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	5/1/2023-5/12/2023*
	FEI NUMBER 3003157498

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

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Limited	458 Plots 457, Sarkhej - Bavla Highway
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382210 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:

OBSERVATION 1

Batch production and control records do not include complete information relating to the production and control of each batch.

A) Our review of parenteral drug product batch records since 2021 found that manual visual inspection data for finished parenteral drug products appeared to be routinely manipulated by your manual visual inspectors to stay just below the established reject particle limits set for General parenteral for one or more particle defect categories (black particle, white particle, fiber, glass). Our review found a pattern of two practices, which your firm confirmed through employee interviews:

1. A pattern of visual inspection records being altered to change the reported counts from values that exceed the individual particle limits (black particle, white particle, fibers, glass) by instead reporting these as other categories or removing reported counts from values that exceed limits without accounting for the removed value. This would mean there would be no required investigation and the inspectors would not be required to fully reinspect the batch. For Example:

   (b) (4) Injection USP (b) (4) mg/ml (b) (4), Batch No. (b) (4) (US). On the visual inspection records for three inspectors the originally recorded value was crossed out (handwritten slash mark) and the number of rejects was moved to a different category.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Rita K Kabaso, Investigator Justin A Boyd, Investigator Arsen Karapetyan, Investigator - Dedicated Drug Cadre	X Justin A Boyd Investigator Signed By 2000358686 Date Signed 05-12-2023 09 12 28	5/12/2023

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Ahmedabad, Gujarat, 382210 India	Drug Manufacturer

	Original White Particle	Altered White Particle	Original Fiber	Altered Fiber	Original Black	Altered Black
Inspector 1	3	0	9	0	0	12
Inspector 2	6	0	9	0	0	15
Inspector 3	5	0	5	5	0	5
Total Inspectors	61 (b) (4) %)	56 (b) (4) %)	102 (b) (4) %)	84 (b) (4) %)	12 (b) (4) %)	44 (b) (4) %)
Limits	(b) (4) %		(b) (4) %		(b) (4) %	
Met Limit	No	Yes	No	Yes	Yes	Yes

A similar pattern, where reject counts originally exceeding a limit were later altered in one or more of the categories for %white particles, %black particles, %fiber, %seal, %glass, %total non-particulate matter rejection, %total particulate matter rejection, and %total rejection, were observed in the following batches:

(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (Europe)
(b) (4) Injection USP (b) (4) mg/ml, Batch No. (b) (4) (US)
(b) (4) Injection USP (b) (4) mg/ml, Batch No. (b) (4) (US)
(b) (4) Injection (b) mcg/ml, Batch No. (b) (4) (US)
(b) (4) Injection USP (b) mg/ml, Batch No. (b) (4) (US)

- (b) (4) Injection USP (b) (4) mcg/ml, Batch No. (b) (4) (US)
- (b) (4) mg Injection, Batch No. (b) (4) (Domestic)
- (b) (4) Injection, (b) (4) ml, Batch No. (b) (4) (Domestic and ROW)

2. Visual inspection records showed a pattern where visual inspection records for multiple operators were identical. Your firm interviewed your personnel, who explained carrying out this practice to make it appear that there were no operator performance issues (for example, one operator not detecting any rejects), by getting together and dividing up what to record on the record, resulting in everyone reporting the same thing. For Example, for drug product (b) (4) Solution Injection (b) (4) mg/ml (b) (4), Batch No. (b) (4) (Europe), nine different manual visual inspectors for (b) (4) different set of trays inspected had the below identical numbers for all listed categories:

Rejection Details	No. of units rejected
Black Particle	01
White Particle	01
Fiber Particle	02
Glass Particle	02
Volume Variation	00
Breakage/Crack	00/00
Without (b) (4) /loose (b) (4)	03/00
(b) (4) Stopper alignment	07
(b) (4) bent	00
(b) (4) without (b) (4) stopper (b) (4) stopper	00/00
Liquid entrapment between ridges of stopper	05
Any foreign material adhered on stopper	00
Others	00

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Total Rejection	21
No. Good Units	(b) (4)

Similar practices for additional batches we reviewed, where identical results were observed in the records of multiple operators are listed below:

- (b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
- (b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (US)
- (b) (4) Injection (b) mg/(b) ml, Batch No. (b) (4) (Europe)
- (b) (4) Solution Injection (b) (4) mg/ml (b) (4), Batch No. (b) (4) (US)
- (b) (4) Solution Injection (b) (4) mg/ml (b) (4), Batch No. (b) (4) (US)
- (b) (4) Solution Injection (b) (4) mg/ml (b) (4), Batch No. (b) (4) (Europe)
- (b) (4) Injection (b) (4) mg/(b) (4) ml, Batch No. (b) (4) (US)
- (b) (4) Injection (b) (4) mg/(b) (4) ml, Batch No. (b) (4) (US)
- (b) (4) Injection (b) mcg/ml, Batch No. (b) (4) (US)
- (b) (4) Injection USP (b) (4) mg/ml, Batch No. (b) (4) (US)

This repeated pattern of altering and/or manipulating visual inspection records was observed since at least 2021 with multiple visual inspectors and supervisors involved. The quality unit used these deficient records to release batches of drug products to the US market.

