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

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| New Jersey District Office<br>10 Waterview Blvd., 3rd Floor<br>Parsippany, NJ 07054<br>Ph: (973)331-4900 Fax:(973)331-4969<br>ORAPHARM1_RESPONSES@fda.hhs.gov<br><br>Industry Information: www.fda.gov/oc/industry | 03/11/2024-04/03/2024* |
| | FEI NUMBER<br>3013024146 |
| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED<br>Frederick E. Weiss, Head of Quality | |
| TO:<br>FIRM NAME<br>Imprimis NJOF, LLC | STREET ADDRESS<br>1705 Route 46 Ste 6B |
| CITY, STATE, ZIP CODE, COUNTRY<br>Ledgewood, NJ 07852 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

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

Drug products failing to meet established specifications are not rejected. Specifically,

The firm received Out-of-Specification (OOS) results for stability or retain samples for the lots listed in the table below which remained in the market through their Beyond Use Dates. The investigations remained open although Change Controls had been initiated, and closed, to change the BUD for the subject products from 360 Days to 180 or 150 days without scientific rationale.

| Product (LIR #s) | Lot # (BUD) | Description | Change Control |
|---|---|---|---|
| Epinephrine (0.25 mg/mL), Lidocaine (7.5 mg/mL) Sterile injectable (LIR-24-015) | (b) (4) (01AUG2024) | Epinephrine Potency OOS (Result: 86.1%, Specification: (b) (4) ) for Retain Sample at day 197 (BUD: 360 Days) | Change Control QE-000032 Changed BUD from 360 days to 180 days. |
| | (b) (4) (30AUG2024) | Epinephrine Potency OOS (Result: 86.9%; Specification: (b) (4) ) for Retain Sample at Day 168 (BUD: 360 Days) | |
| Prednisolone (1%) Moxifloxacin (0.5%), Bromfenac (0.075%) (PMB) Sterile Ophthalmic Solution (LIR-23-073) | (b) (4) (09MAR2024) | Bromfenac Potency OOS (Result: 82.5%; Specification: (b) (4) ) for (b) (4) Temp Stability Sample at (b) (4) (BUD: 360 Days) and (b) (4) (Result: 82.2%) | Change Control CC-GEN-OCT2023008 changed BUD from 360 Days to 150 days. |
| | (b) (4) (09MAR2024) | Bromfenac Potency OOS (Result: 86.3%; Specification: (b) (4) ) for (b) (4) Temp Stability Sample at (b) (4) (BUD: 360 Days) | |
| | (b) (4) (03JUL2024) | Bromfenac Potency OOS (Result: 88.7%; Specification: (b) (4) ) for Retain Sample at Day 185 (BUD: 360 Days) | |

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| | | Janet A. Rajan, Investigator<br>Rose Jean-Mary, Investigator<br>Tomika Crafter, Investigator<br>Annet R. Rajan, Investigator | 04/03/2024 |

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## OBSERVATION 2

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

1) The firm's visual inspection process governed by SOP# VV-QUAL-00606 "(b) (4) Visual Inspection", Version 16.0, Effective Date: 1/4/2024 is deficient in that the SOP does not require the initiation of an investigation after a failure of the 100% visual inspection (deviation initiated only if (b) (4) inspection fails). The current acceptance limits for 100% visual inspection are (b) (4) critical defects, (b) (4) major defects, and (b) (4) minor defects. The firm's investigation process is also deficient in that identification of particulates is not required until they are found in the AQL inspection process. Examples of products released that initially failed 100% visual inspection for critical defects, and for which no deviation was initiated include, but are not limited to, the following lots of Dexamethasone(1mg/mL)- Moxifloxacin(0.5mg/mL)-Ketorolac(0.4mg/mL) (DMK) Preservative Free (PF) Ophthalmic Injection and Dexamethasone(1mg/mL)-Moxifloxacin (5mg/mL) (DM) Solution Sterile Ophthalmic Injection:

