DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
555 Winderley Place, Suite 200 Maitland, FL 32751 (407)475-4700 Fax:(407)475-4768 ORAPHARM2_RESPONSES@fda.hhs.gov	10/16/2023-11/9/2023* FEI NUMBER 3011319445

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mr. Ponswamy Rajalingam, Owner	
FIRM NAME Hybrid Pharma LLC	STREET ADDRESS 1015 W Newport Center Dr Ste 106a
CITY, STATE, ZIP CODE, COUNTRY Deerfield Beach, FL 33442-7707	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 I OBSERVED:

OBSERVATION 1

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

Specifically,

A. The (b) (4) Series (b) (4) laminar flow cabinet serial number (b) (4) used for all your sterile filled batches (b) (4) vials and (b) (4) vials (b) (4) has a HEPA filter that provides first air to your ISO-5 filling area. This HEPA filter has at the time of this inspection observable stains of unknown origin.

On 10/25/2023, I observed the sterile filling of cyanocobalamin 1 mg/ml lot (b) (4) BUD 4/25/2024 in 30 ml multi dose amber glass vials with an actual batch size of (b) (4) vials. The sterile filling process required (b) (4) trays each containing approximately (b) (4) commercially sterile vials to be placed one after another beneath this HEPA filter with a visible stain of unknown origin and filled with cyanocobalamin 1 mg/ml. This cyanocobalamin 1mg/ml bulk solution under the HEPA filter with a visible stain of unknown origin was then (b) (4) dispensed into each open amber glass vial and a grey sterile stopper was then (b) (4) placed onto each vial using (b) (4).

B. On 10/25/2023, during the sterile filling of cyanocobalamin 1mg/ml lot (b) (4) I observed approximately 25 brown spots of unknown origin on the ISO-7 buffer room (b) (4) ceiling HEPA filter located over the table where vial crimping takes place.

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	Joanne E King, Investigator	X Joanne E King Investigator Signed By 1300174867 Date Signed 11-09-2023 17 49 51	11/9/2023

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C. Your firm weighs and aseptically produces hazardous drug products in this non-hazardous suite to include progesterone and testosterone. No evaluation was performed to ensure that there is no ingress of carcinogenic and/or hazardous materials into your sterile filling cabinet or the surrounding aseptic suite.

D. The (b) (4) laminar flow cabinet ISO-5 used for all sterile compounded drugs had surfaces that could collect dust and may be difficult to keep clean to include the (b) (4) work bench appeared scratched, three exposed light bulbs above the operator's head and an electric outlet cover located approximately two inches above the ISO-5 work surface and directly in the path of where aseptic production occurs. In addition, a yellow sticker was observed above the electric outlet inside the ISO-5 hood. The smoke studies provided are inadequate in assessing the air flow patterns. The placement of this electrical outlet could cause eddies/turbulence that could impact the direct compounding area.

E. The buffer room (b) (4) ISO-7 used for all the sterile compounded drugs had surfaces that could collect dust and may be difficult to keep clean to include a (b) (4) table that appeared scratched, beams with exposed bolts running along the top of the room walls, poles supporting these beams in each corner, protruding metal beams on the ceiling near the HEPA filters, wall baseboards with exposed bolts, and ledges above the windows and doors.

F. The ante room used for gowning and used to enter the ISO-7 buffer rooms had surfaces that could collect dust and may be difficult to keep clean to include a (b) (4) table that appeared scratched, (b) (4) door closures, channeled casings at the opened window sashes on each of (b) (4) doors encasing the ante room leading to the ISO-8 drug preparation room, the (b) (4) buffer room (b) (4) and the (b) (4) buffer room (b) (4)

G. The ISO-8 drug preparation room had a door and base boards that were wooden. The ISO-8 painted door frame appeared damaged.

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OBSERVATION 2

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

A. Media fills conducted on (b) (4), were not performed that closely simulated aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

Specifically,the media fill simulations for your pharmacist and pharmacy technicians do not simulate your sterile filling operations. After(b) (4) sterile bulk drug product such as cyanocobalamin 1 mg/ml lot (b) (4) is transferred through commercially sterile (b) (4) (b) (4) to a large glass (b) (4) glass beaker with a (b) (4) and held until dispensed through more commercially sterile (b) (4) and a commercially sterile (b) (4) to open sterile glass vials. The simulations on (b) (4) used (b) (4) batch sizes respectively and your largest batch size is (b) (4). These simulations did not use the sterilizing(b) (4) currently in use and used to sterilize the cyanocobalamin 1 mg/ml lot(b) (4) on 10/25/2023.

This is a repeated observation from FDA inspections ending on 7/28/2016 and 6/24/2019.

