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To,

25th April 2024

U.S Food and Drug Administration,
12420 Parklawn Drive, Room 2032
Rockville ,MD 20857
Reference:Warning letter number 320-24-03
FeI No:3012323885

Subject : Additional Response to warning letter dated October 20 th,2023 w

We are writing this to update on the various remediations that we have undertaken subsequent to the Warning Letter Number 320-24-03, which we received via email.
We had initially sought time during our response to the warning letter on the 20 thoctober 2023 to conduct a comprehensive evaluation of the entire original responses with the help of a qualified consultant . We are now working with the consultant who is assisting us in addressing all the concerns that have been raised by your good office.
We have taken our responsibility to address and rectify all the deficiencies noted by the FDA inspectors with the utmost seriousness. In light of our commitment to resolve these issues we have engaged and continue to maintain the advice of both external committed consultants and internal team members. We have listed the points raised and the response in annexures in this below file .
We would like to once again reiterate the following :

a) We have promptly withdrawn our registrations and canceled all listings at USFDA

b) We have no intentions of resuming manufacturing in the sterile section until all deficiencies have been effectively resolved. We assure our commitment to not circumvent the process.

c) With regards to the concern about our listed drug products containing EG/DEG,we would like to reiterate that we have not manufactured any of the products listed in the drug listing for USA ,also we have cancelled all the drug listings and we have no active drug listing in USA FDA..None of the products listed have been exported to USA .

We hope the response detailed below with annexures are able to address the concerns raised in the Warning Letter.

We humbly request your good office to review our response

Dr A.R Venkatesh

Global Pharma Healthcare Pvt Ltd

Warning Letter Number-320-24-03

Global Pharma response Page No-2 to 33(Exhibit Start page no 34 to 779-When you click on the Exhibits it will go directly to the page on which it is attached)

It has been reported in the warning letter from the FDA that tests were conducted on three different batches of intact bottles of Artificial Tears collected by the USFDA to detect the presence of Pseudomonas aeruginosa.

The test results indicated that three lots were found to be adulterated. Global Pharma has requested (b) (4) to determine the prevalence of the particular organism strain in India."

The report concludes that there is lack of genomic evidence substantiating the definitive origin of VIM-GES-CRPA from India. Analysis of CRPA isolates archived at (b) (4) from 2018 onwards indicates a rare co-occurrence of bla_{GES-9}, and bla_{VIM-80}, the genetic back ground of the presently sequenced Indian isolates carrying bla_{GES-9} differs from that of the USA OUT break isolates, this confirms the independent origin of bla_{GES-9} (of the outbreak strain)and further diversity and evolutionary trajectory of Indian and outbreak strains

Full report enclosed – Exhibit-01.

Consultant- We have appointed a consultant. Worked as a consultant with many Indian pharmaceutical companies.

(b) (4)

(b) (4)

(b) (4) .

(b) (4) data integrity, gap analysis, risk analysis, training, audits and technology transfer as consultant for remediation of all points mentioned in this warning letter.

(b) (4) **– Exhibit-02**

CGMP Violations

We reviewed your March 22, 2023, response to our Form FDA 483 in detail. During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. **Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).**

Inadequate Equipment and Processes

A. You lacked adequate scientific evidence that the aseptic filling machine used for manufacture of Artificial Tears was suitable for its intended use. Your qualification report was inadequate, including a lack of data on any batches filled as part of the qualification study. Further, all batches of Artificial Tears distributed to the U.S. market were manufactured using filling machine parameters that were outside the design specifications of the equipment.

Response- As per manufacturer recommendation we have attached filling change part for 15.0 ml and used for filling of 15.0 ml.

We have done impact assessment on all batches produced and no deviation in filling volume and it is well within the limits.

We have suspended production of artificial tears hence Performance qualification for 15.0ml is done using (b) (4) This performance qualification will be repeated with actual product (artificial tears) if this production gets started .

Design specification declaration is received from manufacture and the same copy is submitted.

Impact assessment for filling volume – **Exhibit-03**

Performance qualification - **Exhibit-04**

Design specification declaration from the manufacture **– exhibit-05**

B. You lacked validation of the processes used to manufacture your aseptically filled ArtificialTears

- You failed to validate methods that were intended to render your ophthalmic drug products sterile. Specifically, you lacked a study to show the (b) (4) performed on your Artificial Tears product using a (b) (4) can reliably achieve sterilization.

Response- Artificial Tears Production is suspended , hence Global pharma has prepared (b) (4) ml artificial tears at microbial department and Validation is performed using (b) (4) (b) (4) for artificial tears 10 mg/ml.

Validation report- **Exhibit-06**

Manufacturing process record for (b) (4) ml- **Exhibit- 07**

Destruction records remaining solution – **Exhibit-08**

- Your media fill program lacked assurance that aseptic processing operations are appropriately performed to prevent microbial contamination. Our inspection found thatyou failed to perform appropriate and sufficient media fills studies, for example:
  - Your media fills failed to adequately simulate the commercial aseptic manufacturing operation. Interventions were not simulated sufficiently or accurately. In addition, you have a manually intensive line with minimal barrier protection where the possibility of contamination is greater. Despite this, you filled (b) (4) - (b) (4) % of the production batch size during media fills.
  - Manufacturing lines used to produce the Artificial Tears and Artificial Eye Ointmentproducts were not qualified by three successful media fills.
  - You removed integral units (i.e., units with intact container-closure systems) from media fills without adequate justification and failed to incubate all integral units forthe full (b) (4) period.
  - The personnel responsible for visual inspection of media-filled units lacked appropriate training and qualification.

