WARNING LETTER

Syntec Pharma Corp

MARCS-CMS 612765 — JULY 06, 2021

Delivery Method:

Email

Product:

Drugs

Recipient:

Mr. Yongsheng Wilson Jiao
Chief Executive Officer
Syntec Pharma Corp
96 Gazza Boulevard
Farmingdale, NY 11735
United States

Issuing Office:

Office of Pharmaceutical Quality Operations Division I
United States

WARNING LETTER

WL # 612765

July 6, 2021

Dear Mr. Jiao:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Syntec Pharma Corp., FEI 3010057717, located at 96 Gazza Boulevard, Farmingdale, New York 11735, from October 7 to October 28, 2020.

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

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 receipt in interstate commerce of adulterated drugs, and the delivery or proffered delivery thereof, is a violation of section 301(c) of the FD&C Act, 21 U.S.C. 331(c).

We reviewed your December 4, 2020, response to our Form FDA 483 in detail, and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. Failure to perform repackaging, relabeling, or holding of API under appropriate CGMP to avoid mix-ups and loss of API identity or purity.

Your firm failed to have adequate controls to prevent cross-contamination between API. Your functions included receipt, storage, weighing, repackaging, and relabeling of API in the same room using non-dedicated equipment and without appropriate procedures.

During the inspection you initially stated that you did not repackage any highly potent API. However, our review of your records found that you charged your customer for repackaging lot **(b)(4)** of Lomustine, a cytotoxic chemotherapy agent. After this was brought to your attention, you acknowledged that you occasionally perform repackaging, but could not remember the specific Lomustine repackaging activity. This repackaging activity lacked basic documentation of the operation, including a batch record and equipment use log.

In addition, you acknowledged that you inappropriately stored Lomustine and human chorionic gonadotrophin (HCG) at room temperature, instead of refrigeration as required by the manufacturers' certificates of analysis (COA) to prevent degradation.

Furthermore, you kept weed killer, engine antifreeze coolant, and dry wall repair products in the same room where you stored your API and packaging components. You also comingled personal food items and unidentified products in unlabeled aluminum bags in the refrigerator where you stored your API and chemicals.

The drugs distributed by your firm were at risk for contamination and other hazards to drug safety because you failed to appropriately design your facility, establish effective procedures, maintain records of your activities, and implement robust controls.

In your response, you stated that you will divide the pharmaceutical storage area into four sections by using a separate shelf for each of the following categories: cytotoxic compounds, beta-lactam, other potent compounds, and other API.

Your response is inadequate. You failed to identify the risks associated with the drugs you handled, and to provide an appropriate corrective action and preventive action (CAPA) plan to ensure the remediations necessary to prevent cross-contamination and mix-ups.

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download).

For additional information, please also refer to our guidance for industry, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*, available at https://www.fda.gov/media/79971/download (https://www.fda.gov/media/79971/download).

We acknowledge that you have temporarily ceased your repackaging operations.

In response to this letter, provide:

• An independent retrospective risk assessment to determine whether any API distributed by your firm were contaminated or label mix-ups may have occurred.

• An independent assessment of your facilities, equipment, processes, and materials to determine suitability for their intended use in the manufacture of all drugs. Provide a report that summarizes all inadequate conditions and practices identified by the qualified consultant, along with CAPAs and associated timelines for completion.

• A comprehensive plan for segregation if you intend to manipulate (e.g., open, sample, weigh, transfer) any beta-lactam or potent compounds. More specifically:
  o For beta-lactam API, provide a detailed CAPA that includes, but is not limited to, a facility that is completely and comprehensively separated from the facility where non-beta-lactam API may be exposed.
  o For highly potent API, provide an appropriate CAPA that ensures containment for these API to prevent cross-contamination and other safety hazards. Include appropriate design and control provisions related to equipment, air systems, rooms, and procedures.

2. Failure to adequately establish written procedures for cleaning equipment and its release for use in manufacture of API and validate written procedures for the cleaning and maintenance of equipment.

Your firm failed to establish adequate written procedures for cleaning non-dedicated production equipment used for your API, some of which were highly potent. In addition, you failed to document the usage and cleaning of repackaging equipment. For example, you did not document equipment used or whether cleaning was performed after repackaging a cytotoxic drug, Lomustine (lot **(b)(4)**), on or around April 9, 2020.

During the inspection, you stated that the laundry detergent "**(b)(4)**" was used to clean the ventilation hood, utensils (stainless steel spoons), and balances. You failed to utilize an appropriate cleaning agent and to conduct cleaning validation studies to demonstrate that your cleaning agent and procedures were effective.

In your response, you stated that "Only small tools and equipment were used for these operations, and these tools were visually clean before use. Thus, we believe the risk of contamination of any materials in the market is exceedingly small." Your response is inadequate because you did not provide compelling evidence to support that cross-contamination has not occurred for your APIs that have been distributed. For example, there were no equipment use logs or records to show when or how cleaning may have occurred.

In response to this letter, provide:

• An independent risk assessment to determine the effect of inadequate cleaning practices on all potentially affected lots of API you distributed. Specify what actions you will take, such as notifying customers and recalling products, if your risk assessment indicates that your drugs may be compromised by your inadequate cleaning procedures.

• A comprehensive plan including your cleaning validation strategy, procedures, protocols, and study timeline.

• An appropriate 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.

3. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.

Your firm lacked adequate quality unit (QU) oversight for the manufacture of your API. For example, your QU failed to:

• Perform adequate testing and approve the results for your API prior to their release and distribution. You did not perform identity tests for your API to ascertain their quality. You relied solely on your supplier's COA without establishing the reliability of the suppliers' analyses through appropriate qualification. For example, you released Oxytocin lots **(b)(4)** and **(b)(4)** that were tested and found to be super-potent by your customer.

