

4. During review of raw data associated with process validation of (b) (4) mg, lot (b) (4):

a. Printouts for (b) (4) for sample #(b) (4) and #(b) (4) during analysis of (b) (4) could not be provided. These determinations would have been performed after samples from (b) (4) #(b) (4).

b. pH printouts and recording of description associated with the (b) (4) and (b) (4) samples from (b) (4) #(b) (4) could not be provided.

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## OBSERVATION 2

Established test procedures and laboratory control mechanisms are not followed.

There is no procedure describing the use of manually entered integration events, including baseline points, tailing sensitivity, fronting sensitivity, and peak slice for processing chromatography data. The analysts are permitted to manually enter these and other integration events and reprocess the chromatograms. The reviewers only review the final chromatogram and do not review the originally processed chromatogram to ensure the manually entered integration events are justified.

Procedure SE/BQC/00165 "Interpretation of Chromatograms" requires manual integration be documented clearly stating the reason the manual integration was performed and the initials of the section head for approval. But when analysts manually enter integration events to force the software to integrate in a specific way, there is no similar documented justification and approval process. The reviewers approved chromatograms integrated with manually entered integration events that were not consistent with procedure SE/BQC/00165. For example:

1. Stability analysis of (b) (4) Injection (b) (4) mg/ml lot (b) (4) at the 36-month 25°/60%RH condition was originally processed by the software with an area that gave a result of (b) (4) %, compared to a specification of not more than (b) (4) % for the impurity (b) (4) (b) (4). This result would have required an OOT investigation according to the General Manager of QC (PQC1). The analyst manually entered baseline points that forced integration at a retention time of (b) (4) and (b) (4) for the sequence and reprocessed the data. The result for lot (b) (4) changed to (b) (4) %, which was used for reporting and did not result in the initiation of an investigation. This data was then used to support the extension of the shelf life for this product from (b) (4) to (b) (4) according to change control SE/CRF/2021/1086.

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Additionally, the 6-month accelerated time point for the same lot (b) (4) was integrated by manually adding a fronting sensitivity and tailing sensitivity factor to the peak for the impurity (b) (4), but not for the standard of the same impurity. This reduced the area of the impurity peak compared to the standard and gave a result of (b) (4) %, compared to a limit of (b) (4) %. When the fronting and tailing sensitivity factors are removed to ensure integration of the impurity consistent with the standard, the reportable result changes to (b) (4) %, a value that would have required an investigation according to the General Manager of QC (PQC1).

2. During the integration of stability samples for (b) (4) Injection (b) (4) mg in sequence (b) (4), the analyst manually entered integration events and accepted inconsistent integration of peaks during the sequence. This reduced the area of multiple impurity peaks. When the data was reprocessed during the inspection to ensure consistency throughout the sequence and to the established laboratory procedures, the result for the (b) (4) impurity in sample (b) (4) changed from (b) (4) % to (b) (4) % compared to a specification of not more than (b) (4) %. The reported result of (b) (4) % would not be considered OOS, but (b) (4) % would be OOS.

3. During the integration of stability samples for (b) (4) Injection (b) (4) mg in sequence (b) (4), the analyst manually entered integration events and accepted inconsistent integration of peaks during the sequence. When the data was reprocessed during the inspection to ensure consistency throughout the sequence and to the established laboratory procedures, the result for the (b) (4) impurity in (b) (4) changed from (b) (4) % to (b) (4) % compared to a specification of (b) (4) % and the total impurities changed from (b) (4) % to (b) (4) % compared to a specification of not more than (b) (4) %.

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**OBSERVATION 3**

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

Specifically,

There is a cascade of failure in your Quality Unit's lack of oversight on the control and management of GMP documents that are critical in ensuring the drug products manufactured and tested at your site are safe and effective. For example,

1. On 22-Nov-2022, we observed your Quality Control (QC) Laboratory, Production and Engineering department employees destroyed GMP documents pertaining to original records and raw data by tearing it into pieces and disposed inside your QC laboratory and General Parenteral Scrap areas. These areas support the manufacturing and testing activities for the drug products sold in the USA market. Additionally, we found a truck full of transparent plastic bags containing shredded documents and black plastic bags mostly containing documents torn randomly into pieces by hand mixed with other scrap materials. This truck was found about 150 meters away from your facility as it was waiting for the clearance to remove scrap materials from Specialized Economic Zone (SEZ). Upon interviewing the truck driver and verifying shredded and torn pieces of documents, we were told that the plastic bags containing disposed documents belonged to your facility that we were inspecting. Your employees told us the disposed material found in the trash areas and a truck was from 21st and 22nd November 2022.

   Among many torn and shredded documents found inside the truck, we specifically observed torn pieces of analytical weight slips (balance printouts) along with spectrums pertaining to (b) (4) by (b) (4) test. Upon putting together some of the torn pieces of documents with the help of your employees, your Senior Officer and General Manager of QC identified the torn pieces pertaining to (b) (4) Tablets USP (b) (4) mg, Batch Numbers:

(b) (4) (commercialized in the USA market) and (b) (4) Capsules (b) (4) mg, Batch Number: (b) (4). We observed your QC employees deviated from your Good Documentation Practices and Data Integrity procedures by destroying "Original record" and "Raw data". Additionally, we observed your Quality Unit lacked an adequate oversight in ensuring the data pertaining to drug products sold in the USA market is complete and reliable to ensure patient health and safety. The details are as follows:

a. There were no weight specific entries in your Laboratory Information Management System (LIMS) "Instrument Usage Logbook" for the time recoded in any of the balance printouts. Your Associate Executive Vice President of Corporate Quality and Compliance, and Manager of QC stated that *"the weighing activities recorded on the "Instrument Usage Log" is not a true representation of samples weight with start and end time for each weighing activities for a specific lot of a product. Further, there is no consistency among the QC employees in term of recording of information in LIMS logbook pertaining to a total number of lots tested. Some QC employees may enter this information whereas others may not, leaving no traceability for the exact number of lots tested and their start and end time of analysis"*. This issue is applicable to all analytical instruments in your QC Laboratory including but not limited to balances, (b) (4), Auto Titrators, HPLCs, GCs, Dissolutions. For example,