B. The LFH smoke flow studies august 2023 (IMG4491) provided by your customer service and shipping representative on 10/25/2023 of the (b) (4) Series(b) (4) laminar flow cabinet serial number (b) (4) did not demonstrate the laminar air flow from the HEPA filter located above the tray of open amber glass vials. For example, it also did not demonstrate if the electric outlet cover in the back of the cabinet created turbulence near the direct compounding area. The smoke studies did not include all aseptic operations,

interventions, and manipulations are not simulated. For example, the smoke studies did not include the filling and capping process of (b) (4) trays.

This is a repeat observation from the FDA inspection ending on 6/24/2019.

C. The acceptance criteria for the post fill fingertip surface sampling listed under *Section 7. of SOP Personnel Monitoring: 1. Personnel Monitoring Post Completion of Aseptic Operations Rev. 2 Effective 10/1/2021* is (b) (4) CFU/plate and this is not adequate for monitoring ISO-5 surfaces.

D. Sterile wipes are refilled into plastic containers and stored and exposed to ISO-7 air during the production of cyanocobalamin 1 mg/ml lot (b) (4) . This process was not validated.

OBSERVATION 3

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

Specifically, the door separating the drug preparation room ISO-8 from the ante room used for gowning and the door separating the anteroom room from the buffer room (b) (4) ISO-7 had sliding windows that were kept open approximately 2 inches at the bottom. The buffer room (b) (4) ISO-7 had only one exhaust vent opened directly to the non-sterile and hazardous drug compounding area that was not classified or maintained under negative pressure. This vent was also blocked by a (b) (4) workbench.

Your facility's differential pressure is monitored using a magnehelic gauges and a digital display. The gauges and digital display are not set up to retain a recording of the pressure differential continuously and require a visual reading to be made of the gauge and display to determine if there has been a

pressure differential change.

This is a repeat observation from the FDA inspection ending on 7/28/2016.

OBSERVATION 4

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

Specifically, on 10/25/2023 I observed the (b) (4) containment hood located in the ISO-8 drug preparation room was used to contain (b) (4) scales and these scales were used to weigh non-sterile drug substances and excipients such as cyanocobalamin USP lot (b) (4) and sodium chloride USP lot (b) (4). It had visible corrosion and contained white, black, and gray stains on the threshold of the (b) (4) containment hood and the pharmacy technician reached over this to weigh ingredients used for sterile compounded drug products using (b) (4) spatulas and weigh boats. Documentation printed on 10/25/2023 from the (b) (4) scale used to weigh the sodium chloride used in the cyanocobalamin 1mg/ml lot (b) (4) at the time of the weighing also did not include the date and time that these activities were performed. During this weighing process I observed the pharmacy technician remove sodium chloride USP from the weight boat and return it to the stock bottle when the target weight was exceeded.

The ISO-8 drug preparation room had a tile and grout floor located under this (b) (4) containment hood which could be a surface that if contaminated by various bulk drug substance would be hard to clean and may be a source for facility wide cross contamination through employee movement and cleaning implements such as mops.

OBSERVATION 5

Aseptic processing areas are deficient in that floors, walls and ceilings are not smooth and/or hard surfaces that are easily cleanable.

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Specifically, the ISO-7 buffer room(b) (4) flooring to include underneath the ISO-5 hood is constructed of vinyl plank like surface with embedded grooves which are not easily cleanable.

This is a repeat observation from the FDA inspection ending on 6/24/2019.

OBSERVATION 6

Your outsourcing facility compounds drug products using bulk drug substances that cannot be used in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because they (a) are not used to compound drug products that appear on the drug shortage list in effect under section 506E of the Act and (b) do not appear on a list developed by FDA of bulk drug substances for which there is a clinical need.

Specifically, you compounded a drug that appears on the Category 2 list for Outsourcing Facilities. Your last batch of disodium edetate (EDTA) 150 mg/ml (15%) for injection in 50 ml multidose vials was lot (b) (4) for IV nutrition BUD 11/02/2023. This was a (b) (4) batch of (b) (4) vials made using the bulk drug substance edetate disodium dihydrate USP lot (b) (4) which was on the Category 2 list of drug substances that have been identified to have significant safety risks.

OBSERVATION 7

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, you do not test ascorbic acid for injection 500 mg/ml in 50 ml multidose vials with a general batch size of(b) (4) vials for oxalate, a known compendial impurity, and have not scientifically established the omission of said impurity testing for the standard. You released (b) (4) batches with an approximate total of (b) (4) vials from 12/7/2021 to 10/4/2023 without testing for oxalate. You did not provide a list of batches released from 9/3/2021 to 12/7/2021and these would also have been released

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without testing for oxalate.