| Product (Lot No.) (Lot Size) | Results of 100% Inspection | Results of (b) (4) Inspection | Results of (b) (4) Inspection |
|---|---|---|---|
| DMK (b) (4) | -Critical (**58% Fail:** (b) (4) units for Particles, (b) (4) units for Fibers) | -Critical (**20% Fail:** (b) (4) units for Particles, (b) (4) units for Fibers) | -Critical ((b) (4) Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) |
| DMK (b) (4) | -Critical (**28% Fail** (b) (4) units for Particles, (b) (4) units for Fibers) | -Critical ((b) (4) Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) | N/A |
| DMK (b) (4) | -Critical (**20% Fail:** (b) (4) units for Particles, (b) (4) units for Fibers, (b) (4) units for Crimp Defects) | -Critical ((b) (4) Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) | N/A |
| DMK (b) (4) | -Critical (**8% Fail:** (b) (4) units for Particles, (b) (4) units for Fibers, (b) (4) units for Crimp Defects (Functional))<br>-Minor (**8% Fail:** (b) (4) units for Crimp Defects (Cosmetic)) | -Critical (**2% Fail:** (b) (4) units for Particles, (b) (4) units for Fibers, (b) (4) units for Crimp Defects) | -Critical (0% Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) |

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| | | | |
|---|---|---|---|
| DMK (b) (4) | -Critical (**4% Fail**) ((b)(4) units for Cracked/Damaged vial, (b)(4) units for Crimp Defect) | -Critical ((b)(4) Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) | N/A |
| DM (b) (4) (b) (4) | -Critical (**40% Fail**: (b)(4) units for Particles, (b)(4) units for Fibers) | -Critical ((b)(4) Pass)<br>-Major (0% Pass)<br>-Minor (0% Pass) | N/A |
| DM (b) (4) (b) (4) | -Critical (**14% Fail**: (b)(4) units for Particles, (b)(4) units for Fibers) | -Critical (**5% Fail**: (b)(4) units for Particles, (b)(4) units for Fibers) | -Critical ((b)(4) Pass)<br>- Major (0% Pass)<br>-Minor (0% Pass) |

Additionally, the firm conducted a Process Verification (PV) study to assess whether the usage of (b) (4) of the (b) (4) was effective in reducing the defect rate for particles/fibers in the filling process of DMK, DM and Moxifloxacin (4 mg/0.8 mL) Preservative Free Injection. The PV DMK Lot (b) (4) failed 100% visual inspection for Critical defects (4% Fail ((b)(4) for fibers, (b)(4) for particles)) and (b) (4) inspection for Critical defects (2% Fail ((b)(4) for fibers, (b)(4) for particles)); no deviation was initiated for failing 100% inspection and no investigation was conducted to identify the source of the particles. The (b) (4) inspection (Critical ((b)(4), Pass) ((b)(4) for fibers, (b)(4) particles)) and AQL Passed.

2) No confirmatory testing was conducted for particles observed during retain sample inspection of four (4) out of five (5) lots of Triamcinolone-Moxifloxacin HCl (TM) (15/1) mg/mL PF Ophthalmic Injection (Suspension product), associated with ADE# 2022124 (9 cases of increased inflammation after injections). During visual inspection of the retain samples, the visual inspector identified the particles as API residue in the vials in TM lot #'s (b) (4) and (b) (4) However, visual inspectors are not trained on identification of API residue during visual inspection qualification.

3) During the deviation investigation QE-000142, no impact and risk analysis was conducted for glass particle found during the (b) (4) AQL visual inspection of DM Lot# (b) (4); the (b) (4) AQL failed with 1 vial for fiber and 2 vials with particles. Per section 5.3.27 of SOP# VV-QUAL-00606 "(b) (4) Visual Inspection", Version 16.0, Effective 1/4/2024, the (b)(4) vials from the (b) (4) AQL were sent out for particle identification (ID); the foreign materials were identified as Polyisobutylene with cilicate contributions, natural cellulose, and glass. The impact and risk analysis section of QE-000142 did not include impact assessment of the presence of the glass.