Response-

GPHC performed Media fill fo (b) (4) section

Batch number (b) (4)

Batch size (b) (4) liters (about (b) (4) bottles of 15 ml)

Date of media fill - (b) (4) start date 18/10/2023 finish date 19/10/2023

During media fill there are 17 routine interventions and 6 non routine interventions

Date of incubation- from (b) (4) to (b) (4) Incubated quantity – (b) (4) bottles in (b) (4) (containers)

Media fill result shows (b) (4) bottles are good and no bottle shows any growth. Date of media fill - (b) (4) start date 19/10/2023 finish date 20/10/2023

During media fill there are 17 routine interventions and 6 non routine interventions

Date of incubation- from (b) (4) to (b) (4) Incubated quantity – (b) (4) bottles in (b) (4) containers)

Media fill result shows (b) (4) bottles are good and no bottle shows any growth. Date of media fill - (b) (4) start date 20/10/2023 finish date 21/10/2023

During media fill there are 17 routine interventions and 6 non routine interventions

Date of incubation- from (b) (4) to (b) (4) Incubated quantity – (b) (4) bottles in (b) (4) containers) Training given to media fill team on 02/09/2023

Training given to Visual inspectors for media fill bottles on 25/08/2023

Media fill result shows (b) (4) bottles are good and no bottle shows any growth.

Training records, media fill reports and photos of visual inspection on bottles are enclosed.

Media fill frequency is (b) (4) since our production suspended as per our Local FDA instruction next media fill was not taken which is due on April 2024, Local FDA inspected our aseptic ophthalmic solution section and we are waiting for their approval , once they give approval , before starting production of any ophthalmic product we will perform media fill.

Deviation is raised for this occasion.

Media fill BMR – **Exhibit-09**
Incubation photo-**Exhibit-10**
Visual inspection of incubated vials-**Exhibit -11**
GPT reports- **Exhibit-12**
Media fill training- **Exhibit-13**
Aseptic behavior training- **Exhibit-14**
Gowning validation- **Exhibit-15**
EM monitoring -**Exhibit-16**
Inspection training-**Exhibit-17**
Deviation-**Exhibit-18**
Media fill comparative report- **Exhibit-19**

C. You lacked meaningful airflow pattern studies for your aseptic processing lines. The studies were not performed under dynamic conditions and lacked simulation of interventions and

other routine activities that occur during aseptic manufacturing operations.

Response- Air flow pattern smoke study was performed with dynamic condition

(dummy manufacturing, (b) (4) and filling sealing).

Frequency to perform air flow pattern is (b) (4)

As per our local FDA instruction we suspended our ophthalmic solution section production and the plant is non-operational, we have not done revalidation of flow pattern (smoke study) in this section

Deviation is raised for this activity. flow pattern study will be conducted after local FDA approval before starting production.

Smoke study report & video - **Exhibit-20**

Deviation for delay of re-flow pattern study-**Exhibit-21**

D. Your firm also shipped an ointment product to the United States that was manufactured using a (b) (4) sterilization process. You failed to ensure the (b) (4) process employedby your contractor to sterilize your Artificial Eye Ointment was validated.

Response- Global Pharma has manufactured only one batch of sterile ophthalmic eye ointment B.NO. H-29 and discontinued sterile ophthalmic ointment section to produce sterile ophthalmic products and informed to USFDA inspector during inspection. Hence global pharma has not carried out validation for sterile (b) (4) process.

Your response is inadequate for reasons that include, but are not limited to, the following:

- You lack details of your internal investigation into the product contamination. Your investigation is not comprehensive, including but not limited to, a lack of descriptions of the activities performed and root cause analysis. You also lack details on sampling and laboratory methods used for environmental and other tests.

- There is a lack of detail relating to future dynamic airflow pattern studies; heating, ventilation, and air conditioning (HVAC) system qualification; or media fill procedural revisions.

- You also fail to include a commitment to validate the (b) (4) sterilization processand sterility test methods for the Artificial Eye Ointment products.

Response-

Response- Global Pharma has manufactured only one batch sterile ophthalmic eye ointment B.NO. H-29 and discontinued sterile ophthalmic ointment section to produce sterile ophthalmic products and informed to USFDA inspector during inspection. Hence

global pharma has not carried out validation for sterile (b) (4) process, media fill and airflow pattern in dynamic condition (b) (4) required for sterile ophthalmic production.

Lack of Container Closure Integrity

You lacked evidence of reliable container closure integrity for your multi-use ophthalmic products that purport to be sterile. While visual inspections revealed leakers during batch manufacture, there was no assurance that your visual inspection procedure was adequate.

Your product distributors received complaints of leaking Artificial Tears and Artificial Eye Ointment units. FDA's laboratory performed container closure integrity testing of Artificial Eye Ointment, batch H29, manufactured at your facility. FDA tested 20 units, and 1 unit was found to allow microbiological ingress, which further confirmed that your container-closure system lacks integrity and is insufficient for maintaining sterility. Notably, batch H29 was also found to be non-sterile through FDA testing.

All sterile drugs must be packaged using a container-closure system that protects product integrity for the duration of its shelf-life. Maintenance of product integrity throughout stresses of its manufacture, storage, distribution, and consumer use is critical to product quality and safety. Loss of container-closure integrity is a direct cause of non-sterility of medicines.

In your response, you state you will perform container-closure integrity testing using a dye ingress method for your Artificial Tears product and a comprehensive sterility assessment. Your response is inadequate because your container-closure integrity testing protocol does not extend to Artificial Eye Ointment. In addition, you do not sufficiently address the sensitivity of your dye ingress method. The sensitivity of the method to be employed for your study is unclear, and you do not indicate whether it is capable of correlating with detection of bacteria comparable in size to *Pseudomonas aeruginosa*. Furthermore, your response does not include details on the comprehensive sterility assessment.

Response-

Global Pharma has manufactured only one batch sterile ophthalmic eye ointment B.NO. H-29 and discontinued sterile ophthalmic ointment section to produce sterile ophthalmic products and informed to USFDA inspector during inspection.

Eye ointment formulation contains no aqueous phase and contain (b) (4) phase only,

(b) (4) will contain or reduce bacterial growth

Leak test is done by (b) (4) test method using (b) (4) dye at the initial stage of production if leak test passes then only filling will be continued and (b) (4) leak test will be performed if dye is going inside tube then the filling tube during that (b) (4) is rejected.

Sterile ophthalmic ointment section is discontinued for production of ophthalmic ointment no further validation study is initiated.

