WARNING LETTER

TAKA USA, INC. dba Cosmetic Innovations

MARCS-CMS 587521 — JULY 29, 2020

Delivery Method:

VIA Electronic Mail

Product:

Drugs

Recipient:

Takako M. McGowan

President

TAKA USA, INC. dba Cosmetic Innovations

2210 Hutton Drive, Suite 100
Carrollton, TX 75006
United States

Issuing Office:

Division of Pharmaceutical Quality Operations II

United States

July 29, 2020

Case # 587521

WARNING LETTER

Dear Ms. McGowan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, TAKA USA, Inc. dba Cosmetic Innovations, FEI #3013239969, at 2210 Hutton Drive, Suite 100, Carrollton, Texas, from June 3 to 6, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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 June 21, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

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

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

You released your over-the-counter (OTC) topical drug products without adequate quality control testing, including but not limited to the identity and strength of each active ingredient. Testing is essential to ensure that the drug products you manufacture conform to all pre-determined quality attributes that are appropriate for their intended use, including both chemical and microbiological specifications. Because you lacked testing of each batch of your drug products, you do not know whether they conform to finished product specifications and are suitable for release to consumers.

In your response, you stated that you were in the process of initiating finished product testing for the identity and strength of each of the active ingredients contained in your drug products. You further stated that you established finished product specifications for each of your manufactured drug products. Your response is inadequate. You did not provide adequate justification for the limited testing you proposed. For example, you did not provide any scientific, analytical data regarding the impurity profile of your drug products.

In response to this letter, provide:

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action plan (CAPA) and provisions for evaluating its effectiveness.
- An updated list of chemical and microbiological specifications, including test methods, used to analyze each batch of your drug products prior to a batch disposition decision.
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter.
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.

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)).

Your firm did not establish written control procedures for manufacturing processes that could cause variability

in the characteristics of the drug product. Further, you did not validate the processes used to manufacture mulitple drug products. You did not perform validation studies to support distribution, and you lacked an appropriate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.

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 and assure the quality of raw material inputs, in-process materials, and finished drugs.

Process validation studies determine whether an initial state of control has been established. Successful process validation studies are necessary before 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.

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 (https://www.fda.gov/media/71021/download).

In your response, you stated that you intend to perform "**(b)(4)**" on the next batch of each of the **(b)(4)** drug products. Your response is inadequate. You failed to comprehensively address the risk to your products that may be posed by lack of validation, including the impact of those batches in commercial distribution. You also failed to provide a statistical basis and sufficient scope for the process validation approach proposed.

In your response to this letter, provide:

- 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 (PPQ), and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. The PPQ studies should include but not be limited to the statistical basis for monitoring all sources of variation in your manufacturing operation, number of batches per product, and other parameters of your study.
- A timeline for performing PPQ for each of your marketed drug products. Include your process performance protocol(s) and written procedures to qualify equipment and facilities. Also include your assessment of the marketed batches of your drug products against your protocol.
- 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.

3. Your firm failed to conduct at least one test to verify the identity or each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

You do not perform at least one specific identity test for each component used in production of your drug products. During this inspection you stated that you review certificates of analysis (COA) for incoming components, including active pharmaceutical ingredients (API), and you **(b)(4)**. You stated that your firm does not test any of the components itself.

In your response, you stated that you would **(b)(4)**. You stated that you would **(b)(4)** verify the identity and potency of each.

Your response is inadequate. You did not address your failure to test all components, including both active and inactive ingredients, for identity.

In response to this letter, provide:

- A comprehensive review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the 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.
- 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 testing results on your supplier's COA in lieu of testing each component lot for purity, strength, and quality, specify in detail how you will first establish the reliability and consistency of your supplier's test results for these attributes through initial validation (followed by periodic re-validation). In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
- A summary of your program for qualifying and overseeing contract facilities that perform testing of the components you use in manufacturing your drug products.
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer.
- A retrospective assessment of all drug product batches within expiry and in distribution within the United States that were manufactured using components that were not adequately tested and controlled.
- Details regarding the design and control of systems used for the production of **(b)(4)** used as a component in your drug products, and the specifications for this **(b)(4)** used in drug manufacture. Also specify whether you conform to the **(b)(4)** monograph. As noted on your formulation records, your firm refers to the **(b)(4)** used in manufacturing as "**(b)(4)**."

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

During the inspection, you stated that your firm does not have any written stability procedures. Further, you do not have appropriate stability data to support your firm's **(b)(4)** expiration date for your drug products.

During the inspection, you provided evidence that you performed a visual check of your finished drug products in your stability study to support the **(b)(4)** expiration date. However, because appearance alone is insufficient to evaluate product stability, you failed to adequately demonstrate that the chemical, physical, and microbiological properties of your drug products remain acceptable throughout the labeled **(b)(4)** expiry period. Therefore, there is inadequate assurance that your drug products can meet their label claims through their expiration period.

In your response, you stated that you would initiate product testing on the drug products that "**(b)(4)**."

Your response cannot be fully evaluated because you did not include your stability study test results used to determine if each of your commercial drug products will meet its specifications at the end of the labeled expiration period.

In response to this letter, provide:

- A comprehensive assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:

o Stability indicating methods
o Stability studies for each drug product in its marketed container-closure system before you permit distribution.
o 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.
o A 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. We also recommend that the qualified third party perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the effectiveness of your corrective actions and preventive actions.

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 systemic flaws to ensure ongoing CGMP compliance.

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.

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 the Warning Letter Number above (**Case # 587521**). Please electronically submit your signed reply on your firm's letterhead to CDR John W. Diehl, M.S., Director, Compliance Branch, at john.diehl@fda.hhs.gov and orapharm2_responses@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Mr. Thao Ta, Compliance Officer, via phone at 214-253-5217 or e-mail at thao.ta@fda.hhs.gov.

Sincerely,
/S/

Monica R. Maxwell
Division Director
Office of Pharmaceutical Quality Operation
Division II

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)