WARNING LETTER

Torrent Pharma Inc

MARCS-CMS 584701 — OCTOBER 28, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Sanjay Gupta

CEO

Torrent Pharma Inc

150 Allen Road, Suite 102
Basking Ridge, NJ 07920
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

United States

WARNING LETTER
CMS #584701

October 28, 2019

Dear Mr. Gupta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Torrent Pharma, Inc., FEI 3004536846, at 2091 Hartel Ave., Levittown, Pennsylvania, from March 11 to April 9, 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).

Your firm manufactures “PHENOBARBITAL ORAL SOLUTION, USP” and “HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg.” These products are unapproved new drugs in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for introduction of such products into interstate commerce is prohibited under sections 301(d) of the FD&C Act, 21 U.S.C. 331(d). Your products “PHENOBARBITAL ORAL SOLUTION, USP” and “HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg” are also misbranded drugs in violation of section 502(f)(1) of the FD&C Act, 21 U.S.C. 352(f)(1). 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 April 30, 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.

1. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your **(b)(4)** water system was not adequately designed, controlled, maintained, and monitored to ensure it consistently produced water that met **(b)(4)** Water, **(b)(4)** specifications and appropriate microbial limits. Among the sanitary design deficiencies in the water system were multiple dead legs and threaded pipe connections.

Notably, your firm isolated *Burkholderia cepacia* from manufacturing equipment rinse samples. An investigation identified your water system as the source of the contamination. Subsequent sampling of your water system revealed an adverse pattern of *B. cepacia* contamination in your pretreatment and downstream distribution system.

Pharmaceutical water must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate microbiological attributes. Systems that produce water for manufacturing and cleaning are critical determinants of the quality and safety of your drug products.

Your firm produced drug products such as rectal suppositories and oral solutions with this inadequate **(b)(4)** water system. Until recently, you also produced nasal solutions with this system.

Your response stated that the design of the pipes and fittings, along with multiple deadlegs, contributed to the **(b)(4)** water system contamination. We acknowledge that you decided to decommission and replace the water system. However, in your response, you proposed to procure and use a temporary system until you install a permanent replacement system.Your response lacked sufficient interim measures to ensure the water generated from your temporary system meets appropriate quality standards for **(b)(4)** water. Your response also lacked sufficient detail about the design of the temporary and new water systems, and your plan to properly monitor and maintain each system.

In response to this letter, provide:
• a comprehensive, independent assessment of the design of your **(b)(4)** water systems (both temporary and permanent), as well as your program for ongoing control and maintenance.

• a thorough corrective action and preventive action (CAPA) plan, including but not limited to:

o blueprints for the **(b)(4)** water systems with identification of all equipment and materials of construction.
o an effective program for ongoing control, maintenance, and monitoring that ensures the remediated systems that you install consistently produce water that meets **(b)(4)** Water, **(b)(4)** specifications and appropriate microbial limits (including both total counts and objectionable microbes). Regarding the latter, ensure that the total count limit for your **(b)(4)** water is appropriately stringent in view of the intended use of each of the products produced by your firm.
o revised procedures governing the updated **(b)(4)** water system, including but not limited to provisions that ensure collection of **(b)(4)** samples from your **(b)(4)** water system for microbiological count and microbial identification testing.

• Validation reports for the new **(b)(4)** water systems. Include the system validation protocol, the complete test results, and the final validation report.
• A list of all products to be made with your interim water system. Denote whether the products are aqueous or non-aqueous formulations.

2. 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 lacked an adequate investigation into failing microbiological results from your **(b)(4)** water system.

For example, investigation 18-EVE-117, from December 2018, revealed that your firm's water testing method was inadequate to reliably detect the presence of *B. cepacia* in your **(b)(4)** water system. A significant trend of microbiological deviations in the system emerged after you adjusted your sampling and testing procedures in December 2018 to be more capable of detecting *B. cepacia*. You did not sufficiently extend the investigation to potentially affected marketed batches until months after you detected the adverse pattern of objectionable microbial contamination, and several weeks after our inspection. The initial investigation also did not adequately address the significance of water system design deficiencies.

(b)(4) water from this system was used in the manufacture of numerous batches of distributed drug products.

Your response stated that you ceased using your current **(b)(4)** water system and recalled all batches of drug product currently on the market. We acknowledge your market actions and corrective action commitments. However, your response is inadequate because it lacked sufficient assurance that your system for investigations will be remediated to ensure timely, thorough, and effective investigations.

