WARNING LETTER

Specialty Process Labs LLC

MARCS-CMS 624281 — MAY 03, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Ricky L. Cox

President and CEO

Specialty Process Labs LLC

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United States

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Issuing Office:

Division of Pharmaceutical Quality Operations IV

United States

WARNING LETTER

May 3, 2022

Dear Mr. Cox:

The U.S. Food and Drug Administration inspected your drug manufacturing facility, Specialty Process Labs LLC, FEI 3017888878, at 1030 E. Lone Cactus Dr., Phoenix, Arizona from November 8, 2021 to November 19, 2021.

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).

We reviewed your December 13, 2021, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to demonstrate that your manufacturing process can reproducibly manufacture an intermediate and API meeting its predetermined quality attributes.

You failed to adequately validate your thyroid, USP API manufacturing processes. Specifically, there were several processing steps prior to the final blend, such as **(b)(4)**, and **(b)(4)**, that you did not include in your process validation. Your quality unit personnel stated that you planned to validate these processes in the future.

Additionally, the **(b)(4)** performance qualification was conducted but it failed to meet your pre-determined acceptance criteria to demonstrate the ability to produce a uniform blend at minimum and maximum blend sizes using a **(b)(4)** blend time. This failed qualification supported process validations of your thyroid, USP API manufacturing processes and commercially released lots.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately to assure the quality of raw material inputs, in-process materials, and finished API. Process qualification studies determine whether an initial state of control has been established.

Successful process qualification studies are necessary prior to commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

The thyroid, USP API you manufactured is used to produce drug products to treat hypothyroidism. Because of the narrow therapeutic range of these products, proper blending and manufacture of your product, appropriately evaluated through process validation, is essential to prevent patients from receiving insufficient or excessive doses.

In your response, you committed to performing a retrospective review of all batches produced on your blender, conducting a risk assessment for these batches, and establishing a master process validation plan.

Your response is inadequate. You failed to provide a detailed process performance protocol for your validations or actions to be undertaken to identify all sources of variability. Furthermore, your response did not provide a timeline for completion of prospective process performance qualification (PPQ) studies for each of your API products. The use of a retrospective validation approach is not acceptable. Lastly, you did not address the impact this violation has on your API products currently in the market.

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.

o This should include the process for selecting API lots to achieve the final API blend.

- A timeline for performing PPQ for each of your API products.
- Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
- Provide a detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control.

Also, include your program for qualification of your equipment and facility.

2. Failure to ensure that, for each batch of intermediates and API, appropriate laboratory tests are conducted to determine conformance to specifications.

You failed to perform laboratory testing to ensure that the thyroid, USP API lots held for extended periods of time met all quality attributes prior to blending into your final API blend. For example, lot **(b)(4)**, tested February 5, 2019, was blended, without retest, into finished thyroid, USP API, lot B20361-FS on February 15, 2021. Your quality unit personnel stated that your firm did not have retest requirements or procedures for lots prior to the final blend.

Additionally, the final API was labeled with a two-year re-evaluation date from the date of blending, rather than based on the manufacturing date of the oldest API lot in the blend.

In your response, you committed to conducting a retrospective review of all lots, a risk assessment of any lots that exceeded the 2-year time limit, and to establish a procedure to prevent recurrence.

Your response is inadequate as you failed to provide timelines.

In response to this letter, provide the following:

- Timelines for completion of your corrective actions and preventive actions (CAPAs). Upon completion, provide your risk assessment report and revised procedure.
- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials, including lots prior to the final API blend, 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.
- 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:

o Stability studies for your API in its marketed container-closure system before distribution is permitted.
o an ongoing program in which representative batches of each API product are added each year to the program to determine if the shelf-life claim remains valid.

o detailed definition of the specific attributes to be tested at each station (timepoint).

3. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

During the inspection, our investigator observed that many of your computerized systems lacked sufficient controls to ensure the integrity of the data being generated. For example:

- Our investigator found "System/Administrator" as the only user role for your **(b)(4)** software. There were no restrictions on deleting or modifying data for this user role. **(b)(4)** was used for assay and identity testing of finished thyroid, USP API from March 2021 to November 2021.
- Our investigator observed numerous deviations to original peak area results for HPLC assays of finished thyroid, USP API validation lots. There was no documentation of these alterations, but your quality unit personnel stated this may have been due to an unapproved update to the **(b)(4)** HPLC equipment. This equipment was never qualified according to your quality unit personnel.
- A non-validated Excel spreadsheet was utilized to calculate finished thyroid, USP API assay results for all validation lot assay calculations. The formulas and outputs of the spreadsheet were printed at the time of the calculation and not saved. You were unable to provide an electronic copy of the original spreadsheet or master spreadsheet during the inspection.
- Manufacturing master batch records held in electronic form on your company's shared drive do not have restrictions on user access. Your quality unit personnel stated that there are no restrictions for any personnel with login credentials to access new and obsolete master records. Our investigator observed during the inspection multiple versions of batch records were utilized for API lot production.

