DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	06/05/2023-06/13/2023
	FEI NUMBER 3002807297

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Arun Chandra Karmakar, Vice President Operation-API and Site Head

FIRM NAME	STREET ADDRESS
Ipca Laboratories Ltd.	P.O. No. 33 Village Sejavata
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Ratlam, 457 002 Madhya Pradesh, India	API 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

Investigations are inadequate to determine the root cause for the failure of a batch of intermediate or API to meet specifications whether or not the batch has been already distributed.

OOS results

A. On 11/16/2022, the lab recorded OOS result RTM/OOS/A/021/2020 for (b) (4) USP API for assay test by HPLC method. The OOS result was reported for two batches out of the three batches analyzed in the same sequence list, including: Batch No. (b) (4) (assay (b) (4) %), Batch No. (b) (4) (assay (b) (4) %), and Batch No. (b) (4) %) against the Specification (b) (4) % - (b) (4) %. In the Phase I investigation it was determined that air bubbles in the (b) (4) was the root cause. This root cause was proved through hypothesis test that used only one of the failing batches, Batch No. (b) (4) Then both the OOS batches were retested and based on the passing assay data, invalidated the initial OOS results. The root cause is not fully supported by the hypothesis test such that the hypothesis test did not include both the failing batches. In addition, the (b) (4) graph is flat, and the %RSD for the initial (b) (4) and for the (b) (4) standard is (b) (4) % that does not support the root cause.

The third-party quality system audit consultant flagged this OOS result investigation (Escalation

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161). The firm submitted the remediation plan but does not have feedback from the quality consultant to verify whether or not the remediation was adequate.

B. On 11/27/2019, the lab recorded OOS result RTM/OOS/A/144/2019 for (b) (4) API for solubility test in (b) (4) The OOS result was reported for two batches: Batch No's. (b) (4) The Phase I investigation did not reveal any assignable root cause and the study proceeded to Phase II investigation. The report stated that no assignable cause was identified in Phase II manufacturing investigation, but no information is available in the investigation report. The investigation continued to Phase II laboratory investigation and determined lower temperature of (b) (4) (< (b) (4) C) as the root cause for hazy solution and undissolved particles settled on the bottom of the test tube. New samples were prepared and retested and based on the passing results, invalidated the initial OOS results.

The root cause is not supported by the hypothesis test. The solvent is stored at room temperature or at (b) (4) C and the laboratory is maintained at NMT (b) (4) C. The third-party quality system audit flagged this OOS result investigation (Escalation 191). The firm submitted the remediation plan but does not have feedback from the quality consultant to verify whether or not the remediation was adequate.

Deviation

C. On June 5, 2021, your firm recorded a Deviation # 202016 for damage (b) (4) Machine IV/(b) (4) 01A during the (b) (4) of (b) (4) API Batch No. (b) (4) You implicated a (b) (4) bolt for damaging the (b) (4) The investigation found that the bolt was dislodged from the (b) (4) IV (b) (4) 10A. The investigation confirmed that a nut was missing, and it was assumed that the nut was drained out with water during partial cleaning of the (b) (4) The investigation does not include picture of the (b) (4) to verify all the parts involved in assembling the (b) (4) and to verify that all the parts were accounted.

D. On February 20, 2020, your firm recorded a Deviation # 158513 for damage (b) (4) Machine L(b) (4)01 during the (b) (4) of (b) (4) API Batch No. (b) (4) You implicated a (b) (4) screw for damaging the (b) (4) The investigation found a missing screw from the SOP display board near the (b) (4) L(b) (4)06. It was assumed that the missing screw of the display board fell inside the (b) (4) material during unloading from (b) (4) L(b) (4)06. No photograph was included of the SOP display board and the surroundings to assess the likely hood of falling the screw in the (b) (4) materials during unloading process.

