DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	01/31/2022 - 02/04/2022
	FEI NUMBER 1000418405

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Luis Solera Blasco, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Bioiberica, S.A.U	Carrer Antic Cami de Tordera 109 - 119
CITY, STATE AND ZIP CODE Palafolls, Barcelona, 08389, Spain	TYPE OF ESTABLISHMENT INSPECTED Drug Substance Manufacturing Facility

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

Cleaning procedures for equipment used in the campaign manufacture of drug substances are not validated to facilitated adequate cleaning and contamination prevention measures.

Specifically, current cleaning operations at your firm consists of cleaning the manufacturing (b) (4) and (b) (4) (b) (4) equipment (b) (4) with water and (b) (4) % (b) (4) and cleaning clean room equipment consisting of a (b) (4) with dry clean (b) (4) cloth and spraying (b) (4) This equipment is used for campaign production of successive batches of (b) (4) USP drug substances and are not adequately validated to be cleaned at appropriate intervals to prevent build-up and carry-over contaminants such as degradants or objectionable levels of microorganisms.

Furthermore, during the current inspection, I reviewed at least five instances where OOS investigations and non-conformities were initiated for microbial contamination for your (b) (4) USP drug substance which resulted in your firm "reprocessing" the batch. In addition, I reviewed a non-conformity for (b) (4) content in the drug substance which was determined to be a result of (b) (4) particles from previous batch production particle buildup blocking the (b) (4) used for (b) (4) in the (b) (4) Similarly, I reviewed multiple customer complaints for (b) (4) or "dark particles" observed in final finished (b) (4) USP drug substance drums which were investigated by your firm and found to be a result of (b) (4) during the (b) (4) process in the (b) (4) equipment.

OBSERVATION 2

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Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of the drug substance.

Critical process parameter established as (b) (4) of the (b) (4) USP drug substance at (b) (4) by your firm is not controlled and monitored during the process validation studies.

Specifically, (b) (4) USP drug substance is "reprocessed" by your firm upon confirmation of an OOS and non-conformity. I observed "reprocessing" operations for multiple batches due to microbiological contamination and high (b) (4) content. Your firm performed a validation study for the microbiological "reprocessing" procedure, which established (b) (4) parameters for (b) (4) at (b) (4) using an industrial (b) (4) for additional (b) (4) which is not an equipment that is used as part of the validated manufacturing process of drug substance (b) (4) USP.

The original validated and approved processing method utilizes a (b) (4) at (b) (4) (b) (4) at greater than (b) (4) with validated time around (b) (4)

As a result of the of the microbiological contamination or high (b) (4) content for non-conformity investigations performed, your firms corrective action consisted of "reprocessing" batches using an industrial (b) (4) with (b) (4) of (b) (4) and (b) (4) time ranging from (b) (4) to (b) (4) for per batch, which is up to 2 times the validated procedure. Additionally, your industrial (b) (4) is not equipped with real time (b) (4) monitoring or (b) (4) summary when (b) (4) has been concluded.

No studies have been performed on the effect of the (b) (4) parameters with respect to microbiological and degradant control in the (b) (4) USP drug substance which considers the validated procedure during normal manufacturing operations using the (b) (4) or the "reprocessing" method using the industrial (b) (4) Furthermore, from the years 2020 – 2021, I observed at least 23 batches which were (b) (4) more than one (b) (4) operation, and up to five (b) (4) operations, with no documented justification or available data to support the additional (b) (4)

In addition, your firm has not performed an impurity profile to study the identified and unidentified impurities

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which may be present in your (b) (4) USP drug substance and consequently does not perform impurity testing for released drug substance. As a result, the validity of the validation of the process cannot be verified.

OBSERVATION 3

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

Specifically,

A. During my review of electronic HPLC data for assay testing, my review found that when undesirable results are encountered during analysis of drug substance, samples are re-tested until desirable results are achieved. The original test results were not reported, and no laboratory investigation was initiated per your firm's OOS procedure. Specifically, during review of your firm's complaint investigation, REC8783, for batch (b) (4) (b) (4) for (b) (4) USP was analyzed in support of the complaint. During testing of this batch for assay for two active ingredients (b) (4) and (b) (4) your firm encountered unknown peaks for the (b) (4) retention time. No investigation was performed. Instead, your firm prepared new sample solutions, and retested the sample, with reported results as within specification.

B. Your assay test method calls for preparing an internal standard from a characterized batch which is used to determine system suitability. During my review of electronic data for (b) (4) USP drug substance I observed multiple occasions where the sample solution was tested more than once due to not meeting internal standard system suitability specifications. In response, your firm discarded all sample solution preparations and internal standard preparations and prepared a new sample solution along with a new internal standard solution for testing. Per your firm, a new sample solution is prepared since a new internal standard is also prepared, for both preparations to have (b) (4) concurrently for testing. However, during my review of your contract laboratory assay method validation, it was determined that the sample solution for (b) (4) USP drug substance is stable from (b) (4) (b) (4) There is no scientific justification or study to support your firm's current practice of preparing new sample solutions for re-testing.

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C. The assay test method used to identify two active ingredients in your (b) (4) USP drug substance has not been adequately verified by your QC laboratory. Your firm contracted a testing laboratory to perform the method validation for your assay test method. Upon receiving this report, your firm only performed a verification study for accuracy. No consideration was given to performing a study which incorporated reproducibility, repeatability, precision, analytical range, limit of quantification (LOQ) and Limit of Detection (LOD).

D. In addition, your firm has not performed an impurity profile on the drug substance to study the identified and unidentified impurities which may be present in your (b) (4) USP drug substance and consequently does not perform impurity testing for released drug substance.

OBSERVATION 4

There is no written testing program designed to assess the stability characteristics of drug substances.

Specifically, the assay test method for active ingredients (b) (4) and (b) (4) used for stability testing of (b) (4) USP drug substance is not stability indicating, where it can detect the change with time in the chemical, physical or microbiological properties of the (b) (4) USP drug substance are specific so that the content of active ingredients and degradation products can be accurately measured without interference. As a result, the validity of the stability of the process cannot be verified, in that your firm is not able to monitor results during stability studies in order to assure safety, efficacy and quality for your (b) (4) USP finished drug substance.

OBSERVATION 5

Written records of investigations into unexplained discrepancies do not always include conclusions and follow-up which are adequately justified.

Specifically,

A. Investigations initiated and performed as a result of microbiological non-conformities for (b) (4) USP drug

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substance do not extend to batches manufactured during the campaign.

B. During the inspection, I reviewed non-conformity investigations due to high (b) (4) as a result of the (b) (4) (b) (4) being blocked due to (b) (4) particle build. Your firm's CAPA consisted of establishing a procedure where the (b) (4) is changed (b) (4) No consideration was given to cleaning operation impact on the (b) (4) during the investigation and CAPA process.

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