During the current inspection, your firm initiated Deviation No. MA/DF/2023/0208, dated May 4, 2023, which reads in part: "*Visual inspection reports have alteration of data for the category of defects reported on visual inspection*". Reasons for this practice identified in your report include: "*correction in quantities to keep the category wise rejections within limits to avoid deviation and investigation*". The deviation also identified "*Visual inspection reports having number of good and reject units which are identical for two or more inspectors*". Reasons for the discrepancy read in part: "*to show uniform performance and productivity among the inspectors*".

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B) Current process controls established to ensure that tablet compression is in a state of control are inadequate. For example,

(b) (4) for tablet rejection is set by the operator at the beginning of a campaign. A justification was not provided demonstrating that setting (b) (4) in this manner will produce tablets of intended quality. (b) (4) % and (b) (4) % low and high (b) (4) were observed; however, a justification was not provided for the limit selected. In addition, production personnel have authorized access to change parameters when manufacturing of a batch is ongoing. The changes are within parameters but are not documented in the electronic Batch Manufacturing Record (BMR) as required. Changes on the Programmable Logical Controller (PLC) are captured on the "Change Report" which is not attached to the BMR or reviewed by Quality. In addition, in-process checks are not always documented when changes are made to ensure that the change did not impact the quality of the tablets being produced. For example,

1. Manufacturing of (b) (4) and (b) (4) Tablets USP (b) (4) mg/(b) (4) mg was initiated April 13, 2023, at (b) (4). At (b) (4) (b) (4) for RHS/S2 changed from (b) (4) mm to (b) (4) mm an in-process sample to analyze (b) (4) (b) (4) was collected but not tested until (b) (4). A reason was not documented addressing testing of tablets in a timely manner. Between (b) (4) to (b) (4) (b) (4) for LHS/S1 and RHS/S2 was being changed from (b) (4) However, the changes are not documented in the BMR. Between (b) (4) and (b) (4), the documented (b) (4) in the BMR is (b) (4). (b) (4) is identified as a critical process parameter, however there is no documented justification for the change. At (b) (4) when the (b) (4) was changed back to (b) (4), an in-process sample for (b) (4) was collected at (b) (4). A documented justification was not provided for the (b) (4) changes and why an in-process sample was taken after the (b) (4) was returned to (b) (4).

2. A (b) (4) -batch campaign ((b) (4)) was initiated for (b) (4) mg tab on (b) (4) . (b) (4) challenge was conducted on the (b) (4) batch (b) (4) which was initiated on April 28, 2023, at (b) (4) using a (b) (4) % rejection limit. At (b) (4) , the rejection limit was changed by the operator from (b) (4) % to (b) (4) %. The BMR does not contain a contemporaneous justification for the change. Additionally, at (b) (4) RHS sample was tested per the frequency, however no LHS was tested. At (b) (4) (next in-process sample), LHS and RHS samples were obtained.

OBSERVATION 2

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

A)Investigations conducted when rejects from visual inspection exceeded total reject limits did not characterize the particles in rejected vials. They were closed with no root cause and implemented no preventive actions:

1.Deviation MA/DF/2023/0013 - (b) (4) Injection lot (b) (4) (US Market, Expiration 11/24) due to exceeding the total reject limit of (b) (4) % with a result of (b) (4) %, exceeding the individual limit for black particles of (b) (4) % with a result of (b) (4) %, and exceeding the individual limit for white particles with a result of (b) (4) %. The particles from rejected vials were not isolated and identified. The investigation was closed without identifying a root cause for the black or white particles.

2.Deviation MA/DF/2023/0038 - (b) (4) Injection lot (b) (4) (US Market, expiration

12/24) due to exceeding the total rejection limit of (b)(4) % with a result of (b)(4) % and exceeding the individual limit for black particles of (b)(4) % with a result of (b)(4) %. The black particles were not isolated and identified to allow for a thorough root cause analysis. The investigation was closed without identifying a root cause for the black particles.

3. Deviation MA/DF/2022/0073 - (b) (4) lot (b) (4) (European Market) due to exceeding the limit for total particulate with a result of (b)(4) % compared to a limit of (b)(4) % and white particles with a value of (b)(4) % compared to a limit of (b)(4) %. The product was filled on Line (b)(4) in the General parenteral facility which is used for aseptic filling of US products. An R&D study confirmed the white particles in reject vials were not product or process related, but did not characterize their composition or identify potential sources.

The batch was reinspected a second time and yielded no additional vials with white particles. A third 100% visual inspection identified 143 additional vials with white particles. The investigation did not thoroughly evaluate why these vials were not detected during the first two 100% visual inspection or the impact to other batches that had been inspected using the same visual inspectors. The R&D study did not identify these as particles that had precipitated from the product.

4. Deviation MA/DF/2023/0019 - (b) (4) Injection lot (b) (4) (European Market) due to exceeding the total rejection limit of (b)(4) % with a result of (b) (4) %, exceeding the individual limits for white particle of (b)(4) % limit with a result of (b)(4) %, and exceeding the glass particle limit of (b)(4) % with a result of (b)(4) %. The product was filled on Line (b) in the General parenteral facility, which is used for aseptic filling of US products. The investigation did not isolate or identify the white particles to allow for a thorough evaluation of the root cause. The filling record did not identify any glass breakage events. The investigation was

closed with no root cause identified for the white particles or the glass particles.