The time stamp on each of the balance printout and (b) (4) spectrum printout did not match with your LIMS "Instrument Usage Log" record for samples weighed and analyze:

**Analytical Balance ID: PC344**

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For (b) (4) Tablets USP (b) (4) mg, Batch Numbers: (b) (4) (b) (4)
"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)
"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)

(b) (4) mg, Batch Number: (b) (4)
"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)

Whereas the weighing time of samples as per the balance printout on 22-Nov-2022 is as follows:
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)

(b) (4) **ID: PC069**

For (b) (4) Tablets USP (b) (4) mg, Batch Numbers: (b) (4)
"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)

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Justin A Boyd, Investigator
Pratik S Upadhyay, Investigator - Dedicated Drug Cadre

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"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)

(b) (4) Capsules (b) (4) mg, Batch Number: (b) (4)
"Used From" date and time: 22-Nov-2022 (b) (4), "Used To" date and time: 22-Nov-2022 (b) (4)

Whereas the testing time of samples as per the balance printout on 22-Nov-2022 is as follows:

Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)
Batch No.: (b) (4), Time: (b) (4)

Both confirmed stating that in the period of about 45 minutes, your Senior Officer of QC weighed-out the same batch sample multiple times and used it for "(b) (4) by (b) (4) (b) (4)" tests. The raw data pertaining to above balance and (b) (4) spectrum printout that has results on it were torn into pieces by hand and disposed inside black color plastic scrap bag. This scrap bag was later found by an Investigator inside a truck that was located outside of your firm.

b. Upon comparing the torn pieces of analytical balance ID: PC344 and (b) (4) ID: PC069, we observed your Senior Officer of QC weighed the same batch of (b) (4) and (b) (4) multiple times in an attempt to hide testing discrepancies. For example,

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I. Torn pieces of (b) (4) spectrum for (b) (4) has sample weight showing xx(b) (4) mg, time (b) (4) with a result of (b) (4) %

II. Torn pieces of (b) (4) spectrum for (b) (4) has sample weight showing xx(b) (4) mg, time (b) (4) with a result of x (b) (4) %

*(x and xx refers to missing pieces of paper)*

III. Three (3) more torn pieces of (b) (4) spectrum found has no has time stamp as (b) (4), (b) (4), and (b) (4). Your Senior Specialist, and GM of QC identified the torn pieces of (b) (4) spectrums pertaining to the (b) (4) test conducted on 22-Nov-2022 using (b) (4) ID: PC069.

The verification of above weight and time stamped on the (b) (4) spectrums did not match with the below balance printouts found along with torn pieces of (b) (4) spectrums in the scrap bag inside the truck. The details of suspicious weights found on the torn balance printouts are as follows:

Balance ID: PC344, weight recorded on this intact balance printout: (b) (4) mg, time: (b) (4)

Balance ID: PC344, weight recorded on this torn balance printout: (b) (4) mg, time: (b) (4)

Balance ID: PC344, weight recorded on this torn balance printout: (b) (4) mg, time: (b) (4)

The justification provided by your Senior Officer was inadequate and as such in deviation of your Good Documentation Practices and Data Integrity procedures.

c. The details pertaining to types of GMP documents (original records and raw data) found destroyed and disposed inside your scrap areas and a truck loaded with scrap materials belonging to your firm is as follows:

**QC Laboratory Scrap area – Block (b) (4) (PQC-01)**

On 22-Nov-2022, we observed torn pieces of GMP documents disposed inside a large black plastic bag that was hid under the staircase. The details are as follows:

I. Torn pieces of Auto Titrator spectrum and results along with analytical balance weight slips (printouts) pertaining to the following analytical balances:

a) Analytical Balance Serial Number: 1123 411120, weighing slip containing Date and Time details was missing (1 weight slip). The torn piece of this balance showed two (2) weights as (b) (4) mg, and (b) (4) mg whereas the third (3rd) weight according to your employee was (b) (4) mg. On 28-Nov-2022, your QC Officer stated that *"on 22-Nov-2022, when he came to know that the Investigators are on the walkthrough inspection of Block (b) QC laboratory and are coming in the direction of balance room, he immediately rushed and tore apart balance printouts along with Auto Titrator spectrums and threw the torn pieces into the small trash container located next to the balance. Later, he threw (b) (4) acid solution inside the same trash in an attempt to destroy the evidence of the tests that he was working on that had issues with high % RSD and*

*weighing of material was not in line with the expectation"*. This trash was removed from the area immediately by your area housekeeper and moved to the QC scrap area. This trash bag was later found hidden under the staircase leading to the (b) (4) floor of your QC laboratory by another Investigator. No justification was provided upon asking by your QC management for hiding the trash bag. Additionally, upon opening this trash bag a very strong smell of chemical spread across the area and documents inside this trash bag were found wet. Your GM of QC stated the strong smell is of (b) (4) Acid (b) (4) and provided a misleading information to an Investigator stating *"QC employee spilled* (b) (4) *on the floor which was cleaned-up using tissue papers. These wet tissues papers were then discarded along with other waste from the area"*. This misleading information delayed interrogation in knowing the exactness of the issue that happened in your PQC-1 laboratory.

On 22-Nov-2022, your Assistant Manager of QC (Reviewer) identified the issues of (b) (4) spectrum and a balance printout destruction by your QC Officer at around 2 pm (Indian Standard Time). He immediately reported the incident to your Senior Manager of QC. However, until our discussion on 28-Nov-2022, your Senior Manager of QC laboratory did not initiate any Investigation and evaluated the impact of your QC Officer's practices on the previous analysis conducted by him and impact to the drug products sold in the USA market.