Market complaint

E. On April 6, 2023, your firm recorded a Market Complaint # 275769 for foreign substance including metal like particles & magnetic particles in API power inside the inner bag of (b) (4) Batch No. (b) (4) non-USA market). Your investigation did not find any assignable root cause. You used (b) (4) machines (IDs # XVI(b) (4)-01 and XVI(b) (4) 02) with (b) (4) to prevent the extraneous matter and magnetic particles in the API. However, you have not qualified the (b) (4) You also do not challenge the (b) (4) before, during, and after the (b) (4) operations. There have been multiple market complaints for metal contaminations in your APIs, including but not limited to; H/M/001/2021 for (b) (4) API Batch No. (b) (4) (non-US market), and LB4/M/005/2021 for (b) (4) API Batch No (b) (4) You have (b) (4) and the (b) (4) on at least (b) (4) of the (b) (4) are not qualified.

F. On January 27, 2021, your firm recorded a market complaint A2/M/002/2021 for foreign particle with metallic appearance for (b) (4) API Batch No. (b) (4) (non-US market). The investigation did not confirm the nature of the black particle whether it was metal or non-metal. The investigation stated "**Machine is not contributing factor for foreign particles**". The investigation is deficient such that it is not inclusive of all the manufacturing equipment including (b) (4) ID # PP-02(b) (4)01. You have recorded a deviation 215206 for black particle in (b) (4) API Batch No (b) (4) and your investigation implicated damaged (b) (4) of the (b) (4) XVI(b) (4)02.

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OBSERVATION 2

The Quality Unit failed to take adequate actions against the failing API batches being sold in the domestic and international market.

Specifically,

The Quality Unit failed to take adequate actions including product recall against batches of (b) (4) API that failed to meet impurity specifications during stability testing.

The QC Lab initiated out of specification (OOS) investigation # RTM/OOS/S/023/2022 on 10/7/2022 when two batches (# (b) (4) of (b) (4) API failed to meet impurity specifications for (b) (4) impurity, any unspecified impurity, and total impurities. Both batches, stored under long-term condition of 25 °C, 60% RH, yielded following results when tested for 24-month stability interval.

Parameter	Specifications	Batch (b) (4)	Batch (b) (4)
(b) (4) Impurity	Not more than (b) (4)%	(b) (4)%	(b) (4)%
Any unspecified Impurity	Not more than (b) (4)%	%	%
Total Impurities	Not more than (b) (4)%	%	%

Subsequent lab testing confirmed the original OOS results. During manufacturing investigation no assignable root cause was identified. However, the manufacturing investigation concluded that the failing batches might have had a high (b) (4) that caused the increased value of the impurities. To mitigate this risk (to lower the (b) (4) a change in washing quantity of water was proposed from

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(b) (4) Liter to (b) (4) Liters via CAPA 258992 (open date: 12/7/2022; close date: 3/16/2023. Both impacted batches (manufacturing Date: 05/2020, expiry Date: (b) (4) were consumed for the domestic market.

For the impacted (b) (4) batches, the Quality Unit failed to take necessary actions such considering a market action, notification to the regulatory authority, and notification to its customers. As per APQR for (b) (4) review cycle: 04/2020 to 03/2021), the firm manufactured about (b) (4) batches (batch size: (b) (4) (b) (4) of (b) (4) API for domestic and international markets. Out of (b) (4) marketed batches the firm tested retains samples for only (b) (4) additional batches during this investigation.

OBSERVATION 3

The reworked API is not subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process

Specifically,

You did not follow procedure, SOP No. CSOP/2018/190/R03 Reprocessing and Rework in API and Intermediate (Effective date 1/15/2021) such that you released multiple reworked APIs batches without satisfactory evaluation of data including 6 month of stability data. The batches of reworked APIs that were released without stability studies includes but are not limited to: (b) (4) API Batch No (b) (4) Mfg. date December 2021, Retest date (b) (4) API Batch No. (b) (4) Mfg. date April 2022, Retest date (b) (4) and (b) (4) API Batch No. (b) (4) Mfg. Date April 2022, Expiry date (b) (4) You did not place the aforementioned API batches on the stability.

