

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

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| DISTRICT ADDRESS AND PHONE NUMBER 158-15 Liberty Avenue Jamaica, NY 11433 (718) 340-7000 Ext:5301 Fax: (718) 662-5661 ORAPHARM1_RESPONSES@fda.hhs.gov | DATE(S) OF INSPECTION 5/3/2021-5/14/2021* |
| | FEI NUMBER 3010943533 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Alfonse J. Muto, Co-owner

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| FIRM NAME Pine Pharmaceuticals, LLC | STREET ADDRESS 355 Riverwalk Pkwy |
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| CITY, STATE, ZIP CODE, COUNTRY Tonawanda, NY 14150-5837 | TYPE ESTABLISHMENT INSPECTED Outsourcing Facility |
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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**

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

Specifically,

- (A) During finished product release testing of (b) (4) (Lot # (b) (4)), your contract lab obtained an OOS potency result of 105.2% (spec. (b) (4)) on 3/24/2021. Re-analysis of the sample (104.0%, 104.6%, and 105.4%) confirmed the initial OOS result. Your investigation concluded, without adequate supporting evidence, that the most probable root cause was "a lack of reliability in the method used to weigh the isotope during production" and the lot was approved for release on 4/5/2021. (b) (4) vials of (b) (4) (Lot # (b) (4); Exp. 09/05/2021) were distributed on 4/5/2021.
- (B) During finished product release testing of (b) (4) (Lot # (b) (4)), your contract lab obtained an OOS potency result of 81.9% (specification (b) (4)) on 9/4/2020. The Phase 1 investigation of OOS # 87 by the contract lab did not identify any lab error. The sample was retested in (b) (4) (85.3%, 83.9%, and 84.6%) and confirmed the initial OOS result. Your investigation noted, "Due to the system suitability failures and limited information relayed regarding the specifics to the failures, it is possible that batches tested prior to the additional samples submitted on 09/15/2020 could be impacted by the findings reported to Pine on 10/7/2020". You subsequently sent the subject lot sample to another contract laboratory for testing using a method that has not been validated and the result (102.2%) was found within specification. Lot # (b) (4) was approved for released on 10/29/2020. (b) (4) syringes of (b) (4) (Lot # (b) (4); Exp. 12/14/2020) were distributed on 11/3/2020.

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| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE Mindy M Chou, Investigator Johnna L Bleem, Investigator | Mindy M Chou Investigator Signed By: 200648922 Date Signed 05-14-2021 15 12 14 X | DATE ISSUED 5/14/2021 |
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(C) During the finished product release testing of (b) (4) (Lot # (b) (4) and # (b) (4)), you obtained OOS potency result of 66.6% for Lot # (b) (4) and 67.5% for Lot # (b) (4) (specification (b) (4) on 10/7/2020. Reinjection of original sample vial and original sample prep confirmed the initial OOS results for both lots. The contract lab was unable to determine an assignable root cause of the OOS; however, noted that the sample went through multiple freeze/thaw cycles. A new sample was submitted for both lots and tested one time with result of 104.0% for Lot # (b) (4) and 104.0% for Lot # (b) (4). The contract lab did not investigate and confirm that the initial OOS was due to the multiple freeze/thaw cycle of the sample to invalidate the initial OOS results. Despite the lack of supporting evidence, both lots were subsequently approved for released on 10/29/2020 and 11/2/2020, respectively. (b) (4) vials of (b) (4) (Lot # (b) (4); Exp. 12/30/2020) were distributed on 10/29/2020; and (b) (4) vials of (b) (4) (Lot # (b) (4); Exp. 01/05/2021) were distributed on 11/9/2020.

(D) During the finished product release testing of (b) (4) (Lot # (b) (4); Exp. 3/17/2021), your contract laboratory obtained an OOS potency result of 88.5% (spec (b) (4) (b) (4)) on 12/11/2020. Three new samples were submitted for retest. The potency result of these samples were 93.0%, 98.5%, 86.4%. Your contract lab was unable to determine an assignable root cause of the variable results from different syringes. In your Final Phase II OOS/OOT Investigation Report for OOS # 95, you indicated that the most probable cause of the OOS results was due to laboratory preparation error and you tested your hypothesis by requesting the lab to test one single syringe of a different (b) (4) in (b) (4). The results for Lot # (b) (4) were 93.6%, 93.5%, and 96.6%. You concluded that the "variability" observed from Lot # (b) (4) demonstrated that there's "a lack of precision accuracy during pipetting/sample preparation" without scientific basis. The investigation was closed on 1/27/2021 with plan to perform testing at an alternate, qualified lab.