5. Deviation MA/DF/2023/0030 - (b) (4) Injection lot (b) (4) (European Market) due to exceeding the total rejection limit of (b) (4) % with a result of (b) (4) %, exceeding the individual defect limit for white particle of (b) (4) % with a result of (b) (4) % and exceeding the glass particle limit of (b) (4) % with a result of (b) (4) %. The product was filled on Line (b) in the General parenteral facility, which is used for aseptic filling of US products. The investigation did not isolate or identify the white particles to allow for a thorough evaluation of the root cause. The filling record did not identify any glass breakage events. The investigation was closed with no root cause identified for the white particles or the glass particles.

6. Deviation MA/DF/2023/0089 - (b) (4) Injection lot (b) (4) (European Market) due to exceeding the rejection limit for white particles of (b) (4) % with a result of (b) (4) %. The product is filled into (b) (4) vials and the investigation identifies the opening of the inner pack for these vials as generating particles. There was no characterization of particles in rejected vials or from the inner pack to confirm this root cause or preventive actions included in this investigation. This product is also manufactured for the US market using these vials.

B) Trending of the visual inspection reject rates is conducted (b) (4), including calculation of Cpk and Ppk values. These values were below (b) (4) for all trending in 2021 and 2022 for liquid vials ((b) (4) and General) and (b) (4) (General), demonstrating the process was not capable. No action has been taken to investigate the sources of the batch to batch variation in reject rates. Additionally, the limits for individual defect categories are evaluated during this trending, but have not been adjusted to reflect the historical data.

C) Non-viable particle count (NVPC) excursions in the Grade A filling areas are not thoroughly

investigated to identify root causes or assess the impact on the product and components present at the time of excursions, including open vials or (b) (4), and sterile stoppers. The filling machine will automatically stop if the limits are not met for (b) (4), but there is no procedure to remove any open containers present at the time of the machine stoppage due to the excursion. Examples included:

1. During the aseptic filling of (b) (4) Injection batch (b) (4) (US Market, expiration 2/26), the limit of NMT (b) (4) µm particles/cubic foot was exceeded at the NVPC probe (b) (4) during filling activities on (b) (4). Additional excursions of the NMT (b) (4) µm particles/cubic foot limit were observed during the aseptic filling of this batch at the (b) (4) probe, the probe at the (b) (4), and the probe at the (b) (4).

2. During the aseptic filling of (b) (4) Injection batch (b) (4) (US Market, expiration 2/25), the limit of NMT (b) (4) µm particles/cubic foot was exceeded at the NVPC probe (b) (4) during filling activities on (b) (4). Additional excursions of the NMT (b) (4) µm particles/cubic foot limit were observed during the aseptic filling of this batch at the (b) (4) probe, the probe at the (b) (4), and the probe at the (b) (4).

3. During the aseptic filling of (b) (4) Injection batch (b) (4) (US Market, expiration 6/25), the limit of NMT (b) (4) µm particles/cubic foot was exceeded at the

NVPC probe (b) (4) 35 times while filling was occurring on July 26, 2022.

D)There have been no effective measures taken to investigate sources and reduce the occurrence of spore forming organisms in the aseptic processing areas. For example, there have been 786 identifications of spore forming organisms in the General Parenteral Facility and 342 identifications of spore forming organisms in the (b) (4) Parenteral manufacturing from January 2020 to April 2023.

E)Investigation MA/DF/2022/0080 into (b) (4) for (b) (4) mg tablets batch (b) (4) did not evaluate the actual parameters set by the production operator during (b) (4) In addition, adequacy of the established sampling process was not evaluated. (b) (4) for Lot (b) during (b) (4) was (b) (4) %w/w, specification: (b) (4) %w/w to (b) (4) %w/w. The operator failed to identify that a deviation had occurred and proceeded with (b) (4) . The batch was released based on (b) (4) meeting in-process specification and the final batch meeting specification. Additional Lot (b) samples were sent for testing; however, the investigation fails to address sample size selection or result variation between the initial certificate of analysis and the additional samples. The release CoA is dated October 6, 2022, with (b) (4) result (b) (4) ppm. The additional test of Lot (b) was approved October 19, 2022, with (b) (4) result of (b) (4) ppm (specification NMT (b) (4) ppm).

F)Investigation MA/DF/2021/0086 for rough surfaces being observed while (b) (4) lot (b) of (b) (4) mg tablets batch (b) (4) failed to include an evaluation of the (b) (4) , (b) (4) and time set by the operator. Gradual increase or decrease of these parameters are left to the operator's discretion. In-process samples ((b) (4) tablets) collected to evaluate uniformity of (b) (4) on the tablets have no scientific basis. It is unknown when the batch samples began trending out of specification for roughness as the operators document "ok" for physical appearance. The investigation was not extended to Lot (b) which was manufactured before Lot (b) .

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Per Quality, Lot (b) was released for distribution on October 30, 2021, based on the lot meeting in-process and finished product specifications. Lot (b) was released for distribution to the US Market without assessing dissolution and impact of inhomogeneous (b) (4) on efficacy and quality of the batch. This batch was not charged on stability.

Visual inspection of the tablets was conducted using equipment S-1246. 7,967 tablets were rejected from Lot (b). According to production, only the major defect category is captured in the batch record. The number of tablets with rough surfaces from the reject tablets is unknown.