Inadequate Formulation for Artificial Tears and Artificial Eye Ointment

You manufactured multi-dose, over-the-counter (OTC) ophthalmic drug products for the product owners, EzriCare LLC, and Delsam Pharma LLC. These products lacked antimicrobial properties to preserve the formulation. Significantly, your firm also marketed this multi-dose product without performing antimicrobial effectiveness studies. It is essential that multi-dose ophthalmic drug products contain one or more suitable substances that will preserve the product and minimize the hazard of injury resulting from incidental contamination during use.

In your response, you state that antimicrobial effectiveness testing (AET) will be initiated for your Artificial Tears product, and you will use these studies to determine if a suitable preservative will be added to the formulation. Your response is inadequate because you do not explain why you failed to perform AET studies prior to launch of your drug product, and how you will correct such fundamental flaws in your product development program. You also make no commitment to conduct AET for the Artificial Eye Ointment formulation. In addition, although your protocol indicates that you follow the United States Pharmacopeia (USP), the acceptance criteria in the Artificial Tears protocol is less stringent and not in alignment with USP
<51> *Antimicrobial Effectiveness Testing*.

Response-
AET test was not performed initially before recall.
Formula was given by the product owner.
Artificial tears contain(b) (4) which is added as one of the excipients ,this acts as (b) (4)
Artificial eye ointment, contains(b) (4) phase (b) (4) will act to prevent or reduce microbial growth.

SOP GPHC-SOP-SFU-EEN-028-00 is implemented which contains check list for new product production from Research and development department. - **Exhibit -22**
Inadequate Gowning Practices and Operator Qualification

Cleanroom operators lacked adequate gowning and qualification for performing aseptic operations. Your deficient practices and procedures placed products at high risk for contamination, for example:

A. A gowning demonstration revealed that cleanroom operators do not don sterile goggles and therefore have exposed skin around their eyes during aseptic operations.

Response-

Global initiated and implemented SOP- procedure for personnel gowning qualification in (b) (4) section -GPHC-SOP-SFU-EEN-025-00 - **Exhibit-23**

Photos for gowning with goggles were taken during SOP preparation without production due to suspension of production activity by local FDA.

Gowning with goggles procedure is explained with photos- **Exhibit- 24**

B. Cleanroom garments were not suitable for their intended use. For example, garments indicated to be clean were observed to be stained, worn out, and stored improperly. In addition, your firm re-used cleanroom garments for an unspecified number of times without tracking or validation.
Response-

Washing and sterilization of aseptic area garments SOP is revised -SOP-GPHC-SOP-SFU-FFS-003- Garment usage cycle is marked in garment itself and determined number of cycles used. **Exhibit-25**

Log is also used for garments washing

C. You lacked written procedures and a training program on proper aseptic behavior and gowning for cleanroom operators. You also lacked evidence that all cleanroom operators arequalified through participation in a media fill, and the microbiological limit set in your gowning validation procedure is unsuitable for aseptic operations.
Response-

Aseptic behavior SOP- GPHC-SOP-SFU-EEN-027-00 implemented and training is given to all personnel involved in aseptic area. – **Exhibit-26**

Training given to all clean room operator participated in media fill- **Exhibit- 27**

Microbial limit is fixed as per USP (1116)

D. You lacked written procedures and a training program on proper aseptic behavior and gowning for cleanroom operators. You also lacked evidence that all cleanroom operators were qualified through participation in a media fill and justification for the microbiological limits used in your aseptic processing operator gowning qualification procedure (i.e., no more than (NMT (b) (4) colony forming units (cfu) for each gowning location). You also lacked a commitment to systematically review staff qualifications and competencies throughout your operation, including but not limited to, ensuring an effective CGMP training program.
Response -

Global pharma implemented Aseptic behavior SOP- GPHC-SOP-SFU-EEN-027-00 and

training is given to all personnel involved in aseptic area.

Training given to all clean room operator participated in media fill-

Commitment as a declaration is attached for aseptic operator staff to maintain effective CGMP is enclosed. **- Exhibit-28**

In your response, you state that gowning qualification will be performed through media fills, and an in-house study will evaluate the impact of repeated sterilization cycles on

cleanroom garmentsto establish an acceptable number of sterilization cycles. Your response is inadequate. You lack a comprehensive review of all aspects of personnel gowning, the qualification program, aseptic technique, cleanroom behavior, and an examination of the role of people as a contamination hazard in your processes. To further illustrate, you continue to lack substantive actions to implement sterile goggles, enhance practices to prevent sterile gown contamination, gowning qualification criteria (e.g., sampling requirements, location descriptions, acceptance limits with justifications), and many other basic elements of a compliant sterile facility. Your response also fails to address how your inadequate gowning practices impacted your sterile drug products.
See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download.

In response to this letter, provide the following:

- Comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
- All human interactions within the ISO 5 area
- Equipment placement and ergonomics
- Air quality in the ISO 5 area and surrounding room
- Facility layout
- Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)

Response-

Comprehensive risk assessment of all contamination hazards with respect to Global pharma facility aseptic processes, equipment, and facilities is done - **Exhibit- 29**

- A detailed remediation plan with timelines to address the findings of the independent contamination hazards risk assessment. Describe specific tangible improvements to be madeto aseptic processing operation design and control at your facility. Explain how your corrective action and preventive action (CAPA) will robustly remediate your deficient sterilemanufacturing operation. Also describe your plans for qualification and validation of your comprehensively remediated facility, processes and equipment.

Response –

Detailed capa plan is done and enclosed – **Exhibit- 30**

- A remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a more data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing

(including both production and packaging) operations meet appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.

Response-

Remediation Plan

	All units manufactured are passed the quality unit test
Raw material receiving	Last three years sodium carboxy methyl cellulose eye drops are manufactured and the batch numbers are (b) (4) All raw materials and excipients and primary packing materials are purchased from approved vendor and analyzed before using the materials in the manufacturing process. Environmental monitoring activities done during raw materials and primary packing materials receiving.