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OBSERVATION 4

You fail to establish optimal processing condition that ensures consistency in critical quality attributes of the APIs

Specifically,

The validation batch production record Batch No. (b) (4) dated 5/16/2018, for the (b) (4) (Pure) (b) (4) API Process Performance Qualification (PPQ) instruct for the (b) (4) process as (b) (4) (b) (4) ' There is no instruction as to how much material should be loaded in (b) (4) and how much and how to (b) (4) On 6/5/2023, during walkthrough of your manufacturing building (b) (4) I saw you were (b) (4) (Pure) (b) (4) Batch No. (b) (4) in (b) (4) ID # XXI (b) (4) 01. I saw the material was (b) (4) and there were (b) (4) as big as 2-3 inches. On 6/12/2023, your General Manager of Production (AJ) confirmed that the manufacturing process of (b) (4) (Pure) (b) (4) API was validated in 2018 and this was the only validation study for (b) (4) API. In the year 2021 and 2022, you have recorded at least thirteen (13) OOS results for (b) (4) Specification NMT (b) (4) %).

OBSERVATION 5

Your firm failed to oversee and control over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of materials used in the manufacturing of drugs. For example:

A. Your firm uses (b) (4) as the raw material to manufacture (b) (4) (b) (4) the critical starting material for the drug substance of (b) (4) USP Your firm tested (b) (4) n the (b) (4) batches of starting material (b) (4) that were used to

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manufacture the (b) (4) batches of drug substance (b) (4) for the U. S. market in 2020. Among the (b) (4) batches of (b) (4) the (b) (4) test results for (b) (4) of the batches were in the range of (b) (4)% to (b) (4)% (Refer to the table below).

However, your firm did not conduct the proper (b) (4) contamination testing in the drug substance of (b) (4) and was not aware of the potential hazards if this testing was not done. Your firm distributed (b) (4) batches of (b) (4) for the U. S. market in 2020. In addition, the retest date of all (b) (4) batches of (b) (4) will be in (b) (4). As of the completion of this inspection, your firm has not initiated any plan for risk assessment of (b) (4) in HCQS.

#	(b) (4) (Drug Substance) Batch#	(b) (4) Batch Size (b) (4)	(b) (4) Manufacture Date	(b) (4) Retest Date	(b) (4) (Starting Material) Vendor Batch#	(b) (4) (FDA Guidance Specification: NMT (b) (4)
	(b) (4)					

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(b) (4)

B. Your firm's Standard Operating Procedure for Complete Cleaning of Equipment Used for Processing of Active Pharmaceutical Ingredients at (b) (4) (SOP Number: P/2108/2008, Revision Number: 05, Effective Date: April 5, 2023; and SOP Number: GMP/RTM/P/2108/2008, Issue Number: 02, Revision Number: 10, Effective Date: March 31, 2020) requires a complete cleaning of various equipment used to manufacture the drug substance of (b) (4) (b) (4) USP during the production campaign. This SOP defines that the frequency to conduct a complete cleaning of the equipment train shall be (b) (4) which comes earlier.

Your firm's carryover study did not provide scientific justification that your commercial manufacturing process does not carry over (b) (4) from the critical starting material, (b) (4) to the final drug substance of (b) (4) USP (b) (4) is the raw material used to manufacture the starting material, (b) (4) As such, your firm's equipment cleaning frequency may cause a risk of (b) (4) cross contamination between drug

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substance batches during the production campaign.

