DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10 Waterview Blvd., 3rd Floor Parsippany, NJ 07054 (973) 331-4900 ORAPHARM1_RESPONSES@fda.hhs.gov	9/26/2023-10/25/2023* FEI NUMBER 3002815949

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Michael Tursi, President & CEO	
FIRM NAME Stokes Healthcare Inc. dba Epicur Pharma	STREET ADDRESS 8000 Commerce Pkwy Ste 600
CITY, STATE, ZIP CODE, COUNTRY Mount Laurel, NJ 08054-2211	TYPE ESTABLISHMENT INSPECTED 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

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

Specifically, according to the Director of Quality and the Director of Manufacturing your firm did not validate the manufacturing process of Tacrolimus AQ and Fluorouracil.

A. Tacrolimus AQ a drug product originally manufactured for animal use, was also made available for human use since approximately July 21, 2022. Since then, approximately (b) (4) lots, including lots (b) (4) , were manufactured and released for commercial distribution. However, there are no process validation protocols or sampling plans written to demonstrate process consistency for this product and its various concentrations.

B. Fluorouracil, a drug product manufactured for human and animal use since February 2023. Approximately (b) (4) lots of which (b) (4) is a part of were manufactured and released into the market. However, there are no process validation protocols or sampling plans written to demonstrate process consistency for this product.

OBSERVATION 2

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	Christina K Theodorou, Investigator Yoriann M Cabrera Bartolomei, Investigator Ruben C Quintana, Investigator	X Christina K Theodorou Investigator Signed By: Christina K Theodorou -S Date Signed: 10-25-2023 13:18:08	10/25/2023

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

Specifically...

A. Your firm has not conducted smoke studies nor media fills under dynamic conditions in rooms C704, and C706 where filling operations under aseptic conditions takes place for human and animal drug products. For example,

1) Air visualization "smoke" study (b) (4) utilized by your firm to validate your aseptic manufacturing process revealed that your operators did not include (b) (4) operations in (b) (4) containers and assembly of sterile filling equipment including necessary aseptic connections such as, but not limited to, the filling nozzle and related tubing.

2) Media fill protocol PR-23-0001 does not include all aspects of aseptic processing such as, but not limited to:

i. The aseptic filling of the (b) (4) (b) (4) and the Tacrolimus (b) (4) concentrate which is (b) (4) vessel

ii. The mixing of the (b) (4) and Tacrolimus (b) (4) concentrate using (b) (4) for the entire duration of aseptic processing, which is aseptically added to the (b) (4) vessel during this process

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iii. The use of (b) (4) (b) (4) to protect your (b) (4) media bottles (b) (4) to the (b) (4), and then (b) (4) ISO 5 classified aseptic processing area. In contrast, your master batch records indicate that you do not use (b) (4) to protect the Tacrolimus AQ drug concentrate and (b) (4) (b) (4) (b) (4).

B. On 06/01/2023, firm personnel conducted (b) (4) for the human and animal drug product Fluorouracil 2500mg/50mL lot (b) (4), exp 12/16/2023, which is intended to be sterile. According to batch record Fluorouracil PF 50 mg/ml Injection Solution, the product was not aseptically filled that same day, nor was the (b) (4) conducted again after aseptic filling operations ceased. After the completion of the (b) (4), the (b) (4) was placed into (b) (4) and (b) (4). On (b) (4) was used to aseptically fill Fluorouracil lot (b) (4). No (b) (4) was conducted after the batch was produced to ensure that the (b) (4) was not compromised after the (b) (4). Your Director of Quality stated on 10/04/2023 that your firm does not perform (b) (4) of (b) (4) after production of the human and animal drug Fluorouracil PF.

OBSERVATION 3

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. In 2022, your firm documented that 15 out of (b) (4) Tacrolimus AQ lots initially tested Out of Specification for potency. In 2023, your firm documented that 18 lots out of (b) (4) Tacrolimus

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AQ lots initially tested out of specification for potency. We reviewed 8 investigations into these OOS events and observed that none documented a definitive root cause with extension to other lots that may have been associated.

