Tris Pharma Inc. 3/26/18

Division of Pharmaceutical Quality Operations I
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WARNING LETTER
CMS # 534537

March 26, 2018

VIA UPS OVERNIGHT

Mr. Ketan Mehta
President and CEO
Tris Pharma Inc.
2033 US Highway 130, Suite D
Monmouth Junction, NJ 08852

Dear Mr. Mehta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Tris Pharma Inc. at 2033 US Highway 130, Monmouth Junction, NJ, from February 14 to March 20, 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 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).

We reviewed your April 7, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

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

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).

Your firm did not adequately investigate product failures and significant defect complaints. You lacked thorough investigations into root causes, and failed to implement prompt and effective corrective actions and preventive actions (CAPA).

In our May 2011, June 2012, and October 2014 inspections, we observed similar failures to conduct adequate investigations that ensure timely and effective corrective actions.

Failing Dissolution Results
Five lots of Quillivant XR (methylphenidate HCl) for extended-release oral suspension failed dissolution testing between May and November 2016. Three lots failed during release testing, and two lots failed when tested for stability. Your investigations typically invalidated out-of-specification (OOS) results and attributed the cause to the dissolution test method rather than manufacturing. However, you failed to adequately investigate the sources of variation in your manufacturing operation that may have caused your dissolution problems.

As part of your response to Quillivant XR dissolution problems, you have modified your dissolution test method several times, deviating from the method deemed acceptable when FDA approved your new drug application (NDA) 202100 in 2013. When you retested the failing lots with a revised test method, one lot still did not meet specifications. Furthermore, your investigation INV-16-222 revealed a trend of batches manufactured after 2014 that appeared to have **(b)(4)** than previous batches.

FDA laboratory analysis of collected samples of Quillivant XR also showed dissolution failures.

An additional assessment involving the sponsor, Pfizer, found that original test results were improperly invalidated and dissolution performance was not assured throughout the shelf-life for at least one lot.
Pfizer determined that all five lots needed to be recalled in 2017.

Your response states that **(b)(4)** during handling of the powder sample is a contributing factor to dissolution method variability. You state that sample preparation was not adequately specified in the test method or addressed in method validation. You indicate that when employing the dissolution test method submitted in NDA 202100, you allowed at least **(b)(4)** to elapse between reconstitution of the sample and initiation of dissolution testing, rather than testing the sample promptly.

Your firm and Pfizer conducted a review of all changes to the manufacturing process and process controls initiated since NDA 202100 approval. You also performed an analysis of process capability. Your review found that one or more steps in the manufacturing process may contribute excessive variation that could cause the dissolution failures. A further assessment of process controls is also being conducted using Failure Mode and Effect Analysis. You expect to complete your process assessment work and perform new process validation studies by **(b)(4)**.

Your response is inadequate because you did not promptly and thoroughly investigate variables in the manufacturing process that may be responsible for inconsistent product quality (e.g., dissolution performance). You also did not fully address the quality of all in-date Quillivant XR lots on hold or released for distribution in the United States.

In response to this letter, provide the following:

- An update on the retrospective review of all dissolution and assay failures for lots within expiry, and a risk assessment that evaluates the quality of all distributed batches;
- An update on investigations and CAPA plans initiated to address dissolution method and manufacturing process variability related to Quillivant XR;
- An update on corrective actions implemented regarding communication with sponsors to enable changes to be promptly submitted to drug applications (e.g., dissolution test method).

Leaking or Under-filled Morphine Sulfate Oral Solution bottles
Between July and December 2016, your firm received at least 24 complaints concerning three lots of morphine sulfate oral solution. The complaints concerned approximately 1,000 leaking or under-filled bottles. Your initial complaint investigation concluded that the bottles were likely damaged during shipment by the distributor or storage outside of your control. Although complaints continued after the investigation, you did not adequately evaluate other possible root causes until after our inspection.

Your response stated you would conduct a “holistic” investigation to identify a root cause for the leaking bottles. After this investigation, you attributed the leaks to a specific lot of caps that had cracks in their liners and remained in inventory for an extended time without retesting. Your response is inadequate.
Defective product remained on the market for an additional eight months before you completed a thorough investigation and initiated a recall in July 2017.

In response to this letter, provide the following:

- A summary of the steps you have taken to ensure timely root cause evaluations and effective corrective action and preventive action (CAPA) for all drug products;
- An assessment to determine whether all containers, closures, and components are assigned appropriate expiration or retest dates, and incoming material controls are adequate to prevent use of unsuitable containers, closures, and components.

