WARNING LETTER

Proquimes S A Productos Quimicos Especializados S.A.

MARCS-CMS 610069 — APRIL 05, 2021

Delivery Method:

VIA Electronic Mail

Product:

Drugs

Recipient:

Mr. Francisco De la Puente

General Manager

Proquimes S A Productos Quimicos Especializados S.A.

Carrera 5 Norte No. 52-61
Cali, VAC, 760002
Colombia

Issuing Office:

Center for Drug Evaluation and Research

United States

Warning Letter 320-21-39

April 5, 2021

Dear Mr. De la Puente:

Your facility is registered with the United States Food and Drug Administration (FDA) as a manufacturer of active pharmaceutical ingredients (API). FDA has reviewed the records you submitted in response to our April 16, 2020, request for records and other information pursuant to section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), along with subsequent communication, pertaining to your facility, Proquimes S.A. Productos Quimico Especializados S.A., FEI 3010165166, at Carrera 5 Norte No. 52-61, Cali Valle del Cauca.

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

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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)).

1. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

Your response to our request for records or other information pursuant to section 704(a)(4) indicates that you manufactured and distributed **(b)(4)** USP API to the United States (U.S.) without validating processes determined to be critical to the quality and purity of the API. For example, in response to our April 16, 2020, request to provide the process validation summary report for all U.S. marketed API, you indicated that you did not perform process validation and therefore did not provide any documents. Our subsequent communication on June 1, 2020, specifically requested process validation for the **(b)(4)** USP API that you distributed to the United States. You, again, indicated that the manufacturing process for this drug was not validated.

Without process validation documentation, you cannot demonstrate that your manufacturing process can consistently produce API that meet predetermined quality attributes.

In response to this letter, provide the following for all API intended for the U.S. market:

• A remediation plan that assures ongoing management oversight throughout the manufacturing lifecycle of all API. Provide a data-driven and scientifically sound program that identifies sources of process variability, and assures that manufacturing, including both production and packaging, operations meet appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

• A timeline for performing process performance qualification (PPQ) for each of your marketed API.

• Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.

• Provide a detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.

2. Failure to adequately perform qualification of critical equipment and ancillary systems.

You have not conducted qualification of critical manufacturing equipment. For example, in response to our April 16, 2020, communication requesting qualification documentation for the equipment used to manufacture API distributed to the U.S., you indicated that you did not perform equipment qualification and thus could not provide any documents. Our subsequent communication on June 1, 2020, specifically asked whether you had performed qualification of the equipment used in the production of the **(b)(4)** USP API that you distributed to the United States. You indicated that this information was not available and the equipment was "unqualified."

The continued and suitable performance of manufacturing equipment is important to ensure batch-to-batch consistency during the manufacturing of API.

In response to this letter, conduct a comprehensive evaluation of the equipment used at your facility throughout API manufacturing, and provide a corrective action and preventive action (CAPA) plan that ensures use of only suitably designed and well-controlled equipment.

3. Failure to adequately validate written procedures for the cleaning and maintenance of equipment.

Your process of cleaning shared API manufacturing equipment is not validated. For example, in response to our April 16, 2020, communication requesting the most recent cleaning validation summary reports for equipment used to manufacture API distributed to the U.S., you indicated that this information was not available and you did not perform cleaning validation. Our subsequent communication on June 1, 2020, specifically requested cleaning validation for the equipment used to manufacture the **(b)(4)** USP API that you distributed to the United States. You, again, indicated that the cleaning procedure was not validated.

Inadequate removal of raw materials and residues from manufacturing equipment during cleaning can result in cross-contamination of your API.

In response to this letter, provide the following for all API manufactured to date and intended for the U.S. market:

• Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
o drugs with higher toxicities
o drugs with higher drug potencies
o drugs of lower solubility in their cleaning solvents
o drugs with characteristics that make them difficult to clean
o swabbing locations for areas that are most difficult to clean
o maximum hold times before cleaning

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

• A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

4. Failure to test the identity of each batch of incoming production material.

Your incoming raw material used to manufacture API intended for the U.S. market was not adequately tested. For example, in response to our April 16, 2020, communication asking whether you perform at least one specific identity test on each lot of each component, you indicated that an identity test is not performed due to the lack of resources.

Such testing is critical to ensure the identity of each lot of each component used in the manufacture of API prior to their use.

In response to this letter, provide the following for all API manufactured to date and intended for the U.S. market:

• A comprehensive review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

• The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.

• A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's Certificates of Analysis (COA) instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.

Additional API Guidance

For more information, see FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, at https://www.fda.gov/media/112426/download (https://www.fda.gov/media/112426/download). This guidance outlines recommended industry practices and represents FDA's current thinking regarding CGMP for the manufacture of API.

CGMP Consultant Recommended

Based on the nature of the deviations we identified, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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 associated with your drug. You are responsible for investigating and determining the causes of any deviations and for preventing their recurrence or the occurrence of other deviations.

Note that FDA placed all drugs manufactured by your firm on Import Alert 66-40 on December 3, 2020, as the methods used in and controls used for the manufacture, processing, packing, or holding of these products do not appear to conform to current good manufacturing practices within the meaning of section 501(a)(2)(B) of the FD&C Act. Drugs that appear to be adulterated or misbranded may be detained or refused admission without physical examination pursuant to section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3).

All drugs manufactured by your firm may remain listed on this import alert until there is evidence establishing that the conditions that gave rise to the appearance of this violation have been resolved, and the Agency has confidence that future entries will be in compliance with the FD&C Act. This may include an inspection prior to the Agency considering the appearance of adulteration to be addressed.

Correct all deviations promptly. FDA may withhold approval of new drug 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.

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 do so 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 3010165166 and ATTN: Carrie Ann Plucinski.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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