The details of analysis for which documents were torn and destroyed by your QC Officer is as follows:

Name of test: Standardization of (b) (4) by Potentiometry using Auto Titrator
Limit: Between (b) (4) N/M and (b) (4) N/M

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b)Analytical Balance Serial Number: 1123 421528, Date: 22-Nov-2022, Time: 08.37.14 (1 weight slip). This balance printout contained (b) (4) performance check weight records. Your Senior Officer of QC stated the reason for disposing this balance printout being *"no date and time stamp on the internal cal. Printout"* whereas the same balance printout continuing to the "(b) (4) Performance Check" has a date and time stamp. Your Senior Officer did not report the issue of missing date and time stamp on balance printout to your QC Manager and instead disposed the balance printout. As such upon bring this issue to your Manager of QC, there was no unplanned deviation initiated by your firm to investigate the issue of balance printout not having date and time stamp along with non-compliance of your analytical balances to 21 CFR Part 11 compliance to restrict employees from potentially changing date and time details.

c)Analytical Balance Serial Number: 1123 421533, Date: 22-Nov-2022, Time: 08.44.45 (2 weight slips). Time stamp on one of the two weight slip was missing a piece of paper. The weighing detail was missing a piece of paper. No justification was provided for the destruction of these printouts.

d)Analytical Balance Serial Number: 0042503966, Date: 22-Nov-2022, Time: (b) (4), (b) (4) (about 7 torn pieces of weight slips). The weight information was partly missing on torn printouts. Your Senior Officer of QC identified the weight details on torn pieces of balance printouts and stated the reason for destroying and disposing it was due to *"the printer of analytical balance (Sr. No.:* 0042503966) *was not working so he moved to the adjacent analytical balance for tablets weighing activity and used this weight in the analysis. Later, when the referenced analytical balance became operational and printed six (6) tablets weights, he tore apart balance printout and disposed it inside the scrap"*. Your Senior Officer of QC stated the weighing activity was pertaining to an individual weight of six (6) tablets for Dissolution by

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HPLC test.

II. Torn pieces of Sheet No.: QC/CDS/001(2), Product: (b) (4) Capsules (b) (4) mg. No justification was provided for the destruction of raw test data.

III. Torn piece of document signed under "REVIEWED BY" along with about nine (9) torn pieces that contained handwritten note in blue ink pertaining to raw data. No justification was provided for the destruction of raw test data.

**Trash truck containing GMP documents mixed with general scrap:**

On 22-Nov-2022, we observed hundreds of transparent and black plastic bags containing torn pieces of analytical balance weight slips (printouts) pertaining to the following analytical balances:

I. Balance ID: PC278, Torn printout with missing a piece of paper for date and month was found as 2022, Time: (b) (4), weight on slip: (b) (4) mg.

II. Torn printout with a missing piece of paper for balance ID, weighing activity dated: 22-Nov-2022, Time: (b) (4), weight on slip: (b) (4). (torn piece was missing *".xx unit"* information)

**Room Number – G1025 (Scrap Room 06) – General Parenteral Area**

On 22-Nov-2022, we observed torn pieces of GMP documents pertaining to your firm disposed inside around 14 black plastic bags. The details are as follows:

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| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857 | 11/22/2022-12/2/2022* |
| | FEI NUMBER<br>3004011473 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Kirti Maheshwari, Chief Operating Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Intas Pharmaceuticals Limited | Plot No. 5 To 14, Pharmez, Near Village Matoda, Sarkhej-Bavla National Highway No. 8-A, Taluka, Sanand |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Ahmedabad, Gujarat, 382213 India | Drug Manufacturer |

I. Executed document titled: *"Pre-approved check list for modification of EMS" "Reference CRF No.: SE/CRF/2021/0819"* along with Form 1 "Assessment after Online / Offline Troubleshooting / Modification Activity", Form 2 "Assessment before Modification Activity", Form 3 "User checks after trouble shooting activity" of SOP No.: SE/ENG/00078. These documents were torn randomly into pieces and disposed inside black scrap bag that was found in your scrap room number 06. Upon putting together some of the torn pieces found in the scrap and interviewing your Senior Officer of Engineering department, we were told these documents were pertaining to Environment Monitoring System (EMS) modification and observations made during the evaluation of EMS by Senior Officer of your Engineering department. These documents contained handwritten notes under "Observation" column in blue color ink and signed under "Checked by" and "Verified by" sections. Additionally, the document contained handwritten information in blue ink pen pertaining to "Event/Problem" for (b) (4) (b) (4), filling room, wash area. The information could not be retrieved and verified due to missing pieces of these documents.

There was no unplanned deviation initiated by your firm for losing these documents until 24-Nov-2022. Your firm filed a FAR on 28-Nov-2022 notifying the FDA about these document's destruction among the other issues.

II. Document pertaining to EMS Alarm monitoring: Your firm maintains a *Format* that is used by your Engineering department to "unofficially" record issues pertaining to alarms triggered as a result of changes in Differential Pressure (DP), % RH and Temperature from the set limits along with other issues during drug product manufacturing, equipment cleaning, and maintenance. This unofficially documented information is not contemporaneously entered into the EMS software.

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | | DATE ISSUED |
|---|---|---|---|
| | Jose E Melendez, Investigator - Dedicated Drug Cadre<br>Justin A Boyd, Investigator<br>Pratik S Upadhyay, Investigator - Dedicated Drug Cadre | X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 12-02-2022 04:31:26 | 12/2/2022 |

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Upon putting together some of the torn pieces of "unofficial" documents recovered from the scrap yard, we observed information recorded as *"Surendra [Under discussion] Unofficial cleaning", "Manan – Door stopper not"*, several entries for *"%RH High"* and *"DP low"* pertaining to 20 and 21-Nov-2022. However, the verification of audit trail log for entries between 20 to 21- Nov-2022, did not have any entry for the above comments in your EMS system. Your Senior Officers classified all the alarms as "Non-critical" and largely entered comment as "Cleaning activity".