In addition, your firm did not use a compendial reference standard and, the non-compendial standard which your firm used has not been characterized and qualified as a reference standard.

OBSERVATION 8

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

Specifically, your test method validation for the (b) (4) used to determine the assay/potency of ascorbic acid for injection 500 mg/ml in 50 ml multi dose vials did not demonstrate the specificity of the test method.

This is a repeated observation from FDA inspections ending on 7/28/2016, 6/24/2019, and 9/3/2021.

OBSERVATION 9

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

Specifically, you do not test all batches of compounded drug products for assay for sterile and non-sterile compounded drugs.

For example:

1.) Assay release testing was not performed on disodium edetate (EDTA) 150 mg/ml (15%) for injection lot (b) (4)
2.) Assay release testing was not performed on 35 mcg liothyronine (T3) sodium capsules lot

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(b) (4)

OBSERVATION 10

Your outsourcing facility has not submitted a report to FDA identifying a product compounded during the previous six months as required by section 503B(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Specifically,

a. The following two drug products were compounded and not identified on your June 2023 report:

- CMP FLU0.3/HYD4/ TRE0.06/ KOJ6
- CMP NAD+ 5MG/ML or 50 mg/ml

b. Multiple drug products were compounded and not identified on your December 2022 report. Examples include, but are not limited to:

- Ascorbic acid 500mg/ml
- Combo drops, Cyclogyl 0.5% Neosynephrine 2.5% Tropicamide 0.5%
- Cyanocobalamin, Methionine, Inositol Choline 1/25/50/50mg/ml
- Lidocaine 1% Buffered
- Magnesium chloride 200mg/ml
- Methionine, Inositol, Choline 25/50/50mg/ml
- Glutamine, Arginine, and Carnitin (G.A.C.) 25mg/100mg/100mg
- Liposupreme
- Myer's Cocktail I and II
- Progesterone capsules
- Sermorelin acetate Injection & Troche

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OBSERVATION 11

Master production and control records lack complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations and precautions to be followed.

Specifically,

A. Control records such as the laboratory notebook for endotoxin testing did not include page numbers and did not include a review by the QCU to include a signature and date.

B. Control records such as the logs used for the environmental monitoring (EM) performed during the sterile filling of compounded sterile drug products were filed in logs that indicated the wrong year.

C. Control records such as EM forms had the same form number and appeared to be the same form with different revisions, but were different due to the equipment used to monitor viable air particles and were still in use for example:

1. (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 4 (is for the (b) (4) {(b) (4) } viable air particle tester) and (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 3 (is for the (b) (4) (b) (4) } viable air particle tester) were both in use from 1/25/2022 to 9/11/2023.
2. (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 5 (for the (b) (4) viable air particle tester) and (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 3 (is for the (b) (4) viable air particle tester) were both in use from 9/28/2023 to 10/12/2023.

D. Control records were missing, there was no record for EM monitoring for viable air particles of the buffer room (b) (4) during the compounding of doxycycline hyclate ophthalmic solution lot (b) (4) .

E. The control records for methylcobalamin lot (b) (4) (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 5 for Buffer Room (b) (4) listed documentation for

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taking the reading in the ISO-7 but had an id that the sample was of the laminar air flow hood (LAFH). This is a critical record as the filling is sterile filling and this is the ISO-5 LAFH.

F. The control records for cyanocobalamin/methionine/inositol/choline chloride 1/25/50/50mG/ml for injection lot (b) (4) (b) (4) Viable Microorganism Monitoring: Collection of Samples Form 69 Rev. 5 dated 10/12/2023 for the LAFH monitoring listed EM during production passing test results under the ISO-7. This is a critical record as the filling is sterile filling and this should have been passing test results recorded under the ISO-5.

G. Test methods for cyanocobalamin 1mg/ml of injection in 30 ml multidose vials for assay, sterility, endotoxin, density, osmolality, and pH are not identified in the batch record under an approved test method. The methods did not include a test method number or a review and approval signature from the QCU. Some of these test methods included written notations that were also not reviewed and approved.

H. The ascorbic acid 500 mg/ml for injection in 50 ml vial (b) (4) test method was not fully validated. *This is a repeated observation from FDA inspections ending on 6/24/2019 and 9/3/2021.*

***DATES OF INSPECTION**

10/16/2023(Mon), 10/17/2023(Tue), 10/18/2023(Wed), 10/19/2023(Thu), 10/20/2023(Fri), 10/23/2023(Mon), 10/24/2023(Tue), 10/25/2023(Wed), 10/26/2023(Thu), 10/27/2023(Fri), 11/09/2023(Thu)

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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."