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4) Approximately 1030 complaints were received for Klarity-Cyclosporine 0.1% (Klarity-C) Sterile Ophthalmic Emulsion, Preservative Free, including but not limited to the following, for clogged bottles (~589 complaints), leaking bottles (~56 complaints), drops pouring out (~38 complaints), empty bottles (~17 complaints), underfilled bottles (~27 complaints), and mold (~14 complaints) between 12/2021 to 03/2024. The following investigations into complaints about possible mold in caps and products for Klarity-C (filled on the (b) (4) filling line (Equipment#: (b) (4) )) did not include an assessment of retain samples associated with the complaint and/or an assessment of other lots of products that may have used the same lot of the (b) (4) container closure system. The investigations also did not assess the appropriateness of the (b) (4) container closure system, which is intended to prevent ingress of contamination, as a potential root cause.

| Complaint # | Lot# | Complaint Description |
|---|---|---|
| 2023270 | (b) (4) | Patient reported that one of the bottles was with black stuff or mold around the lid. |
| 2023536 | | Patient reported mold inside the cap of the bottle. |
| PQC-23-006 | | Patient stated the bottle had mold growing. |
| PQC-23-206 | | Patient reported their bottle of Klarity-C became moldy. |
| PQC-23-065 | | Patient said went to open new bottle and there was mold inside the cap. |
| PQC-23-163 | | Clinic stated patient noted black spot on the lid; subsequently, lid became covered in mold. Clinic reported patient brought in two bottles of lot (b) (4) with mold on them.<br><br>**Note:** An identification test was performed by the firm to identify the observed mold from the customer returned sample. The test result obtained identified the mold as Cladosporium sp. |

5) No deviation was initiated for (b) (4) failures when the number of repeat tests exceeded the allowable attempts as required by Section 11.10.5 and 11.10.6 of firm's SOP# VV-QUAL-00131, "(b) (4) using (b) (4) " Version 7.0, Effective Date: 1/25/2023, which states that "repeat testing is only allowed (b) (4) times" and "in the event, repeat testing attempts are failed contact management for further testing of the (b) (4) at manufacturers end to understand it is a true failure". Additionally, (b) (4) were aborted without justification. Examples of lots for which (b) (4) repeat tests were performed more than (b) (4) times before passing and/or aborted and no deviation was initiated are listed below:

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| Product | Lot # | Date of Test | Number of (b) (4) Repeat Tests | Number of (b) (4) Aborted |
|---|---|---|---|---|
| Tropicamide-Phenylephrine HCl Sterile Ophthalmic Solutions 1% 2.5% Multiple-Dose (M2) | (b) (4) | 02/21/24 | Eight (8) | N/A |
| PrednisoLone-Moxifloxacin-Bromfenac Sterile Ophthalmic Suspension 1% 0.5% 0.075% (PMB) | | 02/22/24 | Five (5) | N/A |
| Klarity-C Drops – Cyclosporine PF-Sterile Ophthalmic Emulsion 0.1% (KC) | | 01/31/24 | Three (3) | One (1) |
| PrednisoLone-Moxifloxacin-Bromfenac Sterile Ophthalmic Suspension 1% 0.5% 0.075% (PMB) | | 11/28/23 | Four (4) | Two (2) |
| Prednisolone Sodium Phosphate-Moxifloxacin-Bromfenac Sterile Ophthalmic Solutions 1% 0.5% 0.075% (PMB) | | 11/15-11/16/23 | Four (4) | Two (2) |

**OBSERVATION 3**

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

1) Although all approved reports of the Airflow Visualization Studies (AVS), conducted in September 2023, within the ISO 5 filling machines documented adequate air flow, the following deficiencies were identified:

   a) During the review of the AVS (Number: VV-QUAL-01987), Approved: 1/10/2024, for the (b) (4) Aseptic Filling line (Equipment #: (b) (4) ) we observed:

      i) The volume and/or location of the smoke was not sufficient to visualize the airflow pattern during the following interventions:

         (1) Aseptic connection of sterile tubing to the (b) (4) during set up of the equipment.

         (2) Change filling tubing set and the needle.

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b) During the review of the AVS (Number: VV-QUAL-01988), Approved: 1/10/2024, for the (b) (4) Aseptic Filling Line (Equipment #: (b) (4) ) we observed:
   i) The AVS was not conducted under dynamic conditions; the filling line remained static and did not simulate the commercial filling operations.
   ii) The volume and/or location of the smoke was not sufficient to visualize the airflow pattern over tubing set up during equipment set up.
   iii) Turbulent and/or upward moving air was observed during the following interventions:
      (1) (b) (4) tubing set up during equipment set up.
      (2) Change of the (b) (4) tubing set and the (b) (4)

c) During the review of the AVS (Number: VV-QUAL-01989), Approved: 1/10/2023, for the (b) (4) Aseptic Filling line (Equipment #: (b) (4) ) within the ISO 5 Laminar Flow Hood (LFH) (Equipment # LFH(b) (4)) we observed:
   i) The volume and/or location of the smoke was not sufficient to visualize the airflow pattern during the following interventions:
      (1) Open cap/tip bag and load filling cap bowl.
      (2) Placement of tip/cap onto bottle.