Your firm's Quality Unit lacked adequate oversight on documents being lost from the system. There was no Unplanned Deviation (UD) initiated for the above two (2) missing documents to investigate the "Root Cause" for missing/lost documents and to take an adequate Corrective Action and Preventative Action (CAPA) to avoid reoccurrence of documents being lost and destroyed by your employees.

Furthermore, your employees from QC, Production, and Engineering departments have deviated from the core principles of Data Integrity and Good Documentation Practices defined under multiple sections of your procedures SE/QAD/00053 – 1, Titled: "Data Integrity", Effective date: 21-Jul-2021 and SE/QAD/00050 – 1, Titled: "Good Documentation Practices", Effective date: 04-Mar-2025. Your firm filed a FAR on 28-Nov-2022 notifying to the FDA about destruction of GMP documents in scrap areas of your firm observed by the FDA Investigators during this inspection of your site.

2. On 22-Nov-2022, we found torn pieces of document from your scrap areas that upon putting together contained handwritten comments on a piece of uncontrolled and unofficial paper by your Production Reviewer. The details are as follows:

(15-Nov-2022)

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | | DATE ISSUED |
|---|---|---|---|
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(b) (4) Dispensing Active 14-Nov-2022
(b) (4) Tablet USP (b) (4) mg
(b) (4) – Closure Logbook

**Date wrong** with the names of your Production Operator and Production Officer.

Your Production Officer that signed this document under "Checked By/Date" section changed number from four (4) to make it look like five (5). Hence changing the date from 14-Nov-2022 to 15-Nov-2022. Your Production Officer has deviated from your procedure SE/QAD/00050 – 1, Titled: "Good Documentation Practices", Effective date: 04-Mar-2025, section 7.38.2 *"Any changes / alteration made to original data or entered data is incorrect, strike out the data using a single line, so that the original word/sentence/value is legible and put correct data above below the incorrect entry with signature and date****".*

3. Your firm has logged five (5) Unplanned Deviations (UDs) for missing/lost documents since 21-Aug-2020. The primary "Root Cause" identified in case of each of the UDs being "Personnel error". There was no CAPA taken for four (4) out of the five (5) UDs. Your firm simply imparted awareness training to your production employees and decided to implement eBMR in a phase wise manner across the site. However, while the implementation of eBMR is currently underway, your employees from QC, Production and Engineering departments have continued to destroy original data, raw data, and meta data. Out of five (5) UDs for missing documents, two (2) events pertain to the products for the USA market. The details are as follows:

   a. (b) (4) Injection ((b) (4) # (b) (4)) (Submission Batch to the FDA with pending approval status). Deviation Number: SE/DF/2021/0080, Date initiated: 06-Sep-2021

b. (b) (4) Tablets USP (b) (4) mg ((b) (4) # (b) (4)) (Commercial batch). Deviation Number: SE/DF/2022/0007, Date initiated: 10-Jan-2022

In both the above cases, your Quality Unit initiated no CAPA.

**OBSERVATION 4**

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

There is no assurance that your process simulation studies (media fills) performed on (b) (4) Block (b) Line (b) (Equipment ID PP 049) and General Parenterals Block (b) Line (b) (Equipment ID SR 1031) are representative of the current commercial manufacturing operations. This is evidenced in that, although corrective and non-corrective operator's interventions are simulated during the media fills, the historical data of the previous commercial filled batches is not evaluated prior to carry out the (b) (4) process simulation activities. Your current practice is to simulate operator's interventions that have been identified in previous media fills without considering those that were carried out during the commercial fill process. Based on that, the duration at which the interventions are also simulated in the process simulations are not accurately established.

In addition, Protocol No. RAPSSP/02-SR0001-03 entitled "Requalification Protocol [Aseptic Process Simulation Study/Media Fill For Vial Filling Line (b) (4)]; approved on 31 May 2022, states that a single non-routine intervention identified as "*maintenance of machine by engineering person*" should be simulated Not Less Than (b) (4) times. However, detailed description about this non-routine intervention is not provided in the media fill batch record (MBR) nor in the commercial batch records. During my review of the data for commercial filled lots, I observed that subject intervention was carried

out in the following distributed drug product batches:

*(b) (4) Injection USP (b) mg/mL; Batch (b) (4); Expiration Date (b) (4); Filling start date 06/21/2021; No USA product.

*(b) (4) Injection USP (b) (4) µm/mL, Batch (b) (4); Expiration Date (b) (4); Filling start date 05/14/2021; No USA product.

* (b) (4) Injection USP (b) mg/mL; Batch (b) (4); Expiration Date (b) (4); Filling start date 04/01/2021; No USA product.

Approximately (b) (4) and (b) (4) commercial lots have been aseptically filled in General Parenterals Line (b) and (b) (4) Line (b), respectively, for the US market.

**OBSERVATION 5**

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

1. Your air flow pattern study conducted on your Mobile Air Flow Unit (i.e., Mobile (b) (4); Equipment ID SR1047); Protocol MQP-SR0005-00; approved on 30 November 2019 and used to ensure unidirectional airflow during the commercial filling process for USA products is inadequate.

   The airflow pattern study video demonstrates how airflow from the mobile unit enters Zone (b) through the (b) (4) during the process of manually transferring sterilized equipment parts/components to the filling line. This process takes (b) (4) to complete. During all this time, the (b) (4) remains open. In addition, the routine operators' intervention "loading of (b) (4) stoppers during filling" is performed by opening the (b) (4)

(b) (4) and (b) (4). The frequency of this intervention during the commercial filling process ranges from (b) (4) to (b) (4) times, depending on the batch size. However, the interior of the (b) (4) unit is not monitored for Non-Viable Particle to ensure it is maintained at IS0-5 (Grade A) classification during routine commercial operations.

