WARNING LETTER

Bioiberica, SAU

MARCS-CMS 629115 — JUNE 30, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Luis Solera Blasco

Chief Executive Officer

Bioiberica, SAU

Plaza Francesc Macia, 7
08029 Barcelona Barcelona
Spain

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-22-20

June 30, 2022

Dear Mr. Blasco:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Bioiberica, SAU, FEI 1000418405, at Carrer Antic Cami de Tordera 109-119, Palafolls, Barcelona, from January 31 to February 4, 2022.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your February 18, 2022, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure to establish written procedures to monitor the progress and control the performance of processing steps that may cause variability in the quality characteristics of your intermediates and API.

You failed to establish appropriate monitoring and controls for reworking batches of **(b)(4)** USP, API. In 2020 and 2021, approximately 23 batches of **(b)(4)** USP, API were reworked in your industrial **(b)(4)** because of microbiological out-of-specification or non-conforming high **(b)(4)**, a class 3 residual solvent, content results. The use of the industrial **(b)(4)** was not part of the established process validation for **(b)(4)** USP, API. The investigator documented this **(b)(4)** was used to rework multiple batches from **(b)(4)** to as many as **(b)(4)** times until acceptable results were obtained. No studies had been performed to establish the effectiveness of this rework step. Additionally, your industrial **(b)(4)** was not equipped with real time **(b)(4)** monitoring or a **(b)(4)** summary to monitor the performance of the **(b)(4)**.

An ongoing program for monitoring process controls to ensure your rework operations can maintain consistent drug quality is essential. The **(b)(4)** USP, API you manufactured is used to produce drug products to treat **(b)(4)**. Because of the narrow therapeutic range of these products, proper blending, and manufacture of your product, appropriately evaluated through process validation, is essential to prevent patients from receiving insufficient or excessive doses.

In your response, you agreed that there was inadequate control and monitoring of **(b)(4)** processes. Additionally, you committed to validating your microbiological contamination reduction process.

Your response is inadequate. Your response repeatedly described the additional **(b)(4)** that was performed as reprocessing. However, the use of equipment that is not part of the validated manufacturing process is considered rework. In addition, you failed to provide interim measures to ensure your manufacturing process can adequately reduce microbiological contamination and **(b)(4)** content until validation can be conducted. You also failed to provide a corrective action to address the lack of process controls for the industrial **(b)(4)** used during rework.

In response to this letter, provide the following:

- An assessment of the **(b)(4)** USP, API manufacturing process, including rework activities performed, to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, reliability of each manufacturing process step and control, and the need to revalidate your manufacturing process.
- Timelines for completing process performance qualification studies on remediated processes for marketed drug products for which a state of control has not been adequately/fully established.
- A comprehensive, independent assessment of the design and control of your firm's manufacturing operations, with a detailed and thorough review of all microbiological hazards.

2. Failure to ensure that reworked batches have been subjected to appropriate evaluation and stability testing to show that the reworked material is of equivalent quality to that produced by the original process.

Reworked **(b)(4)** USP, API batches were not placed on stability. In 2020 and 2021, approximately 23 batches of **(b)(4)** USP, API batches, were subjected to rework in an industrial **(b)(4)** that was not a part of your validated manufacturing process. These batches were reworked because of microbiological out-of-specification or non-conforming high **(b)(4)** results. None of the reworked batches were placed on stability to ensure they were of quality equivalent to that produced by the validated process.

In your response, you committed to develop impurity profile parameters and stability-indicating analytical methods.

However, you failed to provide interim measures until your proposed actions are complete. Additionally, the stability of reworked batches currently on the market have not been evaluated.

In response to this letter, provide the following:

- Interim measures implemented until corrective and preventive actions are completed.
- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:

o Stability studies for **(b)(4)** USP, API that is reworked in its marketed container-closure system before distribution is permitted
o An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
o Detailed definition of the specific attributes to be tested at each station (timepoint)

- All procedures that describe these and other elements of your remediated stability program.
- Rework procedure that describes how reworked batches will be evaluated to determine their equivalence to the validated process.

Process Controls

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.

See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf (https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf).

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of any deviations and for preventing their recurrence or the occurrence of other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any deviations.

Failure to address any deviations may also result in the FDA refusing admission of articles manufactured at Bioiberica, SAU, FEI 1000418405, at Carrer Antic Cami de Tordera 109-119, Palafolls, Barcelona into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be adulterated may be detained or refused admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 1000418405 and ATTN: Joseph Lambert, Pharm.D.

Sincerely,
/S/
Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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