2) During observation of aseptic filling operations, the following deficiencies in aseptic behaviors were observed:

a) On 03/12/2024, during the aseptic filling of PrednisoLONE –Moxifloxacin-Nepafenac Sterile Ophthalmic Suspensions (1%, 0.5%, 0.1%), Lot# (b) (4) , on the (b) (4) filling machine (Equipment #: (b) (4) ), within the ISO 5(b) (4) located in Room (b) (4) (ISO 7), we observed operators open the door of the (b) (4) of the (b) (4) and enter the ISO 5 filling area with their whole body to perform intervention to remove jammed tip SOP VV-QUAL-00342 "Filling Procedure for (b) (4) Filling Machine", Version 4.0, Effective Date: 10/04/2023 does not include instructions for rejection or line clearance after performing the routine intervention "Tip Jam in the Tip Rail". No environmental monitoring is performed in the area where operators enter the ISO 5 filling area to perform interventions such as loading the bottle, tip and cap hoppers.

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b) On 03/19/2024, during the aseptic filling of Klarity-C 0.1% Sterile Ophthalmic Emulsion, Preservative Free, Lot# (b) (4), on the (b) (4) (Equipment #: (b) (4)) filling machine, within the ISO 5 Laminar Flow Hood (LFH) (Equipment # LFH-(b) (4)), located in room (b) (4) (ISO 7), we observed operators cross over open dropper bottles, approximately 4 times, while performing interventions of removing jammed/fallen dropper bottles. The droppers were not rejected, as required by section 10.4 of SOP# VV-QUAL-00339 "Filling for (b) (4) Procedure", Version 7.0, Effective 10/4/2023, which states "If at any time after bottles are introduced into the LFH any intervention is performed where the first air flow is disrupted between the HEPA filters and the opening of the bottles, the bottles must be rejected". Additionally, the bowl which contains the tips was placed close to the front of the LFH and operators were observed reaching inside the bowl for the caps and the bag for the bottles with their gloved hands.

c) During the aseptic filling observed on the (b) (4) and (b) (4) filling machines, forceps and/or scissors that are used to perform interventions, during filling operations were observed placed tip down in the forceps storage jar, preventing the tips of the forceps from receiving first air. Additionally, no written procedures govern the placement of forceps and/or scissors during aseptic filling operations.

3) Media Fill Simulations (MFS) do not closely simulate aseptic operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations. Additionally, the number of interventions performed during routine operations are not tallied in the batch production records. The MFS, as reported in Document No VV-QUAL-02062 "MEDIA FILL SUMMARY REPORT FOR (b) (4) QUALIFICATION OF (b) (4) AND (b) (4) FILLING LINES IN JANUARY 2024", was not representative of actual production processes in that:

a) The interventions MSL (Missing Seal on vial) and MST (Missing stopper on vial) were not simulated in the (b) (4) MFS. Additionally, review of the following batch production records for DMK PF Ophthalmic Injection revealed routine production interventions exceeding the number of interventions simulated in MFS:

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| Intervention | # of times simulated in MFS | Approximate #of times performed in routine production (Lot #) |
|---|---|---|
| LV (Load vials on infeed tray) | 30 | 53 (b) (4)<br>62 |
| RT (Remove exit tray) | 14 | 21 (b) (4)<br>23 |
| SLB (Fill seal bowl) | 8 | 14 (b) (4)<br>16 |
| STB (Fill stopper bowl) | 13 | 16 (b) (4)<br>21 |

b) The intervention AT (Adjustment of Filling Tubing Set) for the (b) (4) filling line was not simulated in the MFS.

