

WARNING LETTER**Unipharma, LLC****MARCS-CMS 585388 – NOVEMBER 06, 2019**

Delivery Method:

UPS Overnight

Product:

Drugs

Recipient:

Raimundo J. Santamarta

President

Unipharma, LLC

10200 NW 67th Street

Tamarac, FL 33321-6404

United States

Issuing Office:

Office of Pharmaceutical Quality Operations, Division II

United States

November 6, 2019**WARNING LETTER**

Mr. Santamarta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Unipharma, LLC, FEI 3011079709, at 10200 NW 67th Street, Tamarac, Florida from April 22 to May 7, 2019.

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 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).

In addition, your firm manufactures “Dr Kids Himasal Natural Nasal Saline Solution” that is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for introduction of such product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d). Additionally, “CVS Health Children’s Nasal Saline Drops Saline Nasal Moisturizer” is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c). Introduction or delivery for introduction of such products into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). These violations are described in more detail below.

We reviewed your May 28, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

CGMP Violations

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You use **(b)(4)** water to manufacture over-the-counter (OTC) drug products. Several drug products that you manufacture are intended for infant and pediatric use. You released multiple batches of OTC drug products manufactured with **(b)(4)** water although test results indicated an adverse trend of *Burkholderia cepacia* (*B. cepacia*) in your water system. Objectionable microbiological contamination of water used in manufacturing could lead to contamination of your drug products and pose a hazard to patients.

Your firm failed to thoroughly investigate the persistent adverse trend of objectionable microorganisms identified in your **(b)(4)** water samples during qualification that you commenced in late 2018, as well as during routine monitoring. Your firm initiated an investigation to address the microorganisms identified during system qualification.

Some of the microorganisms identified by your water sampling are known to contribute to biofilm formation in **(b)(4)** water systems and can be a source of objectionable contamination of drug products.

While the investigation was ongoing, you approved the performance qualification for your water system on December 1, 2018, which included a corrective action that improved the **(b)(4)** water sample collection process. **(b)(4)** water system testing continued to find low levels of *B. cepacia* at points-of-use and in the pretreatment portion of the **(b)(4)** water system. The pretreatment portion also had too numerous to count (TNTC) levels of microorganisms on multiple occasions.

At the end of the inspection, you stopped manufacturing your OTC drug products, placed the **(b)(4)** water system in a quarantine status, and recalled all your distributed drug products in an abundance of caution.

In your response, you started a new investigation, which has identified **(b)(4)** sanitization issues, sampling method errors, and preventive maintenance deficiencies. You implemented a corrective action and preventive action (CAPA) plan and are taking additional actions including revisions to standard operating procedures before restarting the **(b)(4)** water system.

Your response is inadequate because you have not comprehensively investigated all potential root causes for your water system control deficiencies. For example, you did not provide an investigation of the pretreatment

sample location, PWI, where microbial analysis results were deemed as TNTC. Your investigation also did not include a sufficient assessment of equipment design deficiencies and system weaknesses, including but not limited to point-of-use attachments (such as transfer valves and piping), potential dead-legs, and preventive maintenance frequencies for system components. Your response also failed to address how you will ensure investigations in the future will be thorough, carefully reviewed by management, and the effectiveness of CAPAs determined.

In response to this letter, provide the following:

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed CAPA plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
- A comprehensive, independent assessment of your water system design, control, and maintenance.
- A thorough remediation plan to operate a suitable water system. Include a robust ongoing control, maintenance, and monitoring program to ensure the remediated system design consistently produces water adhering to **(b)(4)** Water, USP monograph specifications and appropriate microbial limits. Also include your plan for approving your remediated water system for use in production, and ensuring appropriate quality assurance oversight of both reintroduction of this system as well as oversight of its ongoing state of control
- Validation report for the water system obtained after all identified design issues have been fully corrected and any maintenance repairs have been completed. Include the system validation protocol, the complete test results, and the final validation report.

2. 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 failed to adequately perform process qualification for each of your OTC drug products. Your qualifications did not include appropriate acceptance criteria for all significant variables. You approved a process qualification report containing a Cpk value (process capability index) of **(b)(4)** for fill weight during **(b)(4)** operations.

Your results suggest that your process is not robust. You did not adequately demonstrate that your manufacturing processes are reproducible and controlled to consistently yield drugs of uniform character and quality.

In your response, you stated that *Process Performance Qualification for Acetaminophen 160mg/5ml Bulk Solution Protocol, PV-18-0080* was not completed and that you “inadvertently released” acetaminophen 160mg/5ml lot 80061 to the U.S. market. You also stated that you will establish process validation protocols for each product, and will include predetermined critical process parameter specifications in the revised protocols.

Your response is inadequate because you failed to provide detailed process performance qualification protocols and an overall program for assuring ongoing maintenance of a validated process.

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/media/71021/download>.

In response to this letter, provide the following:

- 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 appropriate process performance qualification for each of your marketed drug products.