G) Approximately 206 (b) (4) complaints recorded between January 2020 to May 1st, 2023, due to "odor" or "smell" are not fully evaluated to determine the root cause. In July 2020, R&D conducted a literature review and determined that odor in the finished is due to (b) (4) being present in the Active Pharmaceutical Ingredients (API). A scientific justification was not provided for failure to evaluate the API being used in the process for concentration of (b) (4). In December 2022, another literature review was conducted which determine that the odor smell is due to (b) (4) in the API and (b) (4) degradation in the finished product. To date, the API used to manufacture the finished product has not been evaluated for (b) (4) concentration nor the finished product analyzed for (b) (4).

In (b) (4), the preapproval supplement submitted to the Agency for the API process change was approved. Presently, the old and new product codes ((b) (4) and (b) (4)) of the API are used to manufacture product. A statistical analysis has not between conducted to evaluate variation between the old and new API process.

H) US Market Complaint MA/MC/2022/0541 for batch (b) (4) of (b) (4) Cream USP (b) % reported the cream was "liquified". During the complaint investigation, retain samples were not tested for viscosity.

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I)When endotoxin tests are invalidated due to suitability failure, a note is written on the record and tests are repeated, without documenting a Laboratory Incident according to the MA/GQC/00073 "Handling of Laboratory Incidents" to allow for tracking, trending, or investigation of a root cause.

OBSERVATION 3

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.

A) Process validation studies executed to assure intended drug quality is achieved are inappropriately designed and executed. For example,

1. All (b) (4) process validation for (b) (4) mg (b) (4)) fail to contain scientific justifications for the establishment of: (b) (4) uniformity sample size and frequency, %RSD established for inter batch variability, and (b) (4) and (b) (4) . (b) (4) and increase or decrease of (b) (4) for the (b) (4) is left to the discretion of the operator. For example,

Batch (b) (4)	Batch (b) (4)
(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	

Quality has not evaluated the inconsistent parameters used against the results obtained. In addition, the sampling size for (b) (4) tablets used is not statistically sound. Furthermore, variation between batches has not been evaluated. No documented evidence was provided to assure uniformity of the (b) (4) tablet (b) (4) . Investigations MA/DF/2022/0080

and MA/DF/2021/0086 have been initiated to address (b) (4) after (b) (4) and rough tablets being observed.

2. (b) (4) Tablets USP (b) (4) mg process validation (PVR-GS-2391-01, approved February 7, 2020) fails to establish statistically sound sampling plans ((b) (4) uniformity, content uniformity, dissolution etc.), %RSD for inter batch results, minimum and maximum batch size for compression (b) (4), and inconsistent (b) (4) and (b) (4) which is determined by the production operator. For example, compression is performed on a (b) (4) (b) (4) machine. (b) (4) percent of the commercial batch size was used to compress tablets at minimum ((b) (4)) and maximum ((b) (4)) (b) (4). There is no evidence demonstrating that use of (b) (4) % (b) (4) is representative of the commercial batch size. For both minimum and maximum (b) (4) in-process sample was collected and analyzed after machine setup. Tablet weight, thickness, hardness, and content uniformity ((b) (4) sample) was not evaluated throughout the minimum and maximum batch run. The established parameters for commercial batch size is (b) (4) to (b) (4). No justification was provided to demonstrate that manufacturing of tablets using the minimum and maximum (b) (4) will produce drug products with the intended identity, strength, quality, and purity. In addition, there is no statistical evaluation measuring repeatability and reproducibility between batch-to-batch variation.

3. Process validation studies have not included establishment of criteria to evaluate intra-batch or inter-batch variability. For example:

   a) (b) (4) Ointment (b) (4) % (b) (4) g:

   The content of (b) (4) impurities (limit of NMT (b) (4) %) showed inter-batch variability with higher values for batch (b) (4) with a range of the (b) (4) samples from (b) (4) %-(b) (4) %, compared to (b) (4) %-(b) (4) % for batch (b) (4) and (b) (4) -(b) (4) % for batch

(b) (4) .

The content of all other total impurities (limit of NMT (b) (4) %) showed intra-batch variability in batch (b) (4) with the (b) (4) sample below the detection limit and the finished product sample at (b) (4) %. There was inter-batch variability as the highest total impurity level for batch (b) (4) was (b) (4) % and for batch (b) (4) was (b) (4) %.

The (b) (4) (limit NMT (b) (4) %) varied from (b) (4) % on the finished product sample of batch (b) (4) to (b) (4) % for the (b) (4) sample of batch (b) (4) .

Variation in viscosity was not considered. Only (b) (4) samples were tested for viscosity.

b) (b) (4) Ointment (b) (4) % (b) (4) g:

The (b) (4) (limit NMT (b) (4) %) showed intra-batch variability with the sample from batch (b) (4) having a (b) (4) at the (b) (4) of filling of (b) (4) %, while the (b) (4) sample was (b) (4) %. Batch (b) (4) had a (b) (4) at the (b) (4) of filling of (b) (4) %, while the (b) (4) sample was (b) (4) %. There was no evaluation of why the initial samples appeared to have a higher (b) (4) .

Variation in viscosity was not considered. Only (b) (4) samples were tested for viscosity.

B) Qualification of the visual inspection process has not utilized challenge defect vials with known particle sizes representative of the typical defect types observed during visual inspection (black particle, white particle, fiber, and glass particle) to determine the threshold that the process can

detect.

1. Defects kits used during qualification of the (b) (4) automated visual inspection equipment used rejected vials taken from previous batches, without knowing the size of the particles. This equipment has been used to visually inspect (b) (4) ml and (b) (4) ml batches for the US market.