OBSERVATION 6

Your firm failed to ensure that all specifications and test procedures are scientifically sound and appropriate to ensure that your raw materials and API conform to established standards of quality. For example:

A. Your firm conducted two carryover studies to justify your commercial manufacturing process does not carry over (b) (4) from the critical starting material (b) (4) (b) (4) to the (b) (4) drug substance of (b) (4) USP (b) (4) is the raw material used to manufacture the starting material, (b) (4)

   a) Your firm's (b) (4) Study Report (Report Reference Number: SYN/QR/2018/030) was designed to spike (b) (4) at its specification limit of (b) (4) % into the starting material (b) (4) Drug substance (b) (4) was produced at lab scale (around (b) (4) using (b) (4) spiked starting material, and (b) (4) was tested in the drug substance and found not detected.

   However, your firm's commercial batch size of drug substance (b) (4) is around (b) (4) which is approximately (b) (4) times larger than the lab scale (around (b) (4) as designed in the (b) (4) (b) (4) Study. Your firm did not provide any scientific justification to prove that the batch size of your lab scale and commercial scale are comparable.

   b) Your firm's Carry Over Study of (b) (4) Impurity in (b) (4) by GC (Protocol Number: AMVP/API/MUM/2016/014;

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Report Number: AMVR/API/MUM/2016/014) was designed to test (b) (4) in the drug substance (b) (4) from (b) (4) commercial batches and found not detected.

However, your firm did not test (b) (4) in the starting material (b) (4) used to manufacture the (b) (4) commercial batches. Your firm did not provide any scientific justification to prove that the (b) (4) level in the starting material does not impact its carryover to the drug substance (b) (4)

B. Your firm's Specification and Analytical Procedures for (b) (4) (Specification Number: TS/RMS/IHY016, Version 3.0, Effective Date: May 28, 2021; and Specification Number: TS/BPC/RMS/IHY016, Version 2.0, Effective Date: Feb 03, 2018) uses GC method to detect the Related Substances of (b) (4) and quantitate Total Impurities (%) of (b) (4) is the critical starting material used to manufacture the drug substance of (b) (4) USP.

(a) Instead of an independent assay test, your firm deducts Total Impurities (%) from 100 (%) to calculate Purity (%) (i.e. Assay) of (b) (4)

Your firm did not provide any scientific justification or conduct any sound study to prove that deducting Total Impurities (%) from 100 (%) to calculate Purity (%) of (b) (4) s equivalent to the independent assay test of (b) (4)

(b) Instead of six standard injections performed in your method validation, your firm executes three standard injections in the test method for the system suitability test. Your firm had been using this method to test (b) (4) in (b) (4) since Feb 2018. (b) (4) is the raw material used to manufacture the starting material, (b) (4)

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Without demonstrating the system suitability, the sample analysis for the related substances test of (b) (4) appears to be inadequate.

OBSERVTAION 7

Laboratory tests conducted to determine conformance to specification for each batch of intermediate and API are deficient.

Specifically, laboratory tests conducted to determine multiple batches of (b) (4) API to the written specifications are deficient. Deficiencies were observed in the processing methods and integration of peaks during analysis of impurities and residual solvents in various batches of (b) (4) USP. The QC Lab used different processing methods with inconsistent peak integration parameters to integrate peaks of the standards, and different lots of the product in the same HPLC/GC run. For example:

A. On 5/7/2020, the QC Lab tested two batches (# (b) (4) of (b) (4) for Impurity Profile. The lab used three different processing methods (method ID: 4159, 4206, and 4239) to integrate the peaks of standards, Lot (b) (4) and Lot (b) (4) respectively. Peak integration parameters used for a US batch (b) (4) (as per processing method ID: 4206) are as below:

Time (min)	Integration Type	Value	Stop (min)
(b) (4)	Valley to Valley	(b) (4)	
	Set minimum Area		
	Set minimum Area		

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(b) (4)	Set minimum Area	(b) (4)	
	Force peak		(b) (4)
	Force peak		
	Allow negative peaks		
	Force peak		
	Set minimum height	(b) (4)	