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

You did not have adequate stability data to demonstrate that the chemical properties of your OTC drug products remain acceptable throughout their labeled two-year expiry period. For example, you had failing assay results for your accelerated stability studies and have not completed long-term stability studies. You lack assurance that each of your drug products can maintain its stability through its expiration period.

In your response, you stated that prior to initial release of commercial OTC drug products, **(b)(4)** batch will be placed on accelerated stability and be required to have **(b)(4)** of acceptable data before a two-year expiry can be assigned.

Your response is inadequate because you did not include a stability protocol or test results to demonstrate that your drug products met specifications throughout the labeled expiration period.

In response to this letter, provide 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:

- Stability indicating methods.
- Stability studies for each drug product in its marketed container-closure system before distribution is permitted.
- An ongoing program in which representative batches of each product are added each year to the program to determine if shelf-life claims remain valid.
- 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.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Unapproved New Drug and Misbranding Charges

"Dr Kids Himasal Natural Nasal Saline Solution"

"Dr Kids Himasal Natural Nasal Saline Solution" 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. Specifically, this product is intended for use as a nasal moisturizer¹ and nasal decongestant.

Examples of claims observed on the product labeling that establish the intended uses (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

"Nasal decongestant . . . For dry irritated nasal passages . . . Moisturizer . . . Provides natural instant, soothing relief to dry, irritated nasal passages due to cold, allergies, dry air"

OTC drug products intended for use as nasal decongestant drug products, such as "Dr Kids Himasal Natural Nasal Saline Solution" are subject to the final rule for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (cough/cold final rule). See 21 CFR Part 341. However, this product is not labeled or formulated in accordance with this final rule for the reasons explained below.

The product label for "Dr Kids Himasal Natural Nasal Saline Solution" does not distinguish active ingredients from inactive ingredients. Therefore, all of the product's labeled ingredients (water, glycerin, Himalayan salt, and benzalkonium chloride) are deemed to be represented as active ingredients as defined in 21 CFR 201.66(b) (2). However, none of these labeled ingredients are permitted nasal decongestant active ingredients described in the cough/cold final rule. See 21 CFR 341.20.

Thus, as formulated and labeled, "Dr Kids Himasal Natural Nasal Saline Solution" does not comply with the final rule described above. Furthermore, we are not aware of sufficient evidence to show "Dr Kids Himasal Natural Nasal Saline Solution" 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). As a new drug, "Dr Kids Himasal Natural Nasal Saline Solution" 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). "Dr Kids Himasal Natural Nasal Saline Solution" 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 or delivery for introduction of such product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d).

"CVS Health Children's Nasal Saline Drops Saline Nasal Moisturizer"

"CVS Health Children's Nasal Saline Drops Saline Nasal Moisturizer" 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. Specifically, this product is intended for use as a nasal moisturizer.

Examples of claims observed on the product labeling for “CVS Health Children’s Nasal Saline Drops Saline Nasal Moisturizer” that provide evidence of the intended uses (as defined in 21 CFR 201.128) of the product, and include, but may not be limited to, the following:

“Saline Nasal Moisturizer . . . provides natural instant, soothing relief to dry, irritated nasal passages due to colds, allergies”

The labeling for such drugs, like all OTC drugs, must comply with all of the applicable requirements of section 502 of the FD&C Act and all pertinent regulations found in title 21 of the Code of Federal Regulations (21 CFR). However, your product does not meet these requirements for the reasons described below.

“CVS Health Children’s Nasal Saline Drops Saline Nasal Moisturizer” is not labeled in accordance with the “Drug Facts” labeling requirements described in 21 CFR 201.66. Specifically, the product label fails to include a Drug Facts panel. Therefore, this product is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c), because the information that is required to appear on the labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

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 “CVS Health Children’s Nasal Saline Drops Saline Nasal Moisturizer” violates this provision of the FD&C Act.

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.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

FDA may also withhold approval of requests for export certificates and approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above violations are corrected. We may re-inspect to verify that you have completed your corrective actions.

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.

Your written notification should refer to case # **585388**.

Please electronically submit your reply, on company letterhead, to Jamillah Selby, Compliance Officer, at ORAPHARM2_RESPONSES@fda.hhs.gov. In addition, please submit a signed copy of your response to Jamillah.Selby@fda.hhs.gov and John.Diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Mrs. Selby via phone at 215-490-8417 or email at Jamillah.Selby@fda.hhs.gov.

Sincerely,
/S/

Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations, Division II

CC:

Renee Alsobrook, Chief, Compliance and Enforcement
Division of Drugs, Devices and Cosmetics
Department of Business and Professional Regulation
2601 Blair Stone Road
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1 For your information, the Agency in its 2003 Call for Data (68 FR 75585, Dec. 31, 2003) discussed nasal moisturizer drug products as products containing certain ingredients, including sodium chloride, normal saline or isotonic saline solution, and labeled the product makes moisturizing claims related to structure/function or disease conditions.

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