In your response, you committed to performing a retrospective review of your raw data, performing a risk assessment of all laboratory activities and establishing a master validation plan to bring all electronic software into compliance.

Your response is inadequate as you failed to provide timelines and interim measures until your proposed actions are completed. Additionally, your plan to perform a retrospective review included batches over the past 18 months despite a 24 month retest date on your labels.

In response to this letter, provide the following:

- Timelines for your response commitments and interim measures implemented until CAPAs are completed.
- Upon completion, provide your risk assessment report and electronic software master validation plan.
- A comprehensive assessment of your data review system used throughout your manufacturing and laboratory operations to determine where else it is deficient. Include a detailed CAPA plan with systemic remediation to address deficient data review, including quality unit oversight. The CAPA should include, but not be limited to, revised master batch records, training, and systemic actions implemented to assure the integrity of all CGMP records.
- An assessment of all Excel spreadsheets used to support CGMP operations to identify and investigate the extent of inaccuracies, such as incorrect formulas and other deficiencies. Include a detailed CAPA plan to address the noted deficiencies and to prevent recurrence.
- A retrospective review and risk assessment of all test data and batch records for API within expiry and distributed in the United States using computerized systems that lack sufficient control to prevent modifications and deletions. If you obtain OOS results based on this assessment, indicate your action plan, such as notifying customers and/or initiating recalls.
- A comprehensive independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight.

4. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your intermediate and API conform to established standards of quality.

The microbiological test methods used for determining the microbial attributes of your thyroid, USP API prior to release were deficient in the following:

- Growth promotion studies were not documented or conducted for either purchased or inhouse media.
- Method suitability and validation was not established or documented.

In your response, you committed to performing a retrospective review of microbiological results, completing a risk assessment, and qualifying your microbiological testing methods.

Your response is inadequate as you failed to provide timelines and interim measures until your proposed actions are completed. Additionally, your plan to perform a retrospective review included batches over the past 18 months despite having a 24 month retest date on your labels. We acknowledge your decision to implement a method "per both ICH Q7 and the current USP", but your response did not include a commitment to conduct and document growth promotion testing for all subsequent media batches used during API testing.

In response to this letter, provide the following:

- Timelines for your response commitments and interim measures implemented until CAPA are completed.
- Appropriate microbiological batch release specifications (i.e., total counts, identification of bioburden to detect objectionable microbes) for each of your API products.
- All microbial test methods used to analyze each of your drug products.
- A summary of results from testing retain samples of all drug product batches within expiry. You should test microbiological quality (total counts and identification of bioburden to detect any objectionable microbes) of each batch. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

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

Your firm's quality unit (QU) failed to perform routine QU functions to ensure drug manufacturing operations were adequate. For example, your QU failed to:

- Establish and maintain adequate evaluation procedures for third-party laboratories that are utilized for finished drug testing, such as fat analysis, inorganic iodides and residual solvents. Your quality unit has not qualified or evaluated any of the contract laboratories used for these tests.
- Ensure that CGMP training is provided to personnel at your facility.
- Perform annual product reviews for API manufactured from 2017 to 2020.

In your response, you committed to develop a comprehensive plan of third-party vendors, perform a retrospective risk assessment of the past 24 months, and develop a system to evaluate and approve vendors.

Your response is inadequate as you failed to provide timelines for your commitments.

In response to this letter, provide the following:

- Timelines for completion of your CAPAs.
- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should include, but should 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. Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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.

Additional API CGMP Guidance

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/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf (https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf).

Repeat Deficiencies at Multiple Sites

FDA cited similar CGMP deficiencies at another facility in your company's network. These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs is inadequate. Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and the products manufactured conform to FDA requirements.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. 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 to address any 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.

Please identify your response with unique identifier CMS 624281 and send electronically to orapharm4_responses@fda.hhs.gov or by mail to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
19701 Fairchild Road

Irvine, CA 92612-2506

If you have questions regarding any issues in this letter, please contact William V. Millar, Compliance Officer via email at william.millar@fda.hhs.gov or by phone at (503) 671-9711 Ext. 30.

Sincerely,
/S/

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

Cc: Thomas K. Langdon
Chief Quality Officer
Specialty Process Labs LLC
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