Sampling	Sampling activity is done as per the SOP No: GPHC-SOP-SFU-STR-006, All the API and Excipients are sampled under LAF ISO class 5.
Dispensing	Dispensing activity is done as per the SOP No: GPHC-SOP-SFU-STR-004, All the API and Excipients are dispensed under LAF ISO class 5.
Unit preparation (b) (4)	1. Unit preparation (b) (4) validation done, 2. Load pattern done for product contact parts (bottle bowl, inner bowl and outer cap bowl, (b) (4) non-contact parts (Forceps, (b) (4) mugs) & miscellaneous (clean room mops, disinfectant and lint free cloth) 3. (b) (4) placed or (b) (4) tape is stick and colour change observed for sterilization. 4. Unit preparation (b) (4) validated with load pattern. (b) (4) utilities like (b) (4) line are qualified. Microbiological indicator reports and records are verified.

Manufacturing	Manufacturing area having separate Entry and Exit. Manufacturing vessels made up of (b) (4) and Transfer lines are made up of (b) (4) It prevents the human interventions control the contamination of the products. (b) (4) reports and (b) (4) reports attached with BMR,
(b) (4)	(b) (4) system (b) (4) using (b) (4) holder is placed in ISO 5 (under LAF) and background area is ISO 6. 1 (b) (4) performed under LAF ISO 5 and surrounding area ISO 6 2. Laminar operation and cleaning sop available 3. Trained production chemist perform the activity under IPQA supervisor. 4. Laminar air flow qualified 5. AHU Qualification done periodically 6. Area Qualification done periodically. 7. Aseptic Behavior SOP is prepared, training given. (b) (4) reports, (b) (4) reports attached with BMR.
Filling	Filling area is placed in ISO 5 (under LAF) and background area is ISO 6. 1. Filling performed under LAF ISO 5 and surrounding area ISO 6 2. Laminar operation and cleaning sop available 3. Trained production chemist perform the activity under IPQA supervisor. 4. Laminar air flow qualified

	5. AHU Qualification done periodically 6. Area Qualification done periodically 7. Aseptic Behavior SOP is prepared, training given. (b) (4) reports, Post (b) (4) reports attached with BMR.

Sterility	All batches are checked for sterility testing as per sterility validation procedure
EM / PM	All batches Environmental monitoring and Personnel monitoring done during batch manufacturing, and reports are attached with the batch manufacturing records and batch packing records.
Labelling and Packing	Packing area separated from filling area, Secondary packing materials stored in secondary packing storage area.
Batch release procedure	

Production review check list	A. Ensure that the product is manufactured at each step as per approved Instructions in Batch Manufacturing Record and documented with all data as and when the activities are carried out. B. Ensure that all supporting documents attached with BMR like • Raw material/Packing material dispensing records • Cleaning Records • Environmental Monitoring / Personnel Monitoring reports • Line Clearances, (b) (4) reports) • In-process analytical reports, (Bio-burden test results) • Packing records • Specimen labels • Reconciliation • Finished product analytical report and Sterility test reports • If any other supporting documents as applicable are attached to BMR C. Ensure that all the operations have been signed by the doer and Verified by the next senior person. . Ensure that process deviations, equipment failures, power failures if any have been documented with the details of corrective and preventive action and implemented as recommended. . Ensure that changes if any have been adequately documented and approved before implementation and any validation requirement has been fulfilled as recommended. F. Ensure that reconciliation details of yield, labels are documented.
QA review check list	➢ Review the completed BMR as per Checklist with a critical attention to ensure that no potential evidences are suspected that could alter the quality, safety and efficacy of the product.

	➢ Review the packing and labelling records as per Checklist to ensure that they have been packaged and labelled as per the specific requirement of Customer if applicable or as per approved Marketing authorization requirements. ➢ Review the complete analytical raw data and supporting chromatograms to ensure that all tests have been done as per approved specification and test procedures. ➢ Review and ensure the validated status of analytical methods followed and the calibration status of analytical equipment's used for analysis. ➢ Ensure that the product meets the requirements of Customer by comparing the Purchase order and other in-house specifications. ➢ Review the completed stability data of the product and ongoing stability to ensure the expiry date on the label is well supported and justified by the analytical data. ➢ Verify any other documents as deemed necessary to ensure the quality, safety and efficacy of the product.
QC review check list	• Verify and ensure that sampling is performed as per approved procedure and submitted for analysis as per approved procedure. • Verify and ensure that the all tests have been carried out as per approved test protocols and recorded in the specified format. • Verify and ensure that analyst signature with date is available in all tests. • Verify and ensure that references are mentioned for the equipment's used for the analysis. • Verify and ensure that references are mentioned for all the standards and reagents used for the analysis. • Verify and ensure the calibration status of all equipment's used for the analysis and they are calibrated as per approved SOP. • Verify and ensure that system suitability checks and other pre-requisites are followed as recommended in the procedure before carrying out the main analysis. • Verify and ensure the working standards and other reagents used for the analysis are current and valid.

	• Verify and ensure all weighments are supported by gross weight, tare weight and net weight and the dilutions wherever applicable are traceable with printouts. • Verify and ensure the calculations are correct and the results are reported to the decimal level as approved in SOP for Data entry. • Verify and ensure the control sample is retained as per SOP and recorded in Control sample register. • Verify and ensure that all supporting chromatograms are reviewed and signed by the analyst. • Verify and ensure that if any OOS is reported, it has been thoroughly investigated as per SOP and resolved.
Robust procedure	
	All batches are manufactured as per validation procedure like Manufacturing (b) (4) and filling are followed validated procedure. Sterility and Bio-burden limits are checked before batch released to the commercial market.
Management Review Meeting	
	All incidents, deviations, market complaints, Out of Specifications and Out of Trend are discussed and make corrective and preventive actions. If any emergency situations immediately arrange management review meeting, and make urgent corrective actions.

		interventions control the contamination of the products	and checked for (b) (4) Bio- Burden limit.