In response to this letter provide:

• a comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification (OOS) results, and failures.
• a detailed CAPA plan to remediate your investigation system. Your CAPA plan should include, but not be limited to, significant improvements in investigation competencies, root cause evaluation, scope determination, quality unit oversight, and written procedures. It should also address how you will ensure that all phases of investigations are appropriately conducted and that the CAPA is effective.
• a CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facility performance issues,

effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

(b)(4)

We acknowledge your decision **(b)(4)**.

In response to this letter, provide **(b)(4)**.
We request that you notify this office **(b)(4)**.

Quality Systems

Your firm's quality systems are inadequate. For guidance on establishing and maintaining CGMP-compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development* at https://www.fda.gov/media/71535/download (https://www.fda.gov/media/71535/download), *Q9 Quality Risk Management* at https://www.fda.gov/media/71543/download (https://www.fda.gov/media/71543/download), and *Q10 Pharmaceutical Quality System* at https://www.fda.gov/media/71553/download (https://www.fda.gov/media/71553/download).

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 Charges

Inspection of your firm and review of the information your firm submitted to FDA's Drug Registration and Listing System revealed that your firm caused the introduction into interstate commerce of "PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" in violation of sections 301(d) and 505(a) of the FD&C Act, 21 U.S.C. 331(d) and 355(a).

Your "PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" are "drugs' within the meaning of section 201(g) of the FD&C Act, 21 U.S.C. 321(g)(1) because they are articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and/or an article (other than food) intended to affect the structure or any function of the body of man or other animals. Examples of claims and statements observed in your product labeling that establish the intended use (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

Phenobarbital Oral Solution, USP, Phenobarbital 20mg and Alcohol 13.5% (NDC 16571-330), product labeling:
"INDICATIONS AND USAGE
A. Sedative
B. Anticonvulsant – For the treatment of generalized and partial seizures"
Hydrocortisone Acetate Suppositories 25mg (NDC 59741-301), product labeling:
"INDICATIONS AND USAGE

Hydrocortisone acetate are indicated for use in inflamed hemorrhoids, post-irradiation (factitial) proctitis; as an adjunct in the treatment of chronic ulcerative colitis; cryptitis; and other inflammatory conditions of anorectum and pruritus ani."

Further, as labeled, these drugs are "new drugs" within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p) because they are not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in the labeled uses. As new drugs, "PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" may not be legally marketed and distributed in the United States absent approval of an application filed in accordance with section 505(a) or (j) of the FD&C Act, 21 U.S.C. 355(b) or (j).

"PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" are not the subject to FDA-approved applications. Therefore, the current marketing of these products violates section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for 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 Charges

"PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" are misbranded under section 502(f)(l) of the FD&C Act. According to section 502(f)(l) of the FD&C Act, 21 U.S.C. 352(f)(1), a drug is misbranded if, among other things, it fails to bear adequate directions for their intended use(s). "Adequate directions for use" means directions under which a layman can use a drug safely and for the purpose for which it is intended (See 21 CFR 201.5).

"PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners and, therefore, are prescription drugs as defined in section 503(b)(1) of the FD&C Act, 21 U.S.C. 353(b)(1).

Because the conditions for which your products are intended require the professional supervision of a practitioner licensed by law to administer drugs for such conditions, adequate directions for use cannot be written so that a layman can use them safely for their intended uses. Your "PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg" are not exempt from the requirement that their labeling bear adequate direction for use under 21 CFR 201.100(c)(2) or 21 CFR 201.115 because no FDA approved applications are in effect for your "PHENOBARBITAL ORAL SOLUTION, USP" and "HYDROCORTISONE ACETATE SUPPOSITORIES, 25 mg." Thus, your products' labeling fails to bear adequate directions for their intended uses, which causes the products to be misbranded under section 502(f)(l) of the FD&C Act, 21 U.S.C. 352(f)(1).

The introduction or delivery for introduction into interstate commerce of these misbranded products violates sections 301(a) of the FD&C Act, 21 U.S.C. 331(a).

Conclusion

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

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 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.

Send your electronic reply to orapharm1_responses@fda.hhs.gov. Please identify your response with FEI #3004536846 and Warning Letter Number #584701.

If you have any questions, contact Compliance Officer James Mason at james.mason@fda.hhs.gov or 570-262-0519.

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
U.S. Food and Drug Administration
OPQO Division I/New Jersey District

cc:
Mr. Samir Mehta
Chairman and CEO
Torrent Pharma, Inc.
Torrent House, Off. Ashram Road,
Ahmedabad – 380009, Gujarat
India

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