B. Your firm failed to complete investigations in a timely manner. Of the requested Notice of Events (NOE), four were opened in 2022, and twelve (12) were opened in 2023 which were still open at the time of this inspection. Recently, your firm closed six (6) NOEs that were opened in 2023, during this inspection. Your SOP QA-ALL-1094 Laboratory Investigation Report states LIR/OOSs must be closed within (b) (4) of the opening date. If an extension is needed it must be issued by QA. None of the LIR NOEs that were open had any extension by your quality unit.

OBSERVATION 4

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

Specifically, according to your Director of Quality and your Director of Manufacturing your firm has not validated your cleaning procedures as described in SOP SC-SAN-1010, *Cleaning and Maintenance of the Aseptic Manufacturing Areas* which provides instructions for cleaning and sanitizing rooms C704, C706 and C709, where human and animal drug products intended to be sterile are manufactured. In addition, your firm's cleaning instructions state technicians are to use (b) (4) for (b) (4) dwell time which is outside of the manufacturer's instructions for sporicidal use of (b) (4) saturation. Furthermore, your technicians were observed on 10/03/2023 not keeping ISO 5 areas, cleaned with (b) (4) for the full (b) (4) Your firm has not conducted an efficacy study to provide a justification for the (b) (4) dwell time.

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OBSERVATION 5

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

Specifically, your firm does not have a validated in-house method for the potency testing of Tacrolimus AQ. Your firm provided *MET-0688-BA: Assay and Impurities Testing of Tacrolimus Products by UPLC-UV* and *RPT-3639 Method Validation Report for Assay and Impurities Testing of Tacrolimus Products by UPLC-UV* which was conducted and validated by your contract testing laboratory at their facility. Further, no method transfer was conducted.

A. Your firm has been conducting the testing in your laboratory and releasing Tacrolimus AQ with an unvalidated potency test method since approximately 2021. According to your Director of Quality, Tacrolimus AQ was made available for human use since approximately July 21, 2022, which was previously only for animal use. Approximately (b) (4) lots, including lots (b) (4) and (b) (4) , were manufactured for commercial distribution since then.

B. Your laboratory technicians have been modifying your unvalidated test method for Tacrolimus AQ after receiving Out of Specification (OOS) results. For example, investigation NOE (b) (4) documents an OOS that was received on 08/22/2022 for Tacrolimus AQ 0.03% after the analyst conducted testing (b) (4) times. A retest was conducted with the retesting analyst under supervision of a senior chemist; however this was also conducted by making changes to the testing method. At the conclusion of the retest under supervision, the tests received a passing result, and the batch was released.

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OBSERVATION 6

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically, your firm's recent certification documentation: Clean Room Certification Report RM C704 (b) (4) (Room C704), Cleanroom Certification Report RM (b) (4) (Room C706) and Cleanroom Certification Report RM (b) (4) (Room C709), where human and animal drug products intended to be sterile are filled into their primary packaging configuration, which was conducted in August 2023, shows that the HEPA filters located in the ceiling for your designated ISO5 areas in these rooms are higher than (b) (4)

OBSERVATION 7

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

Specifically, according to the Microbiology Supervisor, your firm has not conducted a risk assessment or an environmental monitoring qualification that provides a scientifically justifiable determination for the sampling locations selected for your ISO 5 locations in rooms C704, C706 and C709, where human and animal drug products intended to be sterile are manufactured.

OBSERVATION 8

The quality control unit lacks the responsibility and authority to approve and reject all drug products.

Specifically, your firm released products that received an originating Out-of-Specification (OOS) result but was then tested by a second analyst, receiving a passing result. These batches were then released to market. The Notice of Event investigations and batches are

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1. Event 22-0077 Date 02/16/22: Batches (b) (4)
2. Event 22-0275 Date 08/31/22: Batch (b) (4)
3. Event 22-0293 Date 09/28/22: Batches (b) (4)
4. Event 23-0107 Date 05/16/23: Batch, (b) (4)
5. Event 23-0197 Date 08/04/23: Batches (b) (4)

OBSERVATION 9

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

Specifically, your quality unit did not follow its own procedure, POL-QA-1005 *Quality Unit Policy* which defines the responsibilities of all personnel involved in CGMP production operations at Epicur Pharma. For example

A. Your firm's recent certification documentation: Clean Room Certification Report RM (b) (4) (Room C704), Cleanroom Certification Report RM (b) (4) (Room C706) and Cleanroom Certification Report RM (b) (4) (Room C709), where human and animal drug products intended to be sterile are manufactured, which was conducted in August 2023, shows that the HEPA filters located in the ceiling for your designated ISO5 areas in these rooms are higher than (b) (4) Each report was reviewed and signed off by both the contractor and your Director of Quality.