6	(b) (4) Area	(b) (4) system (b) (4) using (b) (4) holder is placed in ISO 5 (under LAF) and background area is ISO 6. 1 (b) (4) performed under LAF ISO 5 and surrounding area ISO 6 2.Laminar operation and cleaning sop available 3.Trained production chemist perform the activity under IPQA supervisor. 4. Laminar air flow qualified 5.AHU Qualification done periodically 6.Area Qualification done	All SOPs are reviewed before validity. Training will be done periodically. Preventive maintenance for (b) (4) vessel (SOP No: GPHC-SFU-SOP- ENG-GEN-007), Validation, Qualification and Calibration should be done as per schedule. Aseptic Behavior SOP is prepared (SOP No: GPHC-SOP- SFU-EEN-027-00), Training is given periodically.
7	Filling Area	(b) (4) nd Filling area is placed in ISO 5 (under LAF) and background area is ISO 6. 1. Filling performed under LAF ISO 5 and surrounding area ISO 6 2. Laminar operation and cleaning sop available3.Trained production chemist perform the activity under IPQA supervisor.4. Laminar air flow qualified 5. AHU Qualification done periodically	All SOP's are reviewed before validity. Training will be done periodically. Preventive maintenance of Filling (SOP No: GPHC-SFU-SOP-ENG-GEN- 008), Validation, Qualification and Calibration should be done as per schedule. Aseptic Behavior SOP is prepared (SOP No: GPHC-SOP-SFU-EEN-027- 00), Training is given periodically.

8	Labelling and Packing Area	Packing area separated from filling area, Secondary packing materials stored in secondary packing storage area.	Secondary packing area separated from filling area and product contamination possibility is less for finished product. Preventive maintenance of Labelling machine done as per schedule.

- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

Response –

Capa plan for routine, vigilant operations management oversight of facility and equipments. **Exhibit- 31**

- Your plan to ensure that inspection and other quality control methods for container-closure systems including, but not limited to, opaque bottles and ointment tubes, can robustly detect integrity breaches.

Response-

Global pharma will perform on line leak test of bottles after (b) (4) before (b) (4) visually and also using leak test apparatus using (b) (4) indicator by applying (b) (4) if any leak dye will go inside bottle, frequency of the leak test by this (b) (4) method will be performed (b) (4)

If leak is found then particular hour from last leak test (b) (4) illed bottes are rejected.

Sop is in place to operate the leak test apparatus GPHC-SOP-PRD-IPC-002-03

Leak test activity is recorded in Batch packing record and log is maintained -

- A comprehensive, independent assessment of the qualifications and competencies of staff to conduct their job duties throughout your operations, including:
- a system that ensures each staff member receives training to enable them to properlyperform each of their job duties in advance of performing job tasks
- a review of your training curriculum, including courses, timing, frequency, and training effectiveness
- supervision to determine ongoing adherence of staff to procedures and proper practices

- provisions for retraining in response to deficient performance or, when appropriate, re-evaluating whether the individual has the appropriate qualifications and expertise (training, education, skills) for the type and complexity of their assigned work
- training of supervisors and managers in CGMPs

Response –
Training SOP GPHC-SOP-SFU-QAD-002-00 is used to train all staff members is sterile section to do their operations- **Exhibit-32**
Training calendar is prepared with training topics with schedule- **Exhibit-33**
After training evaluation is done by written examination if required re-training will be given on the same time to answer the questions.
Training matrix is prepared for all staff in sterile section- **Exhibit-34**

2.Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and 211.84(d)(2)).

You did not ensure that incoming lots of active pharmaceutical ingredient (API) and packaging materials were suitable for use in manufacturing.

Response- Global pharma is testing the incoming Lots of active pharmaceuticals ingredients (API) and packing material as per

Specification and test method (API)-Specification and test method (packing material)- and after QC approval for suitable only used for manufacturing

Your firm released API for use in drug manufacturing based on a component supplier's certificate of analysis (COA), although you neither established the reliability of the analysis through appropriate validation nor performed identity testing. Notably, examples included two lots of carboxy methyl cellulose sodium API used to manufacture Artificial Tears batches distributed to the U.S. market.

Response-
Since only TWO lots of carboxy methyl cellulose sodium is received till date, - SOP for raw material testing and release GPHC-SOP-QC-018-03 is revised and included the identification test and all incoming materials shall be tested and released as per this SOP.
Raw material testing and release SOP- GPHC-SOP-QC-018-03- **Exhibit- 35**
Specification and test method for carboxy methyl cellulose sodium- **Exhibit-36.**

You also failed to adequately test primary packaging materials, including caps and plugs, used in the Artificial Tears container-closure system. For example, between 2019 and 2022, you received (b) (4) shipments of caps and plugs supplied as sterile from a vendor and released them for use based on the supplier's COA without adequate testing.

Response-

Manufacturer of primary packing material sent bottle, inner plug and outer cap separately, stores personnel instead of preparing One GRN (Goods receipt note) he has prepared separate GRN.

All bottles, inner plug and outer caps were tested for sterility.

Primary packing material standard testing method is revised

(b) (4)container- PM//STP/HDB/004-01- **Exhibit-37**

Inner plug- PM/STP/HDP/005-01- **Exhibit-38**

Cap - PM/STP/HDC/006-01- **Exhibit-39**

And all incoming bottles, cap and plugs were tested and reports are enclosed- **Exhibit-40**

Identity testing for each component lot used in drug product manufacturing is required, and you may only rely on the COA for other component attributes if you validate the supplier's test results to ensure their reliability at appropriate intervals.

Response- Each lot is completely tested as per revised spec and test method (bottle, inner plug & cap)

A drug product produced by aseptic processing can become contaminated not only by unacceptable practices in the manufacturing operation, but also due to the use of one or moredefective components, containers, or closures.

Your response is inadequate for reasons that include, but are not limited to, the following:

- You fail to indicate that all existing and new suppliers will be qualified.

Response –

All existing vendor re-qualification and new vendor qualification is done as per

SOP – Procedure for vendor evaluation and approval – GPHC-SOP-QAD-012-06

Exhibit- 41

- It lacks details on procedural revisions to be made, including how you intend to establish and maintain assurance of the reliability of your supplier's COA.