Under these integration parameters, any impurity peak/s with peak area of less than (b) (4) will not be integrated that elute before (b) (4) Similarly, any unknown impurity peak/s with peak height of less than (b) (4) will not be integrated after (b) (4) and will not be accounted for towards the maximum unknown impurity specifications. The peak height for the largest known impurity (b) (4) and largest unknown impurity ((b) (4) was observed to be (b) (4) and (b) (4) respectively. The sample run time for the Impurities analysis is (b) (4)

B. On 5/8/2020, the QC Lab tested two US batches (# (b) (4) of (b) (4) for residual solvent analysis by GC. The lab used three different processing methods (method ID: 3023, 3078, and 3090) to integrate the peaks of standards, Lot (b) (4) respectively. Peak integration parameters selected for a US batch (b) (4) as per processing method ID: 3078) are as below:

Time (min)	Integration Type	Value	Stop (min)
(b) (4)	Valley to Valley		

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(b) (4)		(b) (4)
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Force Peak	(b) (4)
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	
	Set minimum Area	

Under these processing parameters, any potential unknown peak/s with peak area set less than a specific value for specific time frame will not be integrated. The sample run time for the Impurities analysis is about (b) (4)

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Ipca Laboratories Ltd.	P.O. No. 33 Village Sejavata
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Ratlam, 457 002 Madhya Pradesh, India	API Manufacturer

The firm shipped (b) (4) batches (manufactured in 2020; and expiring in (b) (4) of (b) (4) for the US market.

OBSERVTAION 8

The Quality Unit failed to ensure all deviations are reported on the batch certification certified by the third-party consultants.

Specifically,

The firm's Quality Unit failed to ensure that all deviations, generated during manufacturing of the shipped batches of (b) (4) USP and (b) (4) USP were reported by the certifying organization i.e., the third-party consultants. During the Covid-19 pandemic, the firm shipped about (b) (4) batches of (b) (4) USP and (b) (4) USP for the US market after third party certifications (as per Protocol BEC/Ipca/BC-API.00) against each batch.

The third-party consultants failed to document significant incidents such as deviations observed during manufacturing of that particular batch on the batch certificate. For example:

A. Four US batches (# (b) (4) of (b) (4) manufactured by the firm in 04/2020 (expiry: 03/2025) failed to meet the yield specification at (b) (4) manufacturing stage as below:

Batch #	Yield Limit	Actual Yield	Deviation #
(b) (4)			162805
			163181

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	RPS SAA W.Z.	Rajiv R Srivastava, Investigator Saleem A. Akhtar, Investigator Wenzheng Zhang, Investigator	06/13/2023

(b) (4) 163186
163460
(b) (4)

A third-party consulting company certified each of these batches and failed to document on the certification that the batch did not meet the yield specification at the (b) (4) stage.

Additionally, the firm conducted an umbrella investigation covering all four deviations (162805, 163181, 163186, and 163460) for yield failures. It was discovered during the inspection, this umbrella investigation was not initiated and maintained in the firm's Quality Management System such as TrackWise which is used for this purpose.

B. During the release testing of (b) (4) batch (b) (4) for residual solvent analysis by GC, an extraneous/unknown peak was observed at RT of (b) (4) This peak was observed in all three samples i.e., main sample, set A, and set B of this batch. The firm initiated deviation # 163503 to investigate the extraneous peak. The third-party consultants did not document this deviation on the batch certificate. This extraneous peak was not observed during analytical method validation of (b) (4) for residual solvents analysis.

C. During the release testing of (b) (4) batch (b) (4) for residual solvent analysis by GC, an extraneous/unknown peak was observed at RRT of (b) (4) This peak was observed in two of the three samples i.e., main sample and set B, (not observed in Set-A) of this batch. The firm-initiated deviation # 162473 to investigate the extraneous peak. During the deviation investigation, the lab attributed this peak as of (b) (4) that came from laboratory environment. The third-party consulting company did not document Deviation 162473 on the batch certificate. This extraneous peak was not observed during analytical method validation of (b) (4) (b) (4) for residual solvents analysis.