B. Air visualization "smoke" stud (b) (4) utilized by your firm to validate your aseptic manufacturing process revealed that your operators did not include (b) (4) operations in (b) (4) containers and assembly of sterile filling equipment

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including necessary aseptic connections such as, but not limited to, the filling nozzle and related tubing. This video is reviewed and approved by the firm's Microbiology Manager who is part of your firm's quality unit.

C. Per SOP POL-QA-1005 *Quality Unit Policy,* media fill protocols are approved by QA subject matter experts and are observed (b) (4) throughout the process and are simulations that are intended to represent routine operations and non-routine situations. Media fill protocol PR-23-0001 does not include all aspects of aseptic processing such as, but not limited to, the aseptic filling of the (b) (4) (b) (4) and the Tacrolimus (b) (4) concentrate which is (b) (4) the (b) (4) during this process and the use of (b) (4) to protect your (b) (4) media bottles (b) (4), and t (b) (4) the ISO 5 classified aseptic processing area. In contrast, your master batch records indicate that you do not use (b) (4) to protect the Tacrolimus AQ drug concentrate and (b) (4) sterilization.

D. Of the requested Notice of Events (NOE), four were opened in 2022, and twelve (12) were opened in 2023 which were still open at the time of this inspection. Recently, your firm closed six (6) NOEs that were opened in 2023 during this inspection. Per SOP POL-QA-1005 *Quality Unit Policy*, investigations requiring further action are investigated by Quality Assurance (QA) are investigated with the relevant SOP. Your SOP QA-ALL-1094 *Laboratory Investigation Report* states LIR/OOSs must be closed within (b) (4) of the opening date. If an extension is needed it must be issued by QA. None of the NOEs that were open had any extension by your quality unit. In addition, your NOE investigations are incomplete and do not always provide a

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scientifically justified root cause.

OBSERVATION 10

The labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Specifically, under section 503B(a)(10) of the FD&C Act, Outsourcing facilities are required to include certain information on the label and container of compounded drugs products. The following items were not observed, while reviewing your firms drug product labels and containers. For example,

1. The quantity or proportion of each inactive ingredient.

   Examples of your drug product labels that do not contain this information:

   - Tacrolimus (Aqueous) 0.02% Ophthalmic Suspension 10mL
   - Tacrolimus (Aqueous) 0.02% Ophthalmic Suspension 15mL
   - Tacrolimus (Aqueous) 0.03% Ophthalmic Suspension 15mL
   - Tacrolimus (Aqueous) 0.1% Ophthalmic Suspension 10mL
   - Tacrolimus (Aqueous) 0.3% Ophthalmic Suspension 10mL
   - Tacrolimus (Aqueous) 0.5% Ophthalmic Suspension 10mL
   - Tacrolimus (Aqueous) 1% Ophthalmic Suspension 10mL

2. The containers of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(B). Specifically, your containers do not include the following information:

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a. Information to facilitate adverse event reporting: ---www.fda.gov/medwatch and 1800FDA1088 <http://www.fda.gov/medwatch%20and%201800FDA1088>;

Examples of your container labels that do not contain this information:

- Tacrolimus (AQ) 0.5% Ophthalmic Suspension 10mL
- Fluorouracil (AQ) PF 50mg/mL Injection Solution 50mL

***DATES OF INSPECTION**

9/26/2023(Tue), 9/27/2023(Wed), 9/28/2023(Thu), 10/02/2023(Mon), 10/03/2023(Tue), 10/04/2023(Wed), 10/05/2023(Thu), 10/06/2023(Fri), 10/11/2023(Wed), 10/16/2023(Mon), 10/20/2023(Fri), 10/25/2023(Wed)

X Yoriann M Cabrera Bartolomei
Investigator
Signed By: Yoriann M. Cabrera Bartolomei -S
Date Signed: 10-25-2023 13:18:36

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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."