2. Defect kits used during qualification of the manual visual inspectors includes vials containing particles of unknown sizes and a standard containing a (b) (4) µm particle that is not representative of the types of defects typically detected during visual inspection.

Additionally, reference defect libraries have not been established.

C) Annual Product Quality Reviews lack statistical evaluation to identify outliers and trends that will recognize and investigate variability in the process. For example:

1. In the (b) (4) Injection Annual Product Quality Review there was no further investigation into why three batches had higher Impurity (b) levels, one batch appeared to be an outlier for filling time, and there appeared to be shift in the (b) (4) testing results.

2. The (b) (4) Cream Annual Product Quality Review recognized variability in the viscosity data, but did not thoroughly evaluate the causes for the variability.

OBSERVATION 4

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

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CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

A) (b) (4) is used to support (b) (4) sterilization of (b) (4) finished drug product. The adequacy of sterilization for areas that could be considered worst case locations for (b) (4) OP-018 and OP-125 is unknown. For example,

1. (b) (4) OP-018 ((b) (4) Sterilization) located on parenteral line-(b) is equipped with a (b) mm (b) (4) transfer port. The (b) (4) transfers open/empty vials from the (b) (4) to the mobile filling (b) (4). Performance qualification executed using PQR-OP-018-12/06 fails to ensure adequate sterilization of the (b) (4). Chemical indicator and biological indicators were not placed at the (b) (4) of the (b) (4) transfer port for (b) (4) based on equipment design.

2. (b) (4) OP-125 is equipped with a (b) (4) mm (b) (4) transfer port (b) (4). The port is used to transfer components to the filling (b) (4). During (b) (4) sterilization, the (b) (4) port is opened for (b) (4). (b) (4) qualification conducted on November 2, 2022, fails to address adequate sterilization at the (b) (4) of the port. Based on the equipment design, the (b) (4) of the (b) (4) port was not assessed as one of the worst-case locations. Additionally, on May 9, 2023, an overlap/folding of the (b) (4) was observed near the area where the (b) (4) attaches to the (b) (4). The (b) (4) has been in this condition since November 7, 2020. (b) (4) qualification conducted November 25, 2022, failed to address adequate (b) (4) sterilization of the overlap/fold.

B) There is no assurance that your process simulation studies (media fills) performed in your (b) (4) Block and General Parenteral Block are representative of the current commercial manufacturing operations. The validation plans for your media fill studies do not appear to adequately incorporate the nature and frequency of interventions incorporating worst-case activities and conditions with respect to operator interventions, such as start and stop time of interventions performed and the total time for interventions performed during media fill and commercial batches. Additionally, per SOP No. MA/GQA/00061-5, titled "Aseptic Process

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Rita K Kabaso, Investigator Justin A Boyd, Investigator Arsen Karapetyan, Investigator - Dedicated Drug Cadre	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 05-12-2023 09:12:20	5/12/2023

Simulation (Media Fill)", effective date 03/27/2026 describes qualification activities for operators to include "at least any (b) (4) of the critical interventions where there is high risk of contamination due to the activity performed", however, your media fills study reports do not document/verify the performance of the corrective and non-corrective (routine) interventions carried out by each operator.

C) There is no evaluation of the air flow patterns in the (b) (4) LAF where (b) (4) of (b) (4) are unloaded from the Mobile LAF into a Grade B area before transfer into the filling RABS on Line (b) (4) in the General Parenteral facility. The mobile LAF has not been evaluated under dynamic conditions during the smoke studies.

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

1.A (b) (4) machine is used to apply the sporicidal disinfectant in the Grade B areas of the aseptic filling rooms. The process was qualified in a non-representative room in the microbiology laboratory and not in the aseptic filling rooms where it is used. The study could not evaluate if the air flow, equipment, or room design allow for the sporicidal to effectively cover all surfaces using the (b) (4) .

2.Blue wipes used for cleaning and disinfection of surfaces in the aseptic areas were observed to have loose fibers and fraying threads.

OBSERVATION 6

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

The (b) (4) RABS on General Parenteral aseptic filling Line (b) (4) is where the sterile stopper bowl and

exposed sterile stoppers are located throughout aseptic filling. There is a lack of scientific rationale for only collecting (b) (4) non-viable particle count in this (b) RABS (b) (4) during aseptic filling operations.

OBSERVATION 7

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.

GMP related computerized systems and equipment have not been validated/qualified to demonstrate the suitability of computer hardware and software to perform assigned tasks. For Example:

A) The firm has initiated an assessment to evaluate data integrity controls for your manufacturing equipment in (b) (4) and general parenteral blocks per Protocol No. ISP/2022/0190, titled "Protocol for Review and Impact Assessment of Quality System", dated 12/29/2022, where deficiencies regarding individual access controls and privileges, restrictions for changing clocks, saving electronic data, and audit trails have been identified. However, the quality unit has not implemented interim controls as a result of this assessment. For example:

1. Your firm operates (b) (4) portable non-viable particle monitoring equipment used to perform and generate test data for non-viable particle (NVP) count used in environmental monitoring/cleanroom qualification activities in class B, class C, and class D areas in support of general and (b) (4) parenteral manufacturing operations. During our review of your (b) (4) (b) (4) equipment and software, it was observed that the firm was not aware of the equipment data storage capability and consequently does not review or backup the electronic data generated and stored on the equipment, only using printer printouts as primary data. Per your firm's management, the data capability storage for this equipment is up to 1000 tests, after which the data is overwritten with the most recent data. After our identification of this discrepancy during the inspection, your firm initiated a deviation investigation. Your

preliminary review of this data during the inspection resulted in instances where some electronic data from the equipment does not appear to have been attached to data packages where testing was performed.