D. There was no documented evidence available during the inspection that the third-party consultants reviewed system audit trails and project audit trails pertaining to overall assessment of the projects and systems used to certify about (b) (4) batches of (b) (4) USP and (b) (4) USP. Additionally, the protocol used to certify batches did not specifically ensure the review of duplicate sample injections, control injections, and test injections etc.

OBSERVTAION 9

Calibration of the laboratory equipment used in Micro Lab is deficient.

Specifically, (b) (4) verification of pH meter (equipment ID: RTM-QC-287) used in micro lab to test the pH of media is deficient. For example:

(b) (4) verification of this pH meter is performed per SOP (QC/OPE/281/2022) using (b) (4) (pH (b) (4) pH (b) (4) pH (b) (4) pH (b) (4) and pH (b) (4) with Slope acceptance criteria of (b) (4) % to (b) (4) %. Following Slope values were observed during equipment verification on 2/14/2023:

(b) (4)	Observed Slope
	(b) (4) %
	%
	%
	%

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	06/05/2023-06/13/2023 FEI NUMBER 3002807297

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Dr. Arun Chandra Karmakar, Vice President Operation-API and Site Head	
FIRM NAME Ipca Laboratories Ltd.	STREET ADDRESS P.O. No. 33 Village Sejavata
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The micro lab considered the Slope value of (b) (4)% (generated for the (b) (4) i.e., pH (b) (4) – (b) (4) only if acceptance criteria is met or not. This pH meter is used to determine the pH of various media ranging pH (b) (4) – (b) (4) about four medias are tested at the range of pH (b) (4) – (b) (4). The micro lab operator who routinely used this pH meter stated he only looks at the slope for (b) (4) i.e., pH (b) (4) – (b) (4) even if the Slope for other media is not within the specification of (b) (4)% to (b) (4)%. Similar deficiency was observed during the (b) (4) verification performed on 6/5/2023.

OBSERVTAION 10

The determinations made to establish the suitability of secondary reference standard by comparing against the primary reference standard, is deficient.

Specifically, inhouse qualification of (b) (4) batch # (b) (4) (DMF # (b) (4) to use as secondary standard is deficient. For example:

The QC Lab qualified (b) (4) USP batch (b) (4) (manufacturing date: 02/2023; expiry date: (b) (4) to be used as secondary reference standard in 05/2023. This batch was qualified as per SOP (# QC/22/2006), "Reference and Working Standard Management" against the USP Reference Standard Lot # (b) (4) During secondary standard qualification, three replicate assay samples of the API (being qualified as secondary standard) are prepared and compared against the primary reference standard. As per secondary standard qualification SOP, % RSD of triplicate assay should not be more than (b) (4)%. The site does not have a scientific rational for the % RSD criteria.

The firm manufactures about (b) (4) APIs (about (b) (4) DMF APIs) at this site. The purity and strength of all these APIs is tested by using inhouse qualified secondary standards as per SOP QC/22/2006.

OBSEVTAION 11

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE	RRS	Rajiv R Srivastava, Investigator	06/13/2023
	SAA	Saleem A. Akhtar, Investigator	
	W.Z.	Wenzheng Zhang, Investigator	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Arun Chandra Karmakar, Vice President Operation-API and Site Head

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Your firm failed to maintain complete records of major equipment use, cleaning and maintenance.

Specifically,

Partial page and information are missing on page 1 and 2 of the Equipment Use, Cleaning and Maintenance Record in 2020 for (b) (4) Equipment Number: XVIII/(b) (4)12. This (b) (4) was among the major equipment used to manufacture the drug substance of (b) (4) USP for the U. S. market in 2020.

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	Rajiv R. Srivastava Saleem A. Akhtar Wenzheng Zhang	Rajiv R Srivastava, Investigator Saleem A. Akhtar, Investigator Wenzheng Zhang, Investigator	06/13/2023