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 evaluate the effect on product quality of adding a **(b)(4)** to filling line **(b)(4)** to **(b)(4)** the remaining bulk drug formulation from the **(b)(4)** at the end of a batch. The **(b)(4)** was added to the filling line to **(b)(4)**. Your firm decided during your change control process that only **(b)(4)** would be evaluated to assess the change. In October 2015, you obtained superpotent assay results for codeine polistirex and chlorpheniramine polistirex extended- release oral suspension (lots 10115007A and 10115008A). The superpotency was attributed to use of the **(b)(4)** at the end of the filling operation.

Your firm failed to adequately evaluate this change and its effect on the homogeneity of oral suspension products known to be susceptible to segregation. In addition, your investigation found that operators collected **(b)(4)** samples prior to use of the **(b)(4)**, instead of at the end of the operation when the **(b)(4)** was used.

Your firm used the **(b)(4)** in the manufacture of additional lots of codeine polistirex and chlorpheniramine polistirex, hydrocodone polistirex and chlorpheniramine polistirex, and carbinoxamine maleate extended-release oral suspension drug products. You segregated and destroyed shipper cases of only certain product lots filled using the **(b)(4)** and suspected to include superpotent units.

There is no assurance that all potentially superpotent products were destroyed. You acknowledged that you lost shipper case traceability for approximately 50 lots of hydrocodone polistirex and chlorpheniramine polistirex extended-release suspension due to a prior relabeling operation. Because testing of one potentially worst-case lot (Lot 08614114A) that had not been relabeled yielded results within specification, you felt it was representative of the other lots. You failed to address the remaining risk of potency issues in the many other lots that lacked traceability of shippers. Your investigation was inadequate and did not support your decision to allow potentially defective products to remain on the market.

Your response contains discrepancies concerning your disposition of affected codeine polistirex and chlorpheniramine polistirex extended-release oral suspension lot 10115006A. For example, your response stated that you segregated five shipper cases, 0621 to 0625, for rejection. Your supporting destruction documents do not demonstrate that you destroyed shipper case **(b)(4)**.

Your response is also inadequate because it does not adequately address your sampling operations, investigation process, and change management program, including evaluation of the potential effect of manufacturing changes.

In response to this letter, provide the following:

- A review of changes implemented since March 2015 to determine potential effect on product quality;
- An update on your improvements in risk management and include the relevant procedure(s);
- A risk assessment of the lots released to the market with possible OOS units and an explanation for why potentially defective lots remained in distribution;
- An independent evaluation of your change management system. This review should include but not be limited to review of your procedure(s) to ensure changes are sufficiently justified and adequately reviewed and approved by your quality unit. The change management program should also include specific provisions for determining change effectiveness;
- A comprehensive, independent assessment of your overall system for investigations and deviations, atypical events, complaints, OOS results, and failures. The CAPA should include but not be limited to improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight of investigations;
- An independent assessment of your sampling operations to improve detection of upstream process variation with special focus on process steps that can introduce significant variation
- A CAPA plan to improve upstream controls and sampling plans;
- Documentation to support the destruction of all rejected shipper cases of codeine polistirex and chlorpheniramine polistirex extended-release oral suspension.

Responsibilities as a contractor

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 and your customer, Pfizer, have a quality agreement regarding the manufacture of drug products. You are responsible for the quality of drugs you produce as a contract facility, regardless of agreements in place with application sponsors. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for 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/g**

(http://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf)uidances/ucm353925.pdf. (http://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf)

Communications with Sponsor

You are responsible for ensuring that your firm complies with all applicable requirements, including the CGMP regulations. You should immediately notify the drug application sponsor of changes to the manufacturing or testing of the drug product, and any relevant drug master file updates, so they can file an appropriate submission to the application (supplement or report in annual report). A major change should not be implemented until a prior approval supplement is approved by FDA.

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 fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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.

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 (/Drugs/default.htm)**, 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.

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.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 the Warning Letter Number above (534537). Please send your electronic reply to **Barbara.Wilimczyk@fda.hhs.gov or mail your reply to: (mailto:Barbara.Wilimczyk@fda.hhs.gov)**

Barbara Wilimczyk-Macri
Compliance Officer, Division of Pharmaceutical Quality Operations I
United States Food and Drug Administration
10 Waterview Blvd., 3rd Floor

Parsippany, NJ 07054

If you have any questions about the contents of this letter, please contact Barbara Wilimczyk-Macri, Compliance Officer at (973) 331-4951.

Sincerely,
/S/
Diana Amador-Toro
Director, Division of Pharmaceutical Quality Operations I

cc:
Mr. John F. Kelly, Vice President, Quality Operations and Environment, Health and Safety
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