2. There is a Mobile Air Flow Unit (i.e., mobile (b) (4); Equipment ID SR1047) that is used to provide IS0-5 (Grade A) quality air during the manual transferring process of sterilized equipment parts/components into the (b) (4) General Parenterals Block (b) Line (b) (Equipment ID SR 1031). This unit is also used during the commercial filling process to store the plastic bags that contain the (b) (4) stoppers. In addition, the routine operators' intervention "loading of (b) (4) stoppers during filling" is an intervention performed through the (b) (4) port by opening the (b) (4) mobile airflow unit (b) (4) and (b) (4). The frequency of this intervention during the commercial filling process ranges from (b) (4) to (b) (4) times, depending on the batch size. However, the interior of this mobile airflow unit is not monitored to ensure it is maintained at IS0-5 (Grade A) classification during routine dynamic operations. Rather, the Non-Viable Particles (NVP) are monitored previous to the filling operation in static conditions. This deficiency also affects the mobile air flow units of (b) (4) Line (b).

3. There is no surface monitoring on the material transfer (b) (4) of the mobile airflow unit (b) (4) (Equipment ID SR1047) and the (b) (4) located in the Zone (b) of General Parenterals Line (b). This location is used to manually transfer sterilized equipment parts/components into the (b) (4) and adding the (b) (4) stoppers to the stopper (b) (4) during the commercial filling process. While reviewing the smoke study videos of General Parenterals Line (b), I observed the operator adding (b) (4) stoppers to the stopper (b) (4). The top portion of the stopper bag was inside the (b) (4) line and touching the top area of the stopper chute. This area is not sanitized after the intervention and is not surface sampled upon completion of commercial filling operation. The frequency of the loading (b) (4) stopper intervention during the commercial filling process ranges

from (b) (4) to (b) (4) times, depending on the batch size.

4. The risk analysis report entitled "Evaluation and Rational for selection of non-viable particle counter location"; approved on 24 August 2017, was found inadequate. The report does not describe the conditions in which the assessment was carried out (i.e., dynamic/static conditions). In addition, there is no documented evidence in the report that describes how the critical operations (e.g., operator's interventions, set-up activities and exposition time of open/partially open containers) were evaluated to consider the current isokinetic probe locations as sampling critical locations.

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**OBSERVATION 6**

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

1. Process validation studies do not include complete data to demonstrate the manufacturing process is in a state of control and there is no establishment of criteria to evaluate intra-batch or inter-batch variability. Failure to establish criteria to evaluate intra-batch and inter-batch variability during process validation is a common approach that has been used for all products distributed to the US market. For example:

   a. During the (b) (4) Injection (b) (4) mg/vial process validation, batch (b) (4) was not evaluated for intra-batch variability. Samples collected from different (b) (4) on the (b) (4) ranged from (b) (4) % to (b) (4) % for the (b) (4) impurity, compared to a limit of (b) (4) %.

   There was no evaluation of inter-batch variability. Process validation data showed the

(b) (4) impurity for batch (b) (4) did not exceed (b) (4) % for any position on the (b) (4), while batch (b) (4) had samples with a maximum result of (b) (4) % and batch (b) (4) had samples with a maximum result of (b) (4) %.

Additionally, the (b) (4) showed intra-batch and inter-batch variability. Compared to a limit of not more than (b) (4) %, the process validation batches had the following (b) (4) results:

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

The (b) (4) Injection (b) (4) mg/vial process validation study was intended to include three batches. Incidents SE/PQC2/IN/2020/0125 for an interrupted sequence in batch (b) (4), SE/PQC2/IN/2020/0113 for retention time shifting in batch (b) (4), and SE/PQC2/IN/2021/0148 for interrupted sequence in batch (b) (4) all occurred during related substances testing and resulted in stopping chromatographic sequences and incomplete data for impurities in each of the three process validation batches, because testing could not be repeated. The incidents did not result in the initiation of any preventive actions to ensure extra samples are collected.

Due to the incomplete data, a fourth process validation batch (b) (4) was initiated to evaluate related substances from different positions within the (b) (4). The batch failed to meet specifications for the (b) (4) impurity. The investigation OOS/PQC2/F/2022/0001 attributed the OOS result to extended API dispensing time. This conclusion was not supported by development data or historical data from other batches. A preventive action was implemented to limit API dispensing time to (b) (4). The implemented time limits were not supported by validation data.

This OOS fourth process validation batch (b) (4) is not referenced or discussed in the approved process validation report. Subsequently, a fifth process validation batch was initiated and this data was used for concluding the process validation was successful on December 8, 2021.

Following the validation, a commercial batch for the US market, (b) (4) was rejected due to an OOS for the (b) (4) impurity. Which was attributed to foaming following API addition and fast addition of (b) (4) during (b) (4).

The variability observed in the process validation data, stability data, and release testing data for the batches that have been distributed to the US market do not provide assurance the random sampling of vials for chemical testing will ensure the reported results are representative of the entire batch.

b. (b) (4) injection (b) (4) mg uses the same product formulation and vial, but a lower fill volume, compared to (b) (4) mg. Similarly, the process validation studies did not evaluate intra-batch or inter-batch variability. The (b) (4) impurity from the different (b) (4) positions sampled in the (b) (4) included batch (b) (4) with a range of (b) (4) %-

(b) (4) %, batch (b) (4) with a range of (b) (4) %-(b) (4) %, and batch (b) (4) with a range of (b) (4) %-(b) (4) %, compared to a limit of (b) (4) %

The (b) (4) showed intra-batch and inter-batch variability. Compared to a limit of not more than (b) (4) %, the process validation batches had the following (b) (4) results:

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

Batch (b) (4) had a range of (b) (4) %-(b) (4) % from vials taken from different (b) (4) positions, with a finished product test result of (b) (4) %.