2. Your firm operates (b) (4) leak test equipment used to perform container closure integrity testing for products manufactured in your general and (b) (4) parenteral manufacturing facilities. During our review of your (b) (4) equipment and software, it was observed that the firm was not aware of the equipment data storage capability and consequently does not review or backup the electronic data generated and stored on the equipment, only using printer printouts as primary data. Per your firm's management, the data capability storage for this equipment is only one test, after which the data is overwritten with the most recent data.

3. Your firm operates (b) (4) filter integrity test equipment in support of general and (b) (4) parenteral manufacturing operations. During our review of the (b) (4) equipment and software, it was observed that the firm was not aware of the equipment data storage capability and consequently does not review or backup the electronic data generated and stored on the equipment, only using printer printouts as primary data. Per your firm's management, the data capability storage for this equipment is up to 200 tests, after which the data is overwritten with the most recent data.

4. Your firm operates (b) (4) integrity test equipment in support of general and (b) (4) parenteral manufacturing operations. During review of the equipment and Linux software, it was observed that the firm does not review the electronic data generated and stored on the equipment, only using the printer printouts as primary data.

B) The firm has initiated an assessment to evaluate data integrity controls for your laboratory

equipment, however the quality unit has not implemented interim controls as a result of this assessment. 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 was not utilized until just recently during the inspection. Instead, the process relied on the paper printouts without having any second check that can ensure all print outs are maintained and reported.

OBSERVATION 8

Routine checking of automatic, mechanical and electronic equipment is not performed according to a written program designed to assure proper performance.

A) Periodic performance qualification is not adequately performed to ensure that (b) (4) of the (b) (4) automated visual inspection machines are performing as intended. Per MA/GOA/00016-4, performance verification is conducted "as expected under simulated real-world conditions". However, evaluation of the qualification documents revealed that periodic verification is conducted using operation qualification parameters, which include evaluating the physical condition of the machine, operational ranges, and safety features of the equipment. A logical explanation was not provided demonstrating that the current periodic performance process is suitable. During initial performance qualification, a defect kit was generated however, qualification conducted was inadequate. For example,

1. (b) (4) S-1248 qualification report (PQR-GS-1248-01) approved on May 26, 2016, failed to include assessment of rough surface, color, and shape variation. Specifically, for the round (b) (4) tablets, (b) (4) defect tablets were created and challenged on the equipment. A justification is not provided for the quantity selection for each defect or detailed instructions on how the defect kit will be generated. After challenge of the (b) (4) defect tablets, (b) (4) tablets were run on the equipment: for run (b), 165 tablets were

rejected and (b) (4) were passed as good tablets. The good tablets were not inspected to ensure that defects were adequately removed. The equipment was not challenged for printed tablets. The equipment is used to visually inspect printed tablet. Periodic qualification which consists of checking the equipment and safety features was conducted on June 3, 2022, under protocol EPQR-GS-1248-02/01. A logical explanation was not provided demonstrating how the current process simulates actual manufacturing conditions where tablets are inspected by the equipment and released for distribution.

Performance qualification for the following visual inspection machines were qualified as the example given above: (b) (4)

2. Specifically, (b) (4) S-1246, performance verification report PQR-GS-1246-02 was approved on December 6, 2022. The qualification conducted is inadequate as the quantity sample size for each defect is not selected based on historical trend data. Printing defect was not part of the evaluation. Additionally, evaluation of thickness and shape variation is inadequate. Furthermore, the inspected tablets which were considered free of defects were not physically inspected to ensure defected tablets are removed.

Prior to commercial batch visual inspection, the visual inspection machine is challenged with (b) (4) defect tablets. However, this evaluation fails to include defects containing rough surfaces, color, or shape variation. Additionally, production operators confirmed that only the majority defect rejection category is documented in the batch record. Examples of complaint investigation documented regarding foreign tablets include MA/MC/2019/0458, MA/MC/2021/0221, and MA/MC/2023/0036.

B) Installation, operation and performance qualification is not conducted after (b) (4) tablet testers

are moved around in (b) (4) Dosage-(. After initial qualification, the location of the testers not fixed and can move around the (b) (4) rooms. When the equipment is moved, installation, operation and performance qualification is not conducted. Calibration verification is performed on the equipment. A scientific justification illustrating that calibration conducted is equivalent to performance qualification and that the equipment will function as intended was not provided. On April 20, 2023, (b) (4) tablet tester S-1202 was moved from general compression IPQC area to (b) (4) area. Calibration was performed on the equipment on April 20, 2023 at 3:24PM. At 3:33PM the equipment was used to test (b) (4) batch (b) (4) (Domestic Market). Samples taken for in-process tests failed (b) (4) specifications: (b) (4) to (b) (4) results: (b) (4). Deviation investigation MA/DF/2023/0178 (interim) was initiated for the continuous out of specification. Per the investigation "(b) (4) shall be released after satisfactory finished product result."