OBSERVATION 2

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

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Specifically,

- (A) (b) (4) are filled into (b) (4) empty vials. Prior to filling, the (b) (4) glass vials which were (b) (4) in the ISO 7 Buffer Room. The aseptic filling process performed inside the ISO 5 LAFW requires (b) (4) (b) (4). After filling, the vials are transferred to ISO 7 Buffer Room for (b) (4) (b) (4). Environmental monitoring is not performed during the (b) (4) (b) (4) process. There is no assurance that such practice does not expose the interior of the sterile vials to less than ISO 5 quality air.
- (B) During aseptic processing of (b) (4) (Lot # (b) (4)) on 5/4/2021, we observed that the operators did not sanitize all materials prior to introducing into the ISO 5 hood except for the large bulk compounded IV bags. The Director of QA stated their procedure does not require operators to sanitize or wipe down the materials immediately before placing the materials into the ISO 5 hood since it was previously wiped down in the ISO 7 Anteroom. (This observation is a repeated objectionable condition reported during the previous inspections of 2018 and discussed at the Regulatory Meeting in 2019)
- (C) The firm has (b) (4) ISO 5 hoods (b) (4) that are not process or product dedicated in the buffer rooms. The dynamic smoke study of the ISO 5 hood is only performed at (b) (4), then every (b) (4) (b) (4). The firm categorized its production into (b) (4) types of aseptic filling processes. According to the Director of QA and the Training Supervisor, the (b) (4) syringe" and (b) (4) syringe" processes are considered low risk compounding. The worst-case process is not always used to conduct the dynamic smoke study. For example, (b) (4) was used in the production of (b) (4) (Lot # (b) (4)) on 4/22/2021; and (b) (4) was used in the production of (b) (4) (Lot # (b) (4)) on 5/3/2021. The firm has only performed dynamic smoke studies with (b) (4) syringe" and (b) (4) syringe" filling processes for (b) (4) and (b) (4) syringe" filling process for (b) (4)

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(D) During the review of dynamic studies and observation of operators' aseptic technique practices, we observed the following:

- i. During our review of the dynamic smoke study video for (b) (4) performed in 2020, which simulated the (b) (4) Pump filling for IV bag (b) (4) turbulent airflow was observed in between the large volume parenteral IV bags at approximately 6:47 min and 7:48 min of the video (File name: PEC-V IV Bags.wmv).
- ii. During our review of the production video for (b) (4) (Lot # (b) (4); Exp. 08/01/2021), operator was observed at around 8:30 a.m to 8:33 a.m. temporarily stacking IV bags at the edge of the ISO 5 hood in close proximity to the IV port of another IV bag, where solution was being withdrawn with the aid of the (b) (4) pump.
- iii. During the aseptic filling of (b) (4) (Lot # (b) (4)) on 5/4/2021, the operators were observed with their arms reaching over open eye drop bottles and bottle tips during the filling process. Part of the filling process also involves the operating grabbing the bottle cap with their gloved hands and (b) (4) into the cap. The operator was also observed holding the tray containing the bottle tips above the trays of caps with product contact surface facing upward. Additionally, the (b) (4) (b) (4) used to wrap the (b) (4) cap trays is identified as low lint, not lint-free, by the manufacturer. The unwrapping of this (b) (4) wrap occurred in the ISO 5 LAFW. There is no assurance that these practices did not generate particles inside the ISO 5 LAFW during production.

OBSERVATION 3

The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality and purity of drug products.

Specifically, the following lots of products were released and distributed based on the result obtained using potency test method which has not been validated:

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| Product Name | Lot # | Exp. Date | QA Approval Date | Distribution Date | Qty. Distributed |
|----------------|-------|------------|------------------|-------------------|------------------|
| (b) (4) | | 12/14/2020 | 10/29/2020 | 11/3/2020 | (b) (4) |
| | | 12/30/2020 | 10/29/2020 | 10/29/2020 | |
| | | 01/08/2021 | 10/27/2020 | 10/27/2020 | |
| | | 02/02/2021 | 11/18/2020 | 11/20/2020 | |
| | | 02/22/2021 | 12/08/2020 | 12/15/2020 | |

This observation is a repeated objectionable condition reported during the previous inspection of 2015 and 2016 Warning Letter.

OBSERVATION 4

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, Growth promotion testing is not performed for the in-house prepared growth media **(b) (4)** **(b) (4)** used for media fills, such as the simulation of aseptic filling of eye drop product and large volume parenteral drug products. Bulk **(b) (4)** was used in the growth media preparation for the aseptic process

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qualification of operator (b) (6) on 9/16/2020 (b) (4), operator (b) (6) on 9/29/2020 (b) (4) (b) (4) and operators (b) (6) on 4/22/2020 (b) (4). Growth promotion testing were not performed for the prepared media used in these aseptic process simulations to assure media viability to allow growth of microorganisms.

OBSERVATION 5

Records of the calibration checks and inspections of automatic, mechanical or electronic equipment, including computers or related systems are not maintained.

Specifically, the temperature sensors and the pressure sensor of the (b) (4) have not been calibrated since its installation in February 2018. This (b) (4) is used in sterilizing non-product materials which are used in the ISO 5 LAFW. The bottle trays, cap trays, and vial trays which were (b) (4) around 4/19/2021-4/28/2021 were used for the production of (b) (4) (Lot # (b) (4)) on 4/22/2021 and for the production of (b) (4) (Lot # (b) (4)) on 5/3/2021.

***DATES OF INSPECTION**

5/03/2021(Mon), 5/04/2021(Tue), 5/05/2021(Wed), 5/06/2021(Thu), 5/07/2021(Fri), 5/10/2021(Mon), 5/11/2021(Tue), 5/12/2021(Wed), 5/13/2021(Thu), 5/14/2021(Fri)

Johnna L. Bleem
Investigator
Signed By: Johnna L. Bleem -S2
Date Signed: 05-14-2021 15:12:55
X _____

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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."