During the related substances testing at different (b) (4) positions there were incidents that resulted in incomplete data. These included SE/PQC2/IN/2020/0138 in batch (b) (4) for a software license error and SE/PQC2/IN/2021/0145 in batch (b) (4) for shifting retention time. The incidents did not result in the initiation of any preventive actions to ensure extra samples are collected.

c. Process validation for (b) (4) Tablets USP (b) (4) mg used (b) (4) sampling that did not demonstrate if there was intra-batch variability. For example, (b) (4) sampling was used for (b) (4) analysis (b) (4) and at the finished product analysis stage.

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2. Validation studies for (b) (4) Injection (b) (4) mg and (b) (4) mg have not included (b) (4) analysis to ensure complete stoppering and evaluate whether there is any (b) (4) into vials between the stoppering and capping of (b) (4) vials.

## OBSERVATION 7

Results of stability testing are not used in determining.

1. Change control SE/CRF/2021/1086 approved the change of the expiration date for (b) (4) Injection (b) (4) mg/ml ((b) (4) ml) from (b) (4) to (b) (4). Stability data showed the impurity (b) (4) increased during the shelf life and for the three stability batches ((b) (4)) used to support the change, the value for this impurity was (b) (4) %, (b) (4) %, and (b) (4) % (reportable value of (b) (4) %), compared to a specification of not more than (b) (4) %. There was no thorough evaluation of whether all commercial batches, including batches released with a higher initial amount of (b) (4), such as lot (b) (4), would meet this specification until (b) (4).

2. Change control SE/CRF/2021/1086 approved the change of the expiration date for (b) (4) Injection (b) (4) mg/vial from (b) (4) to (b) (4). Stability batch (b) (4) was used to support the change. This batch had a reported value of (b) (4) % for the Sum of (b) (4) Impurities at the 36-month time point, compared to a specification of not more than (b) (4) %. There was no thorough evaluation of whether commercial batches would meet this specification until (b) (4) if they have similar increases in the impurity.

3. Change control SE/CRF/2022/0039 approved the change of the expiration date for (b) (4) mg from (b) (4) to (b) (4). The stability data used to support the change was based on manufacturing at the Intas Matoda site. This data showed the (b) (4) impurity, with a specification of not more than (b) (4) %, incrementally increasing through the 36-month timepoint.

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For example:

Matoda stability batch (b) (4) : initial timepoint, below quantitation limit "BQL", followed by incremental increases until the 36-month timepoint with a result of (b) (4) %.

Matoda stability batch (b) (4) : initial timepoint, below quantitation limit "BQL", followed by incremental increases until the 36-month timepoint with a result of (b) (4) %.

Matoda stability batch (b) (4) initial timepoint, below quantitation limit "BQL", followed by incremental increases until the 36-month timepoint with a result of (b) (4) %.

Batches manufactured at this site have been released to the US market with higher initial reported results for the (b) (4) impurity. For example, (b) (4) ((b) (4) % (b) (4) impurity at release) or (b) (4) ((b) (4) % (b) (4) impurity at release). The change control did not thoroughly evaluate whether these batches with higher initial (b) (4) impurity would have similar increases during the shelf life that could cause them to be out of specification before the labeled expiration date.

## OBSERVATION 8

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

On November 14, 2022, a US market complaint was received for a carton labeled as (b) (4) mg that contained a (b) (4) mg vial, lot (b) (4) . Accord Healthcare, the Intas US subsidiary, received the complaint sample and provided pictures on November 16, 2022, confirming the incorrect carton was used. The carton and vial were received on site on November 21, 2022, further confirming the mix-up.

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Procedure SE/QAD/00125 "Product Recall and Withdrawal", requires action to be taken within (b) (4) for Class II (Major Defects), including "Mix up of product containers". As of November 28, 2022, QA had made no decision regarding a recall and the incident was still under investigation. Additionally, the investigation had not been expanded to review other lots or other products.

Following discussions during the inspection, (b) (4) .

**OBSERVATION 9**

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.

1. The summary of closed laboratory OOS investigations conducted by the firm during the period beginning from January 2020 to November 22, 2022, is as follows:

| Samples | OOS investigations | Valid | Invalid | % Invalid |
|---|---|---|---|---|
| Raw materials/in-process materials/finished products/ | 479 | 215 | 264 | 55 |

Review of the firm's OOS investigation reports found that the original failed results were invalidated without a scientifically sound root cause, and results of passing re-test results were reported as the result of record.

For example,

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a. Laboratory Investigation Number SE/PQC2/F/OOS/2022/0069 for (b) (4) Tablets USP (b) (4) mg pertaining to batch number (b) (4) (Exp. Date September 2024), was initiated on 15 October 2022 to probe the following OOS result generated during Assay test for in-process sample ((b) (4)) at (b) (4) stage. While two (2) other batches for in-process samples of (b) (4) Tablets USP (b) (4) mg (i.e., (b) (4) and (b) (4)) analyzed in the same chromatographic sequence run showed results on the lower side of the specifications.

| *Sr. No.* | *Batch No.* | *% Results* | *Specification Limit* |
|---|---|---|---|
| 1 | (b) (4) | % | (b) (4) % to (b) (4) % of label Claim |
| 2 | | % | |
| 3 | | % | |

The OOS result was confirmed during preliminary investigation and (b) (4) hypothesis testing (i.e., (b) (4) . There is no assignable cause identified for the OOS and low results obtained in the initial analysis. Re-analysis of all three (3) batches from original samples was performed.

| *Sr. No.* | *Batch No.* | *Initial Results* | **Re-test Results** | *Specification Limit* |
|---|---|---|---|---|
| 1 | (b) (4) | % | (b) (4) % | (b) (4) % to (b) (4) % of label Claim |
| 2 | | % | (b) (4) % | |