• Ensure that there was stability data to support retest or expiration dates, as well as storage conditions, of API (e.g., lomustine; azelaic acid) when you repackaged them into different container-closure systems from their original ones.

• Establish specifications for the API that you received.

• Establish adequate written procedures for your API receiving, release, and distribution activities.

• Establish and approve master production instructions and have batch production records for every lot of API manufactured (e.g., repacking, relabeling) at your facility.

• Establish adequate procedures for CAPA, change control, and investigations (e.g., out-of-specification results, non-conformances, complaints).

In your response, you provided a recently established procedure for receipt, storage, and release of your incoming materials. You stated that you will reject or approve your incoming materials based on whether a manufacturer reports passing their specifications on a COA.

Your response is inadequate because you did not provide any CAPA for establishing specifications that will be used to evaluate and release each lot of your incoming API, containers, and closures. You also failed to provide details of your supplier qualification program.

We acknowledge that you implemented a procedure for good documentation practices. However, you have not established and provided the master production instructions for future API manufacturing operations.

In response to this letter, provide:

• A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  o A determination of whether procedures used by your firm are robust and appropriate
  o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
  o A complete and final review of each batch and its related information before the QU disposition decision
  o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products

• 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 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.

• Master production instructions for future manufacturing operations (e.g., opening, sampling, weighing, transfer, repackaging, relabeling), and the first five executed batch records if you resume your operations.

• A comprehensive independent review to determine whether 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.

• Stability studies to support retest or expiration dates of each API that are repackaged into different container-closure systems from their original ones. The studies should include, but not be limited to:
  o Stability-indicating methods
  o Detailed definition of the specific attributes to be tested at each station (timepoint)
  o All procedures that describe these and other elements of your remediated stability program

• A summary of your program for qualifying and overseeing contract facilities that will be used to test the drugs you distribute.

Receipt of Adulterated Drugs

We reviewed a list of your suppliers and noted that all drug products from three (3) of your API suppliers were subject to an import alert at the time you imported drugs from these firms. Drugs from two of the API suppliers used by your firm were listed on import alert IA 66-40 for the supplier's failure to conform to current good manufacturing practice within the meaning of section 501(a)(2)(B). Drugs from one API supplier used by your firm were listed on IA 99-32 for the supplier's conduct in delaying, denying, or limiting FDA inspections of foreign facilities or providing reasonable access to FDA's inspectional personnel. Additionally, the FDA has issued warning letters to two of your API suppliers explaining that the issues related to CGMP compliance cause the drugs to be adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B). Your receipt in interstate commerce of adulterated drugs and the delivery or proffered delivery thereof, is a violation of section 301(c) of the FD&C Act, 21 U.S.C. 331(c).

For example:

• All drug products from **(b)(4)** have been listed on FDA IA 66-40 since **(b)(4)**, and they remain on import alert at this time. On **(b)(4)** received a warning letter from the FDA for failure to comply with CGMPs. Your firm imported multiple lots of Nitrofurantoin manufactured on June 24 and October 21, 2019 by this manufacturer and distributed the drug to your customer from August 16 to November 18, 2019.

• All drug products from **(b)(4)** have been listed on FDA IA 66-40 since **(b)(4)**, and they remain on import alert at this time. On **(b)(4)** received a warning letter from the FDA for failure to comply with CGMPs. Your firm imported Pimobendan EP (European Pharmacopeia) manufactured on **(b)(4)** by this manufacturer and distributed the drug to your customer on May 15, 2019.

• All drug products from **(b)(4)** have been listed on IA 99-32 since **(b)(4)**, and they remain on import alert at this time. Your firm imported multiple lots of Estriol USP (United States Pharmacopeia) manufactured on August 3, 2017, June 9 and October 10, 2018 by this manufacturer, and distributed the drug to your customer from February 21, 2018 to February 26, 2019.

You are responsible for ensuring that the drugs you distribute are manufactured in compliance with all relevant CGMP requirements for drugs. Up-to-date information regarding import alerts can be found at the following FDA website: https://www.accessdata.fda.gov/cms_ia/ialist.html (https://www.accessdata.fda.gov/cms_ia/ialist.html).

Quality Systems Guidance

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download (https://www.fda.gov/media/71023/download).

CGMP Consultant Recommended

We strongly recommend engaging a consultant qualified to thoroughly evaluate your entire operation 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.

Drug Production Suspended

We acknowledge your commitment to suspend manufacturing of drugs at this facility. In response to this letter, clarify whether you intend to conduct any operations at this facility in the future. If you plan to resume drug operations, notify this office prior to resuming these activities.

In addition, if you decide to transfer your ownership, contract out any processes, or move to a new location, notify this office prior to resuming your operations.

Conclusion

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

Correct any deviations promptly. Failure to promptly and adequately address this matter may result in regulatory or legal action without further notice including, without limitation, seizure and injunction. Unresolved deviations may also prevent other Federal agencies from awarding contracts.

Failure to address deviations may also cause FDA to withhold issuance of Export Certificates. FDA may withhold approval of new 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 address 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 since our inspection to correct your 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 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. Your written notification should refer to the Warning Letter number above (#612765).

If you have questions regarding the contents of this letter, please contact Nancy Scheraga and Emmanuel Ramos, Compliance Officers, at Nancy.Scheraga@fda.hhs.gov and Emmanuel.Ramos@fda.hhs.gov.

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
Office of Pharmaceutical Quality Operations

Division I

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