Response-

Global pharma discontinued usage of supplier coa and approved incoming material without testing. All incoming material shall be tested and approved

Specification and test procedure are implemented for incoming Raw material and packing material

- It also lacks details on your retrospective testing, including the scope of materials to be tested, sampling and testing methods, and how you intend to ensure that incoming materials are suitable for their intended use.

  Response-

  All lots of incoming material shall be sampled tested and released as per

  Receipt, sampling, testing and release SOP – GPHC-SOP-QCD-018-04- **Exhibit-42**

  And packing material as per SOP- GPHC-SOP-QCD-061-03 **-Exhibit-43**

- It also lacks details on your retrospective testing, including the scope of materials to be tested, sampling and testing methods, and how you intend to ensure that incoming materials are suitable for their intended use.

  We also note that you listed drug products with FDA as being manufactured at your facility and intended for distribution in the United States, including paracetamol syrup, clotrimazole 1%, andDiaprene Children Maximum Topical Creams, that contain components with a high risk of diethylene glycol (DEG) or ethylene glycol (EG) contamination, such as glycerin and propylene glycol. The use of ingredients contaminated with DEG or EG has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document *Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol* to help you meet the CGMP requirements when manufacturing drugs containing ingredients at high-risk for DEG or EG contamination ("high-risk drug components"), at https://www.fda.gov/media/167974/download.

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

- The chemical and microbiological quality control specifications you use to test and releaseeach incoming lot of components for use in manufacturing.

- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure (SOP) that describes this COA validation program.

- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture.

- A commitment to provide DEG and EG test results, no later than 30 calendar days from the date of this letter, from testing retains for all lots of high-risk drug components used in the manufacture of drug products. Alternatively, if a retain of a component lot is unavailable, perform retain sample testing of all potentially affected finished drug product batches for the presence of DEG and EG.

- A full risk assessment for drug products that are within expiry which contain any ingredient at risk for DEG or EG contamination (including but not limited to glycerin). Take prompt and appropriate actions to determine the safety of all lots of the component(s) and any related drug product that could contain DEG or EG, including customer notifications and product recalls for any contaminated lots. Identify additional appropriate corrective actions and preventive actions that secure supply chains in the future including, but not limited to, ensuring that all incoming raw material lots are from fully qualified manufacturers and free from unsafe impurities. Detail these actions in your response to this letter.

- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic revalidation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot. In the case of glycerin, propylene glycol, and certain additional high-risk components, we note that this includes the performance of parts A, B, and C of the USP monograph.

Response-

Response- Global pharma does not intend to do manufacturing of the listed product registered in OTC and has withdrawn all OTC registration on 23-feb-2023

List is enclosed- **Exhibit-44**

3.Your firm failed to establish a system for monitoring environmental conditions in aseptic processing areas and an adequate system for cleaning and disinfecting the room to produce aseptic conditions (21 CFR 211.42(c)(10)(iv) and 211.42(c)(10)(v)).

Sterilization and Cleaning

You failed to adequately sterilize and clean your equipment used for drug product manufacturing, for example:

A. You failed to ensure that all equipment with direct product contact was sterilized. During the inspection, you were not able to provide records showing sterilization of product contact equipment on the "(b) (4) Line," including the filling (b) (4) tubing, and (b) (4) bowls. Review of sterilization records revealed that you only documented that

garments and tools were sterilized. You also lacked written procedures describing sterilization of the manufacturing equipment.

Response-

During inspection certain documentation failure is pointed out and they have been corrected in revised SOP

SOP is revised and implemented for operation and cleaning of filling machine SOP- GPHC-SOP-SFU-EEN-013-02 for cleaning and sterilization of product contact parts in unit preparation(b) (4) **Exhibit-45**

B. You failed to adequately clean the equipment used to aseptically produce Artificial Tears. Significantly, our investigators observed visible grease-like residue on product contact surfaces of your filling machine after they had been cleaned.

You also lacked written procedures and other documentation describing cleaning of the manufacturing equipment.

Response-

All dismantling parts of the filling machine like filling(b) (4)bowl etc., are removed(b) (4) (b) (4)sterilized , SOP is revised and implemented for operation and cleaning of filling machine SOP- GPHC-SOP-SFU-EEN-013-02 for cleaning and sterilization of product contact parts in (b) (4) before production it will be attached in instrument.

Other non-removal equipment's are cleaned and sterilized using(b) (4) systems as per SOP – GPHC-SOP-SFU-EEN-005-001. **Exhibit- 46**

C. You lacked cleaning validation studies for the shared manufacturing equipment on the "(b) (4) (b) (4) Line."

Inadequately cleaned and maintained equipment can lead to cross-contamination and poorly drug products.

Your response is inadequate for reasons that include, but are not limited to, the following:

- You fail to provide cleaning procedures or cleaning validation protocols. In addition, no commitment is made to comprehensively evaluate the suitability of your filling machine and other equipment for the manufacture of sterile drug products.

Response-

Cleaning validation protocol for carboxy methyl cellulose sodium is enclosed- **Exhibit-47**

Worst case product selection for cleaning validation matrix is also prepared and enclosed- **Exhibit- 48**

No production and it is suspended by Local FDA if production gets started cleaning validation will be performed and report will be prepared,

- You fail to provide details of your proposed testing of retain samples.
  Response-

  Only one batch is produced after (b) (4) and swab results are enclosed for (b) (4) contamination (previous product)- **Exhibit- 49**

  Other batches produced are sodium carboxy methyl cellulose (same product- previous product is sodium carboxy methyl cellulose only)

- You fail to provide explanations for the conflicting information provided to FDA investigators during the inspection. For example, investigators were initially told that (b) (4) bowls on the filling line were not cleaned or sterilized. These statements werelater retracted; however, you were unable to provide sufficient information to support claims that (b) (4) bowls were cleaned and sterilized.
  Response-

  We have cleaned the and sterilized the bowl which attaches to the filling line but it is recorded as tools in sterilization log.