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EMPLOYEE(S) SIGNATURE
Jose E Melendez, Investigator - Dedicated Drug Cadre
Justin A Boyd, Investigator
Pratik S Upadhyay, Investigator - Dedicated Drug Cadre

X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 12-02-2022 04:31:26

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| | | | | |
|---|---|---|---|---|
| 3 | (b) (4) | (b) (4) % | (b) (4) % | |

The initial OOS result was invalidated based on passing result from single analysis. No manufacturing investigation was carried out. The investigation report states that the initial failure occurred due to "*sample handling weight loss have occurred during sample transfer in volumetric flask at time of sample preparation*". This presumptive root cause is not scientifically proven nor substantiated in the investigation report. (b) (4) Tablets USP (b) (4) mg; batch (b) (4) was released to U.S. market.

b. Laboratory Investigation Number SE/PQC2/F/OOS/2022/0073 for (b) (4) USP ((b) (4)) pertaining to batch numbers (b) (4); Re-test date October 2023, was initiated on 05 November 2022 to probe the following OOS results for any unspecified impurity (at RRT (b) (4)) generated during Related Substances test. There was a total of ten (10) samples analyzed in the same sequence. First two (2) samples were prepared by analyst ((b) (6)), while other remaining batch samples (8) were prepared by analyst ((b) (6)).

| *Raw Material Batch number* | *Any unspecified impurity (at RRT (b) (4))* |
|---|---|
| (b) (4) | BDL |
| (b) (4) | BDL |
| (b) (4) | BDL |
| (b) (4) | BDL |
| (b) (4) | BDL |
| (b) (4) | BDL |

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EMPLOYEE(S) SIGNATURE
Jose E Melendez, Investigator - Dedicated Drug Cadre
Justin A Boyd, Investigator
Pratik S Upadhyay, Investigator - Dedicated Drug Cadre

X Justin A Boyd Investigator Signed By 2000358686 Date Signed 12-02-2022 04 31 26

DATE ISSUED
12/2/2022

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857 | 11/22/2022-12/2/2022* |
| | FEI NUMBER<br>3004011473 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kirti Maheshwari, Chief Operating Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Intas Pharmaceuticals Limited | Plot No. 5 To 14, Pharmez, Near Village Matoda, Sarkhej-Bavla National Highway No. 8-A, Taluka, Sanand |
| CITY, STATE, ZIP CODE, COUNTRY<br>Ahmedabad, Gujarat, 382213 India | TYPE ESTABLISHMENT INSPECTED<br>Drug Manufacturer |

| | | |
|---|---|---|
| (b) (4) | | (b) (4) % |
| (b) (4) | | (b) (4) % |
| (b) (4) | | (b) (4) % |
| (b) (4) | | (b) (4) % |
| ***Limit*** | | ***NMT*** (b) (4) % |

Based on preliminary investigation and discussion with analyst ((b) (6)), no obvious laboratory error was identified. Hypothesis studies were performed using sample of Batch (b) (4) that showed the highest result for any unspecified impurity.

| ***Study Name*** | ***Any unspecified impurity (at RRT*** (b) ) |
|---|---|
| (b) (4) | |
| ***Limit*** | ***NMT*** (b) (4) % |

The results obtained were significantly higher than the original OOS result. Force degradation data of (b) (4) Tablets (b) (4) mg/(b) (4) mg was reviewed and disclosed that any unspecified impurity (at RT (b) (4)) increased in acid degradation study. Analytical method of related substance test by GC is the same for finished product and raw material.

Per Investigation Number SE/PQC2/F/OOS/2022/0073, "Solubility" testing using

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | | DATE ISSUED |
|---|---|---|---|
| | Jose E Melendez, Investigator - Dedicated Drug Cadre<br>Justin A Boyd, Investigator<br>Pratik S Upadhyay, Investigator - Dedicated Drug Cadre | X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 12-02-2022 04:31:26 | 12/2/2022 |

(b) (4) acid (b) (4) was performed for a different raw material when analyst ((b) (6)) was performing the Related Substances test for (b) (4) USP ((b) (4) raw material. Analyst ((b) (6)) mentioned that he used same beaker that was used in solubility testing after rinsing and washing it. Therefore, the initial four (4) OOS results were invalidated based on acid contamination at the time of initial sample preparation. Specifically, the investigation report states, "*some traces of the* (b) (4) *may be there and degradation happen using same beaker for the diluent and same is reflected in analysis of "Related Substances" for* (b) (4) *USP* ((b) (4) *)*". However, the laboratory investigation did not discuss how the remaining four (4) (b) (4) USP ((b) (4)) raw material samples (b) (4) prepared by the same analyst under the same test conditions were not affected by such contamination. (b) (4) USP ((b) (4)); batch numbers (b) (4) are still on hold.

c. Laboratory Investigation Number SE/PQC2/F/OOS/2022/0032 for (b) (4) Tablets USP (b) (4) mg pertaining to batch number (b) (4); Exp. Date March 2024, was initiated on 03 May 2022 to probe the following OOS result generated during Assay test for in-process sample ((b) (4)) at (b) (4) stage.

| ***Batch Number*** | ***% Results*** | ***Limit*** |
|---|---|---|
| (b) (4) | (b) (4) % | (b) (4) % to (b) (4) % of label claim |

The initial OOS result was confirmed during preliminary investigation and (b) (4) hypothesis testing (Phase I) with no identified root cause. Manufacturing investigation was initiated, and no discrepancies were noted during the manufacturing and sampling process. As there is no assignable root cause identified, Phase II investigation was initiated to perform the re-testing on existing available (b) (4) in (b) (4) set by two different analysts.