C) Your firm operates (b) (4) portable non-viable particle monitoring equipment used to perform and generate test data for non-viable particle (NVP) count used in environmental monitoring/cleanroom qualification activities in class B, class C, and class D areas, (b) (4) leak test equipment used to perform container closure integrity testing and (b) (4) filter integrity test equipment in support of general and (b) (4) parenteral manufacturing operations. The qualification of these equipment have not been adequately performed, with at least one equipment in usage since the year 2011. As a result, the Quality Unit has not demonstrated the suitability of the equipment to perform assigned tasks and has not reviewed the electronic data since the implementation of these equipment.

OBSERVATION 9

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

Your Quality Unit has not been effective in carrying-out its duties of ensuring that drug products are

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manufactured in accordance with current good manufacturing practices (cGMP) to ensure safety, efficacy, purity, and overall quality of drug products manufactured at your firm. This is demonstrated by observed deficiencies in your Quality Unit responsibilities related to controls on review of production data, conducting investigations and assessments, and conducting activities per written procedures. The inspectional observations listed on this form document that your firm have not performed the adequate assessments/reviews to ensure the quality of drug products manufactured and tested at your firm. For Example, but not limited to:

Supervisory oversight over quality/production unit operations and laboratory electronic system and data is deficient. For example,

A)During the inspection, we observed multiple incident reports where HPLC and GC testing operations were interrupted during testing. At times, due to these interruptions and the investigation process, fresh sample preparations were prepared for testing, in which at least one incident fresh preparations were prepared for related substance testing even though the initial standard and sample solutions were within expiry time, without adequate justification. Your firm performed an assessment of chromatography system interruptions during the current inspection, Report No. ASR-LCE-01-23-01, titled "Report for the Retrospective Assessment and Investigation of Laboratory Incidents due to Communication Errors", dated May, 9, 2023, however this assessment does not consider laboratory incidents in categories such as "data processing error", "hardware error", "power failure", and "software malfunctioning", for which your firm has initiated approximately 200 such laboratory incidents for the since January 2022. As a result, your firm has not demonstrated understanding of the different types of communication errors and circumstances which may lead to interruptions.

B)The Quality Unit lacks adequate control over the issuance of worksheets and logbooks in support of manufacturing operations which are purported to be controlled by your quality unit under SOP No. MA/GQA/00047-5, titled "Issuance and Reconciliation Procedure for Log book, Register,

Worksheet and Loose form", effective date 03/29/2023. For example, during the inspection, we observed that visual inspection forms for vial and (b) (4) products are issued to your general parenteral production without adequate QA control, in that production personnel are responsible for storge, issuance, and reconciliation of these forms.

C)Your firm maintains and utilizes Chromeleon Enterprise 7.2 SR5, a networked chromatography data software system, which is used to perform HPLC and GC testing for raw material, in-process, and non-sterile and sterile finished drug product testing. Your current data is organized under a "FP" folder for finished product, with each sample set followed by the next sequentially, making data review inefficient during the inspection. There is no consideration for adequate data review procedures, which include an adequate organization of test data with respect to different products or different types of tests. This practice is a gap in your Data Integrity Program.

D)There is no adequate data integrity program in place to include a statistically sound comprehensive review of all electronic data by the Quality Assurance Unit for standalone and network systems, to ensure completeness, consistency, and accuracy of all chromatographic and non-chromatographic electronic data generated by the Quality Control Laboratory. Specifically, per your firm's procedure, only QC unit personnel perform review of electronic data, after which the Quality Unit completed a hardcopy checklist confirming QC review. No electronic data is reviewed by the Quality Assurance unit, whether batch to batch, or an established time frame.

E)In (b) (4) Dosage-((b) (4) testers are used to analyze in-process tablet samples for (b) (4) of compressed tablets. Between April 1 to 10, 2023, (b) (4) system contained the following instances that were not reviewed by quality to ensure that data generated and reported is accurate: Balance time out error, 201 times; and Magazine not in inner position error 28 times.

F)In-process batch results captured in the (b) (4) system for an entire batch are not reviewed by quality. This data captures the number of in-process tests started for the entire batch. Specifically, on January 11, 2023, the following measurement were initiated for (b) (4) (b) (4) mg batch (b) (4) : at (b) (4) LHS analysis was started (measurement not finished), another LHS sample was started at (b) (4) (measurement not finished), and at (b) (4) RHS measurement was started (measurement not finished). Measurements for LHS and RHS were captured at (b) (4) . In-process quality assurance and production personnel failed to provide a reason or explanation why the equipment failed to complete a measurement.

When a specific in-process timepoint analysis is completed, a report is generated, and the results are manually entered in the electronic Batch Manufacturing Record. The pdf of the in-process results generated is attached to the BMR, however the pdf is not reviewed by the reviewer.

OBSERVATION 10

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

A)The (b) (4) associated with (b) (4) Line (b) (4) were not sealed to the wall on May 1, 2023. Air could be felt moving from the Grade A side of the wall, where (b) (4) vials are loaded, to the Grade D technical area along the sides of the (b) (4) .

B)The (b) (4) for filling Line (b) (4) (General Facility) had a missing gasket and incompletely installed gaskets in the (b) (4) zone, which are intended to seal the (b) (4) zone from the Grade C room.

C)There was a gap in the cover intended to protect the vials from the Grade C environment after vial washing, before entering the (b) (4) .

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OBSERVATION 11

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

The aseptic filling rooms Lines (b) (4) in the (b) (4) parenteral facility are not designed to permit viewing of all aseptic operations via windows or alternatives, such as cameras. For example, (b) (4) loading cannot be appropriately viewed for any of these lines.

