Interquim S.A. 11/22/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
10903 New Hampshire
Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-08

November 22, 2016

Dr. Francesc Xavier Camps
Director
Interquim, S.A.
C/ Joan Buscalla, 10
Sant Cugat del Valles, Barcelona 08173
Spain

Dear Dr. Camps:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Interquim, S.A., at C/ Joan Buscalla, 10 Sant Cugat del Valles, Barcelona, from May 2 to 6, 2016.

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 May 27, 2016, response 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 have adequate cleaning procedures that define and justify acceptance criteria for residues.

Our investigator found that the interior surfaces of your non-dedicated drug manufacturing equipment (**(b)(4)**, **(b)(4)**, **(b)(4)**) were not clean as required by your cleaning SOP. For example, our investigator pointed out the presence of **(b)(4)** residue inside **(b)(4)**/A-2572 and **(b)(4)**/A-6364 that were labeled "clean." Inadequate removal of residues from manufacturing equipment during cleaning can lead to cross-contamination of API subsequently manufactured on the same pieces of equipment.

In your response, you acknowledge that the **(b)(4)** residue resulted from inadequate cleaning of the **(b)(4)** after production of **(b)(4)**. You said that you have revised your cleaning method to include an **(b)(4)** solvent step. However, your response is inadequate because you did not determine that the revised cleaning procedure was effective. In addition, you did not determine if your cleaning procedures are effective for all API that you manufacture on your non-dedicated equipment. You did not define the acceptance criteria for carryover of residues.

In response to this letter, provide the following:

- an action plan to determine whether your manufacturing equipment cleaning procedures are effective, including your cleaning validation approach, verification sampling program and acceptance criteria. Provide the scientific rationale for each of these.
- a risk evaluation of potential cross-contamination due to inadequate cleaning for API within expiry in distribution in the United States
- a timeline for completion of these activities

2. Failure to construct equipment so that surfaces that contact raw materials, intermediates, or API do not alter the quality of API beyond established specifications.

Our investigator observed that the interior surfaces of two non-dedicated **(b)(4)** (**(b)(4)**/A-2544 and **(b)(4)**/A-0459) were discolored. You indicated that the discoloration was due to deterioration from "**(b)(4)**." Your equipment maintenance contractor, **(b)(4)**, had previously noted the damage and repaired it with an **(b)(4)** material (**(b)(4)**). However, you failed to demonstrate that the **(b)(4)** used to repair the interior **(b)(4)** surfaces did not affect API quality.

In your response, you note that your current preventive maintenance plan is to measure and monitor the thickness and **(b)(4)** of the **(b)(4)** surfaces in these **(b)(4)**. Your response is inadequate. You did not provide a root cause for the "**(b)(4)**" on the **(b)(4)** surfaces of the **(b)(4)**, nor did you demonstrate that your preventive maintenance plan ensures that the repaired surface is suitable for manufacturing.

In response to this letter, provide an evaluation of whether your repaired equipment and the **(b)(4)** are suitable for use in your manufacturing processes. Provide your investigation and conclusion regarding the root cause for the "**(b)(4)**" on the **(b)(4)** surfaces of the **(b)(4)** and associated corrective actions and preventive actions. You

should continually monitor the repaired equipment in order to detect the potential for undesirable changes in quality of your API.

3. Failure of the quality unit to ensure that there is stability data to support retest or expiry dates and storage conditions on API and/or intermediates.

During the inspection your firm did not provide stability data to support the **(b)(4)** retest period assigned to reprocessed API, **(b)(4)** (lots **(b)(4)** and **(b)(4)**). You provided 12-month stability data for the reprocessed API. In your response you only discussed the reprocessing activities but not the lack of stability data. Without stability data for your reprocessed API, you cannot assure that your reprocessed API meets specifications throughout its assigned shelf life. This could adversely affect the quality of the drugs that your customers manufacture from your API.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations for determining the causes, for preventing their recurrence, and for preventing 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) and 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.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at Interquim, S.A., C/ Joan Buscalla, 10, Sant Cugat del Valles, Barcelona, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of 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).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. 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 or mail your reply to:
Runa Musib, Interdisciplinary Scientist

U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002807304.

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