  Cleaning and sterilization procedure is implemented in the SOP and revised this sop

  - SOP- GPHC-SOP-SFU-EEN-013-02 for cleaning and sterilization of product contact parts in unit preparation (b) (4) (bowls and filling (b) (4) etc.)- **Exhibit-50**

  Monitoring Environmental Conditions

  Your environmental monitoring (EM) program (including personnel monitoring (PM)) was inadequate for classified areas used to produce sterile ophthalmic drug products. For example, non-viable air samples were not collected inside the Grade A filling zone or the Grade B surrounding areas during active filling, you lacked studies to demonstrate that residual disinfectant would not interfere with the swabs used for viable surface monitoring, and you lacked identification data on isolates recovered from EM and PM sampling.

  Response-

  Global has implemented IOT sensor which will measure non-viable particle count in filling and (b) (4) area GRADE A and grade B

  (b) (4) which is used as residual disinfectant neutralizer and validation is done and reports are enclosed- **Exhibit-51**

  SOP for Identification of isolates is implemented –GPHC-SOP-MBD-053-00-**Exhibit-52**

  Isolate identification report- **Exhibit- 53**

  Vigilant and responsive environmental and personnel monitoring programs should be designed to provide meaningful information on the state of control of your aseptic processing environment. Operations that include highly manually intensive aseptic activities warrant a moreextensive environmental and personnel monitoring program including, but not limited to, heightened emphasis on well-timed sampling to appropriately monitor batch manufacturing

conditions.

In your response, you mention a limited number of environmental samples taken in January 2023 were sent to a third-party laboratory and these samples did not reveal *Pseudomonas aeruginosa* in your environment. This response is inadequate. The last batches of Artificial Tears shipped to the United States had been manufactured many months before (in April 2022) your limited sampling was conducted, according to records provided by your firm. Environmental sampling that occurs several months after batch manufacture is of little temporal significance. There is also minimal scientific value in testing sterile drug manufacturing areas solely for the presence of a single microbial species. You also had batch retain samples tested by a third-party laboratory and you reported in your response that these samples did not fail sterility testing. However, it is not unexpected that sterility testing of retains of otherwise contaminated batches may pass sterility testing because of the non-uniform nature of microbiological contamination. As noted above, many of your firm's batches were found to be non-sterile upon FDA testing and were associated with grave adverse events.

Response-

SOP for Identification of isolates is implemented –GPHC-SOP-MBD-053-00 and Isolates were identified and tested at external laboratory report is enclosed and exhibited as 53

In response to this letter, provide the following:

- A comprehensive, independent assessment of the design and control of your firm's manufacturing operations, with a detailed and thorough review of all microbiologicalhazards.

Response-

A comprehensive, independent assessment of the design and control of manufacturing operations, with a detailed and thorough review of all microbiologicalhazards is done – **Exhibit- 54**

- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices and encompass each piece of manufacturing equipment used to manufacture more than one product.

Response –

A comprehensive, independent retrospective assessment of cleaning of manufacturing process more than one product is done – **Exhibit- 55**

- A CAPA plan, based on the retrospective assessment of your cleaning and disinfection program, that includes appropriate remediation's to your cleaning and disinfection processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning and disinfection. Describe improvements to your cleaning and disinfection program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning and disinfection execution for all products and equipment; and all other needed remediation's.

Response-

A CAPA plan, based on the retrospective assessment of cleaning and disinfection program, that includes appropriate remediation's to cleaning and disinfection processes and practices is enclosed-**Exhibit-56**

- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include, but not be limited to, identification and evaluation of all worst-case:
- Drugs with higher toxicities
- Drugs with higher drug potencies
- Drugs of lower solubility in their cleaning solvents
- Drugs with characteristics that make them difficult to clean
- Swabbing locations for areas that are most difficult to clean
- Maximum hold times before cleaning

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

Response-

Worst case scenario for all the eye drops produced is done ,based on this product is selected and cleaning validation will be performed, if the new product falls within this limit, we will follow same washing procedure and swab places to take swab for analysis-
Worst case scenario chart- **Exhibit- 57**

- A summary of updated SOPs that ensure an appropriate program is in place for verificationand validation of cleaning procedures for products, processes, and equipment.

Response-

Updated SOP list is enclosed- **Exhibit-58**

- A comprehensive, independent review of your personnel and environmental monitoring programs including, but not limited to, a plan to fully remediate these programs. For example, describe changes to equipment, procedures, and practices that will ensure meaningful ongoing data is collected to promptly detect and respond to emerging risks in your classified areas. Provide an updated timeline for implementation of your program, including a summary of the CAPA steps you will be undertaking to ensure effective remediation.

Response -

A comprehensive, independent review of personnel and environmental monitoring

programs- **Exhibit-59**

1. Your firm failed to establish the accuracy, sensitivity, specificity, and reproducibility of its test methods, and you also failed to conduct appropriate laboratory testing to determine whether each batch of drug product purporting to be sterile conforms to such requirements (21 CFR 211.165(e) and 211.167(a)).

Your firm lacked adequate sterility testing, for example:

A. You failed to show that your sterility test method was suitable to detect microorganisms in your ophthalmic drug products.

Method suitability testing ensures the method can reliably determine the presence of microbial growth in the product. Method validation and verification is necessary to support reliable determinations of identity, strength, quality, purity, and potency of drugs. Without evaluating the validity of methods, you lack the basic assurance that the data provided to customers was an accurate reflection of pharmaceutical product quality and safety.

Response-

sterility method is validated and shown suitable to detect microorganism growth in the product.

sterility method is validated for eye drops and report is enclosed - **Exhibit- 60**

sterility method is validated for eye ointment and report is enclosed - **Exhibit-61** You lacked growth promotion tests of the media used for media fills and personnelmonitoring.

The validity of your microbiological testing cannot be ensured without appropriate testing ofmedia.

In your response, you make commitments to review your sterility testing and other analytical method validations, initiate sterility method verification, and revise your media preparation procedures. Your response is inadequate because you fail to provide revised procedures and you do not address your failure to perform adequate sterility testing on your distributed finished drugproducts.

