U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-18

December 18, 2017

Mr. Fernando Vidal Millan
Director General
Prosana Distribuciones S.A. de C.V.
Oriente 225 97-1 Agricola Oriental
Iztacalco, Mexico City DF 08500
Mexico

Dear Mr. Millan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Prosana Distribuciones S.A. de C.V. at Oriente 225 97-1 Agricola Oriental, Iztacalco, Mexico City, from March 6–9, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

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

Our investigator also collected labeling for Bicaruvas Antacid Effervescent Powder. For the purpose of this letter, we will refer to the product as Bicaruvas. Based on our review of the product label, FDA has determined that, as formulated and labeled, Bicaruvas is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c).

We reviewed your March 29, 2017, response in detail.

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

CGMP Violations

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

You distributed two batches of Bicaruvas before receiving certificates of analysis (COA) containing the finished product test results from your third-party testing laboratory, **(b)(4)**.

Your management could not locate the COA for Bicaruvas batches EBU02 and EBU03. During the inspection, you retrieved the COA from your third-party testing laboratory. You had already distributed batches EBU02 and EBU03 to the United States.

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You are responsible for the quality of drugs you produce, regardless of agreements in place with your contract testing laboratory. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to establish the reliability of component supplier analyses on which you rely in lieu of certain tests through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

You did not test for identity of incoming active pharmaceutical ingredients and other components used to manufacture over the counter (OTC) drug products. You also failed to establish the reliability of all your suppliers' analyses, and to test each component for conformity with all appropriate written specifications for purity, strength, and quality. You relied on unqualified suppliers' COA. In some instances, you accepted raw materials without COA.

3. Your firm failed to prepare batch production and control records for each batch of drug product that include complete documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch, including a statement of the actual yield, and a statement of a percentage of theoretical yield at appropriate phases of processing. (21 CFR 211.188(b)(7)).

During the inspection, your firm's management stated that operators "made up" yield results in your batch records for processing steps such as weighing, **(b)(4)**, and filling, as well as for label reconciliation. Management informed our investigator that operators falsified batch records because there were no established calculations for determining yields.

4. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

You have not validated the processes used to manufacture your drug products. You did not perform process performance qualification studies, and lacked an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.

You also lacked adequate master production and control records for Bicaruvas with established process controls. For example, you did not have a master batch record for each batch size that you manufacture. Our investigator noted that you manufactured Bicaruvas batches EBU01, EBU02, and EBU03 with five times the amount of calcium carbonate specified on the product label. Firm management stated that personnel performed a calculation on the spot for customer orders of more than **(b)(4)**, and that they used a wrong formula for these three batches.

See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and elements of process validation at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

Inadequate Response

Your March 29, 2017, response to FDA's inspectional observation was inadequate and did not provide sufficient evidence of corrective actions to bring your operations into compliance with CGMP. For example, you failed to provide:

- The quality control test methods and specifications used to analyze each drug product batch prior to a batch release decision, including both chemical and microbial quality attributes.
- A procedure detailing your batch release program and the responsibilities of your quality unit.
- An evaluation of all batches of Bicaruvas distributed to the U.S. that are still within expiry to ensure they met specifications prior to release. If your evaluation reveals substandard quality drug products, provide your proposed corrective actions, such as notifying customers or recalling product.
- Specific timelines for process performance qualification for each of your drug products, and a detailed summary of your approach for routinely monitoring intra-batch and inter-batch variations.
- A master batch record with defined process parameters.
- A summary of test results obtained from full testing of each of your incoming components to validate vendors' certificates of analysis. Provide your current incoming raw material batch release specifications for each component. Also include your procedures to ensure that you test for the identity of each incoming lot of components.

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses, and evaluate the nature of the data integrity deficiencies.

CGMP Consultant Recommended

If your firm resumes manufacturing drugs for the United States market, based upon the nature of the violations we identified at your firm you should undertake a comprehensive and global assessment to ensure that your systems and processes, and ultimately the drug products you manufacture, conform to FDA requirements. We strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, 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 fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Unapproved New Drug Violation

Examples of claims observed on the product label for Bicaruvas that establish the intended use of your product include, but may not be limited to, the following.

"FAST RELIEF OF: Heartburn, Acid Reducer, Upset Stomach" and "Uses (sic) for the relief of: Heartburn, Sour stomach, Acid indigestion, upset stomach associated with these symptoms."

Based on the above claims, Bicaruvas is a drug as defined by section 201(g)(1)(B) of the FD&C Act 21, U.S.C. 321(g)(1)(B) because it is intended for the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or under section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C) because it is intended to affect the structure or any function of the body of man.

Specifically, this product is intended as an antacid. OTC drug products intended as antacids, such as Bicaruvas, are subject to the Final Monograph for Antacid Drug Products for Over-the-Counter Use. See 21 CFR Part 331. However, this product is not formulated in accordance with this final monograph for the reasons explained below.

The product's labeled concentration for citric acid does not comply with the required concentrations for this active ingredient as specified in the final monograph. Specifically, Bicaruvas is labeled to contain 1.927 grams of citric acid per packet and includes directions for adults to dissolve one packet every 4 hours with the warning, "Do not exceed more than 5 packets in 24 hours period (sic)."

The final monograph requires that the maximum daily amount of citric acid not exceed eight grams per day. However, if taken as directed, it is possible for a consumer to exceed the eight-gram daily maximum under the final monograph (21 CFR 331). Thus, as formulated, Bicaruvas does not comply with the final monograph described above.

Furthermore, we are not aware of sufficient evidence to show Bicaruvas, as formulated and labeled, is generally recognized as safe and effective. Therefore, this product is a new drug within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p) because it is not generally recognized among scientific experts as safe and effective for its labeled uses.

As a new drug, Bicaruvas may not be legally marketed in the United States absent approval of an application filed in accordance with section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Bicaruvas is not the subject of an FDA-approved application, and therefore, the current marketing of this product violates section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction of such products into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d).

Misbranding Violation

Bicaruvas is misbranded under Section 502(c) of the FD&C Act 21 U.S.C. 352(c) because, although the labeling includes both English and Spanish, some of the information required under authority of the FD&C Act does not appear in both English and Spanish. For example, the Drug Facts panel only appears in English while the Principle Display Panel (PDP) appears in both English and Spanish. Under 21 CFR 201.15(c)(2) and 201.15(c)(3), if a product's label or labeling contains any representation in a foreign language, all words, statements, and other information required by or under authority of the FD&C Act appearing on the label shall appear thereon in the foreign language.

Bicaruvas also is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c) because neither the outer carton nor the individual packets include a lot or control number and expiration dating, which are required under 21 CFR 201.18 and 21 CFR 211.137, respectively.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). Therefore, the marketing of Bicaruvas violates this provision of the FD&C Act.

We note that the Directions section in the Drug Facts panel is unclear. The directions state that "adults and children under 12 years older (sic)" should dissolve one packet every four hours, but also states that "children under 12 years" consult a doctor.

Conclusion

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

FDA placed your firm on Import Alert 66-40 on July 12, 2017.

Until you correct all violations 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 violations may also result in FDA continuing to refuse admission of articles manufactured at Prosana Distribuciones S.A. de C.V. at Oriente 225 97-1 Agricola Oriental, Iztacalco, Mexico City 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 violations 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:

Towanda Terrell
Compliance Officer
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 3011473501.

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