OBSERVATION 12

The procedures for the annual quality standards record evaluation are deficient in that they do not address a review of a representative number of approved and rejected batches.

The current process metric used to annually evaluate product quality consistency is inadequate. Annual product reviews are conducted using procedure MA/GOA/00015 which fails to address inter and intra batch variation. Section 7.7 indicates that a statistical evaluation (95% confidence interval) is evaluated for $\geq$(b) (4) batches manufactured within the APQR review year. Quality affirmed that if less than (b) (4) batches are manufactured consecutively for multiple years a statistical evaluation will not be conducted. Specifically, for solid dosages, a statistical evaluation is conducted for (b) (4) assay, and finished product weight and assay. Quality failed to provide a scientific justification why other parameters such are impurities are not evaluated. In addition, there is lack of knowledge regarding application of confidence interval to the analytical data during evaluation. For example:

(b) (4) mg 2022 review year, (b) (4) batches were manufactured. Confidence Interval (CI) was applied by comparing the mean average of the (b) (4) batches and whether the mean average is above 95%. A CI formula was not applied to the results to determine variability. Similar examples were noted with Annual product quality reviews for: (b) (4) mg, review year Oct 2021 to Nov 2022 (MA/PQR/ 2022/1160); and (b) (4) Tablets USP (b) (4) mg, review year Oct 2021 to Sep, 2022 (MA/PQR/ 2022/1051).

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OBSERVATION 13

Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not.

There is no routine identification of the microorganisms recovered from the purified water system to understand the microbial flora. Identification to a genus and species level occurred (b) (4) during 2022 and has not occurred in 2023.

There is no further investigation when Gram negative organisms that could produce biofilms were identified in the purified water systems, including: *Burkholderia kururiensis, Ralstonia pickettii, Acinetobacter baumannii,* and *Sphingomonas paucimobilis*. After initial identification, these organisms are considered normal microbial flora of the water systems and if similar colony morphology is observed again, there is no identification performed. Purified water is used in cleaning of equipment used in areas that manufacture non-sterile finished drugs, including (b) (4) preparations.

OBSERVATION 14

Procedures for the cleaning and maintenance of equipment are deficient regarding the removal or obliteration of the previous batch identification.

On May 1, 2023, during the inspectional walkthrough of General (b) (4) Dosage-(b), a non-dedicated (b) (4) container (ID: 803) used to store raw material was observed to contain whitish residue. Per the displayed status label, the container was cleaned on May 1, 2023, prior to the inspectional walkthrough with a clean hold time of (b) (4). The label shows that the equipment was verified clean by the production supervisor on May 1, 2023. Per production, raw materials are placed in a (b) (4) bag and then placed in the (b) (4) container which is then transferred to the manufacturing area. Traceability of potential products stored in the (b) (4) is unknown as a usage log is not kept. An assessment has not been

conducted evaluating the efficiency of cleaning and possible cross-contamination of raw materials.

OBSERVATION 15

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

Environmental monitoring samples were not counted accurately. On May 1, 2023, our review of plates from (b) (4) QC microbiology laboratory that had been counted by your analyst found the reported result to be less than the number of colonies on the plate. This was an interim reading. For example:

A) Point (b) (4), Aseptic area (b) (4) -4, settle plate in the Grade C area of (b) (4) parenteral manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was "Nil", but the plate was observed to have 2 CFU, which the analyst had marked with a marker upon reading.

B) Point (b) (4) Right Hand, personnel monitoring sample from Grade C area of (b) (4) parenteral manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was 1 CFU, but the plate was observed to have 2 CFU.

C) Point (b) (4) Chest, personnel monitoring sample from Grade C area of (b) (4) parenteral manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was 3 CFU, but the plate was observed to have 6 CFU.

D) Point (b) (4) Elbow, personnel monitoring sample from Grade C area of (b) (4) parenteral manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was 2 CFU, but the plate was observed to have 4 CFU.

E) Point (b) (4) Armpit, personnel monitoring sample from Grade C area of (b) (4) parenteral

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manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was 3 CFU, but the plate was observed to have 6 CFU.

F) Point (b) (4) Chest, personnel monitoring sample from Grade C area of (b) (4) parenteral manufacturing Line-(b), associated with aseptically filled batch (b) (4) of (b) (4) Injection on April 27, 2023. The reported result was 6 CFU, but the plate was observed to have 8 CFU.

OBSERVATION 16

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

Your firm has not performed analytical method validation of inhouse test 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 approximately (b) (4) materials, for approximately (b) (4) ((b) (4) approved, (b) (4) pending). The analytical test methods include but are not limited to (b) (4) by GC, Related substance by GC, Assay by GC, Assay by HPLC, and Related Substance by HPLC.

*DATES OF INSPECTION

5/01/2023(Mon), 5/02/2023(Tue), 5/03/2023(Wed), 5/04/2023(Thu), 5/05/2023(Fri), 5/08/2023(Mon), 5/09/2023(Tue), 5/10/2023(Wed), 5/11/2023(Thu), 5/12/2023(Fri)

X Rita K Kabaso
Investigator
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Date Signed: 05-12-2023 09:14:52

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Rita K Kabaso, Investigator Justin A Boyd, Investigator Arsen Karapetyan, Investigator - Dedicated Drug Cadre	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 05-12-2023 09:12:26	5/12/2023