Response-

Global has initiated three consecutive media fill and growth promotion test has been done on media used for media fill and personnel monitoring

GPT test report on media used for media fill and personnel monitoring- **Exhibit- 62**

Global has performed sterility test of retained sample and reports are enclosed- **Exhibit- 63**

In response to this letter, provide the following:

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

Response-

A comprehensive, independent assessment of laboratory practices, procedures, methods, equipment, documentation, and analyst competencies is done and evaluated the effectiveness of laboratory system. **- Exhibit- 64**

- A detailed risk assessment addressing the hazards posed by distributing contaminated drug products.

Response-

Global pharma is contract manufacturer for Artificial tears eye drops and ointment, if we identify any potential contamination at our end, we inform product owner to recall the product from consumer level.

- Complete investigations into all batches with confirmed and potential microbial contamination. The investigations should detail your findings regarding the root causes of the contamination.

Response-

Investigation is done and report for potential microbial contamination of artificial tears is enclosed - **Exhibit- 65**

Investigation is done and report for potential microbial contamination of ointment is enclosed – **Exhibit-66**

- All chemical and microbial test methods used to analyze each of your drug products.

Response-

chemical and microbial test methods as per specification and test method- GPHC/SPEC-DRP-A-079-01 & GPHC/STP-DRP-079-01- **Exhibit- 67**

2. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Your firm failed to establish an adequate quality unit (QU) with the responsibilities and authority to oversee the manufacture of your drug products, for example:

A. You failed to perform adequate batch release to ensure the acceptability of all batches of Artificial Tears, prior to release for the U.S. market.

Response –

LOCAL FDA has inspected the site and took documents for their verification at their end hence we were unable to show batch release documents during FDA inspection.

Batch is released as per procedure for approval and release of finished product to market SOP- GPHC-SOP-QAD-027-05- **Exhibit-68**

Batch release document is enclosed- **Exhibit-69**

B. Your quality system does not adequately ensure the accuracy and integrity of data to support the quality of the drugs you manufacture. For example, your firm permitted the unacceptable practice of using pre-filled batch release documents.

Response-

Pre filled Batch release document is discontinued and we never used this type of documentation for Artificial tears eye drops and sterile formulation unit products

We have reviewed the subjected person involved in the activity against the GDP requirements and found no abnormalities. And all the persons involving in the batch release activity were trained. A copy of training attendance sheet is enclosed

Batch release training record is enclosed- **Exhibit ---70**

3. You failed to follow your change management procedure. The impact of the change to the specification for the inner cap (plug) used as part of your Artificial Tears container-closuresystem to a plug "with prehole" was not evaluated.

Response-

Impact assessment for no prehole and with prehole is done and report is enclosed- **Exhibit-71**

In your response, you state you will perform an impact assessment for all change controls initiated. Your response is inadequate for reasons that include, but are not limited to, the following:

- You do not assess all records potentially affected by lapses in data integrity. You also do not assess how poor documentation practices affected distributed drug product nor how you could strengthen QU oversight. You also do not provide copies of the missing batch release documents you indicated that you have now recovered.

Response-

All poor documentation practice is removed by frequent training of documents control

and data integrity SOP training

Batch release records were taken by our local FDA during inspection; hence we are unable to produce at that time of USFDA audit

Data integrity training records- **Exhibit- 72**

Batch release records- **Exhibit-73**

You do not perform a review and impact assessment for changes made outside of your change management system and not previously evaluated.

Response-

Global has performed impact assessments of changes made outside pf change management

Risk Assessment report for "No Pre hole and With Pre-hole" and change of (b) (4) Specification is attached- **Exhibit-74**

Impact Assessments for "No Pre hole and With Pre-hole" is attached **as Exhibit-75**

Impact Assessments for "Modified (b) (4) Specification" is attached as **Exhibit-76**

In response to this letter, provide the following:

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limitedto:
- A determination of whether procedures used by your firm are robust and appropriate
- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
- A complete and final review of each batch and its related information before the QUdisposition decision
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products

  Also describe how top management supports quality assurance and reliable operations including, but not limited to, timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

  Response -
  A comprehensive assessment and remediation plan is done to ensure Global pharma QU is given the authorityand resources to effectively function
  Exhibit-77

- A comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your quality unit. Your change management program should also include provisions for determining change effectiveness.

  Response-

  A comprehensive, independent assessment of Global pharma change management system is done to ensure changes are justified, reviewed and approved. – **Exhibit-78**

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

Response-

A complete assessment of documentation systems used throughout Global pharma manufacturing and laboratory operations is done to determine where documentation practices are insufficient and CAPA plan- **Exhibit---79**

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP: Questions and Answers* for guidance on establishing and following CGMP-compliant data integrity practices at https://www.fda.gov/media/119267/download.

Your firm should retain a qualified consultant to assist in your remediation. In response to this letter, provide:

Response

Global pharma engaged a qualified consultant (b) (4) (b) (4)

(b) (4) (b) (4) data integrity, gap analysis, risk analysis, training, audits and technology transfer as consultant for remediation of all points mentioned in this warning letter

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

Response-

Based on the report generated by the DI consultant, the decision was taken to appoint DI cum document review manger.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

Response-

Ongoing operation for all markets has been suspended or stop completely due to suspension of the sterile manufacturing eye drops and ophthalmic section by local FDA .

If local FDA gives clearance then Re-assessment will be done by consultant before starting production activity.

C. A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

Response-

Because of severity of the problem highlighted in sterile ophthalmic section, decision taken by the management is not to produce any product to US market and discontinue sterile ophthalmic section.
We have discontinued production of sterile eye drops to US market.

Global pharma will inform in the case of transfer of ownership or any contract manufacturing of any process involves with ophthalmic drops or ointment if moving to new location.
The firm does not intend to manufacture any drops for US market. A cGMP consultant will be engaged to perform comprehensive SIX systems audit before taking any decision is taken to reenter in to US market.
Global pharma uses external testing laboratory for some sophisticated testing of its products and same has been qualified by the QA team.

In the case of contract manufacturing where (b) (4) sterilization was done for sterile ophthalmic ointment decision has been taken to discontinue the product since only one batch has been manufactured till date.