c) Review of the following batch production records for Klarity-C 0.1% Sterile Ophthalmic Emulsion, PF, on the (b) (4) filling line, within the ISO 5 LFH, revealed routine production interventions exceeding the number of interventions simulated in MFS:

| Intervention | # of times simulated in MFS | Approximate #of times performed in routine production (Lot #) |
|---|---|---|
| FC (Fill cap bowl/hopper) | 16 | 29 (b) (4)<br>42 |
| LB (Loading bottles) | 38 | 42 |
| SC (Spill clean/change gloves) | 3 | 7 (b) (4) |

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## OBSERVATION 4

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. Specifically,

All drug products manufactured at the firm are not tested for impurities/degradants at release or during stability. Examples of drug products that have been released include:

1. Prednisolone Sodium Phosphate (1%)-Moxifloxacin (0.5%)-Bromfenac (0.075%) Sterile Ophthalmic Solution, Lot# (b) (4)
2. Epinephrine (0.25 mg/mL)-Lidocaine (7.5 mg/mL) Solution Sterile Injectable, Lot# (b) (4)
3. Prednisolone acetate (1%)-Moxifloxacin (0.5%) Suspension Sterile Ophthalmic Drop, Lot# (b) (4)

## OBSERVATION 5

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

On 03/22/2024, the sterile bottle hopper lid of the (b) (4) filling machine (Equipment #: (b) (4) ), within the ISO 5 (b) (4) System, appeared to have a visible orange, brown to black residue on the metal hinges that spanned the length of approximately 8 inches in between the wall and plexiglass barrier of the ISO 5 area. The status of the ISO 5 (b) (4) filling machine on 03/22/2024 was "clean"; firm's management was not aware of the residue or how long the residue had been present on the filling machine. Similar residue was observed in the sterile bottle hopper during smoke studies conducted in September 2023. Approximately (b) (4) lots of products were filled on the (b) (4) and released for commercial distribution since September 2023; these include, but are not limited to, the following:

- Prednisolone-Moxifloxacin-Bromfenac Sterile Ophthalmic Suspension (1%, 0.5%, 0.075%) Lot # (b) (4) (Date of Manufacturing: 02/05/2024, BUD: 09/01/2024).
- Prednisolone Acetate 1%-Moxifloxacin 0.5%-Nepafenac 0.1% Sterile Ophthalmic Suspension Lot # (b) (4) (Date of Manufacturing: 02/01/2024, BUD: 07/29/2024).
- Klarity Preservative Free Ophthalmic Solution Lot # (b) (4) (Date of Manufacturing: 01/31/2024, BUD: 01/24/2025).

| | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| SEE REVERSE OF THIS PAGE | JAR<br>KJ<br>ARR | Janet A. Rajan, Investigator<br>Rose Jean-Mary, Investigator<br>Tomika Crafter, Investigator<br>Annet R. Rajan, Investigator | 04/03/2024 |

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| New Jersey District Office<br>10 Waterview Blvd., 3rd Floor<br>Parsippany, NJ 07054<br>Ph: (973)331-4900 Fax:(973)331-4969<br>ORAPHARM1_RESPONSES@fda.hhs.gov<br><br>Industry Information: www.fda.gov/oc/industry | 03/11/2024–04/03/2024*<br>FEI NUMBER<br>3013024146 |
| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED<br>Frederick E. Weiss, Head of Quality | |
| TO:<br>FIRM NAME<br>Imprimis NJOF, LLC | STREET ADDRESS<br>1705 Route 46 Ste 6B |
| CITY, STATE, ZIP CODE, COUNTRY<br>Ledgewood, NJ 07852 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

## *DATES OF INSPECTION

03/11/2024 (Mon), 03/12/2024 (Tue), 03/13/2024 (Wed), 03/14/2024 (Thu), 03/18/2024 (Mon), 03/19/2024 (Tue), 03/20/2024 (Wed), 03/21/2024 (Thu), 03/22/2024 (Fri), 03/25/2024 (Mon), 03/26/2024 (Tue), 03/27/2024 (Wed), 03/28/2024 (Thu), 04/03/2024 (Wed) (14 Days)

| | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| SEE REVERSE OF THIS PAGE | | Janet A. Rajan, Investigator<br>Rose Jean-Mary, Investigator<br>Tomika Crafter, Investigator<br>Annet R. Rajan, Investigator | 04/03/2024 |

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."