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| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857 | 11/22/2022-12/2/2022*<br>FEI NUMBER<br>3004011473 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Kirti Maheshwari, Chief Operating Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Intas Pharmaceuticals Limited | Plot No. 5 To 14, Pharmez, Near Village Matoda, Sarkhej-Bavla National Highway No. 8-A, Taluka, Sanand |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Ahmedabad, Gujarat, 382213 India | Drug Manufacturer |

| *Sr. No.* | *Batch No.* | *% Result* | *Mean of (b) samples set* | *Mean of (b) samples set* | *Limit* |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

Results of (b) (4) set by Analyst 1 and Analyst 2 were observed within specification limits. Therefore, the QC laboratory invalidated the initial OOS result and considered as valid the average assay result of the (b) (4) determinations of Phase II investigation. However, the laboratory investigation did not address in the investigation the facts that Analyst 1 obtained lower side assay results; Analyst 2 showed a significant variability among sample preparations and the variability obtained between two analysts of 3.6 %. (b) (4) Tablets USP (b) (4) mg; batch (b) (4) was released to USA market.

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | | DATE ISSUED |
|---|---|---|---|
| | Jose E Melendez, Investigator - Dedicated Drug Cadre<br>Justin A Boyd, Investigator<br>Pratik S Upadhyay, Investigator - Dedicated Drug Cadre | X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 12-02-2022 04:31:26 | 12/2/2022 |

2. The summary of aborted chromatographic sequence of your QC laboratory from January 2020 to November 22, 2022, is as follows:

| Laboratory Incidents | Automatically aborted | Manually aborted |
|---|---|---|
| 719 | 571 | 148 |

These incidents involve multiple sample types such as raw materials, in-process, finished products, validation, stability, and cleaning samples. Based on your assessment, the events are attributed to a combination of factors such as; missing vial, lost communication, software malfunction, communication error, hardware error, and connectivity lost between software and analytical instrument. Although each of the aforesaid incidents are investigated by your Quality Unit, systematic corrective actions have not been implemented to effectively decrease the frequency of such atypical laboratory events.

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**OBSERVATION 10**

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. Assessments to evaluate data integrity controls were conducted for 183 manufacturing equipment and systems as part of PQ160193. The assessment report approved March 5, 2018, found there were 149 equipment that required upgraded individual access controls and privileges; 76 that required restrictions for changing the clocks; 113 that needed upgrading for saving electronic data; and 119 that needed upgrading for audit trails. There was no documentation in the quality system to ensure proper controls were implemented through upgrading of the software or

implementing interim controls as a result of this assessment. For example,

a. The (b) (4) Compression Machine (PS045) captures electronic data including changes to the machine settings, alarms, and in-process monitoring data. This data is not saved electronically or printed. The failure to maintain this data was identified in the 2018 assessment, but no action has been taken.

   Additionally, the operators were observed to have the ability to turn on and off the automatic weight control and change its parameters, without any verification of the electronic data to ensure unauthorized changes are not made.

b. The (b) (4) Machine (PS015) allows the operator to make changes to operation settings. The machine is not configured to allow saving or printing of the operating parameters or alarms. The 2018 assessment identified the audit trail was available in an excel format that was not saved, but no corrective actions have been taken to ensure it is maintained or part of the batch record review.

2. No similar assessment for data integrity controls has been conducted for laboratory equipment. The titrator instruments are standalone systems used for (b) (4) and assay testing. The instruments have the ability to electronically store results data, but this function is not utilized. Rather, the process relies on the paper printouts without having any second check that can ensure all print outs are maintained and reported. On November 22, 2022, original (b) (4) (b) (4) printouts were founded discarded in a scrap area.

3. Electronic batch records are not configured to ensure contemporaneous recording of data.

a. Electronic batch records are used to document production activities. Personnel can make changes to data entries without triggering an event in the audit trail until they manually click the save button. An operator was observed to make entries into multiple boxes for in-process check during (b) (4) Tablet (b) (4) mg USP (b) (4) prior to manually saving.

Routine review and approval of production data by a second person would not be able to determine if the data was original or had been changed prior to the operator manually saving the entries.

b. The operators can adjust the date and time when creating entries for in-process checks. For example, in (b) (4) an operator was observed removing the value for seconds from the entries. Additionally, the audit trail showed an entry that an in-process check documented on November 23, at 4:46 was entered into the batch record at 5:52. QA does not review the audit trails as part of the batch record review.

**OBSERVATION 11**

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

Your firm has not performed analytical method validation of inhouse tests methods and verification of compendial test methods for the approved and pending drug applications. The number of raw materials pending for validation and verification is tabulated below:

| US Market Drug Products StatusRaw Materials Pending for Validation of Inhouse Analytical MethodRaw Materials Pending for | | |
|---|---|---|

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857 | 11/22/2022-12/2/2022* |
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| CITY, STATE, ZIP CODE, COUNTRY<br>Ahmedabad, Gujarat, 382213 India | TYPE ESTABLISHMENT INSPECTED<br>Drug Manufacturer |

| Verification of Compendial Analytical Method | | |
|---|---|---|
| Approved | 34 | 46 |
| Un-Approved/Pending Approval | 14 | 34 |

The analytical test methods include but are not limited to Residual Solvent by GC, Related substances by GC, Assay by GC, Assay by HPLC, Related Substances by HPLC, etc.

***DATES OF INSPECTION**

11/22/2022(Tue), 11/23/2022(Wed), 11/24/2022(Thu), 11/25/2022(Fri), 11/28/2022(Mon), 11/29/2022(Tue), 11/30/2022(Wed), 12/01/2022(Thu), 12/02/2022(Fri)

X Pratik S Upadhyay
Investigator - Dedicated Drug Cadre
Signed By: Pratik S. Upadhyay -S
Date Signed: 12-02-2022 04:32:05

X Jose E Melendez
Investigator - Dedicated Drug Cadre
Signed By: Jose E. Melendez -S
Date Signed: 12-02-2022 04:32:51

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EMPLOYEE(S) SIGNATURE

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12/2/2022