WARNING LETTER

Clientele, Inc.

MARCS-CMS 607476 — DECEMBER 03, 2020

Delivery Method:

VIA Electronic Mail

Product:

Drugs

Recipient:

Patricia A. Riley

CEO

Clientele, Inc.

14101 NW 4th Street

Sunrise, FL 33325

United States

Pat@mdr.com (mailto:Pat@mdr.com)

Issuing Office:

Division of Pharmaceutical Quality Operations II

United States

December 3, 2020

Case #: 607476

WARNING LETTER

Dear Ms. Riley:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Clientele, Inc., FEI 3012481086, at 14101 NW 4th Street, Sunrise, Florida, from February 3 to 7, 2020.

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).

Your firm manufactures the over-the-counter (OTC) drug products “Age Blocker” and “Estro-Lift Day Therapy.” “Age Blocker” and “Estro-Lift Day Therapy” are misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c). “Age Blocker” is further misbranded under section 502(a) of the FD&C Act, 21 U.S.C. 352(a). Introduction or delivery for introduction of such products into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

We acknowledge receipt of your July 2, 2020, correspondence. However, you did not provide specific information or evidence of corrective actions to the observations identified during the inspection in our Form FDA 483.

During the inspection, you told the FDA investigator that you would stop making drug products and plan to outsource the manufacture of your drug products to a third-party facility moving forward. In your July 2, 2020, correspondence, you mentioned that you engaged the services of a consultant with expertise in both cosmetic FDA regulations and GMP requirements. You should ensure your consultant is qualified as set forth in 21 CFR 211.34 to advise on compliance with the drug CGMP regulations.

CGMP Violations

1. Failure to establish an adequate quality unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed (21 CFR 211.22(a) and (d)).

Your firm manufactures OTC topical drug products that include sunscreen active ingredients and pain-relieving active ingredients. Your Quality Unit (QU) did not provide adequate oversight for the manufacture of your OTC drug products. For example, your QU failed to ensure the following:

- Microbiological testing was performed and reviewed for each batch before release;
- Ongoing stability program was established;
- Suppliers were adequately qualified;
- Out-of-specification (OOS) results were thoroughly investigated and written procedures were established for investigations; and,
- Annual product reviews were performed.

An adequate QU overseeing all manufacturing operations is necessary to consistently ensure drug quality.

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).

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:

- A determination of whether procedures used by your firm are robust and appropriate.
- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
- A list of chemical and microbial test methods and specifications used to analyze each lot of your drug product before making a lot disposition decision, and the associated written procedures.
- A complete and final review of each batch and its related information before the QU disposition decision.
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
- Your consultant's evaluation of your operations.

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 validate the processes used to manufacture your drug products. You have not performed process performance qualification (PPQ) studies to support an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality for products in U.S. distribution. For example, you have not performed studies to support in-process hold times of your drug products.

For example, your firm performed at least **(b)(4)** filling operations of your OTC drug product Age Blocker, lot Q09108, between **(b)(4)**. Your firm stored your bulk drug product in plastic lined buckets that you opened at each filling operation. In addition, you told our investigator that the bulk drug product can be held for filling operations until your stated three-year expiry. During a review of the laboratory test report for this lot, it was noted that only one microbiological test was conducted on June 7, 2019, for total aerobic count. The testing could not be attributed to a specific filling date nor did it include examination for specific objectionable microorganisms. You cannot ensure that lots you release after years of storage in bulk plastic-lined buckets under sporadic monitoring would conform to all your specifications.

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 ensure the quality of raw material inputs, in-process materials, and finished drugs. Failure to conduct these studies could result in product quality attribute failures. Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to 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 response to this letter provide the following:

- An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems (including analytical methods used by you and contract testing labs), quality of input materials, and reliability of each manufacturing process step and control.
- 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.
- A timeline for performing PPQ for each of your marketed drug products.
- Your process performance protocols, and written procedures for qualification of equipment and facilities.
- 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 establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your firm used **(b)(4)** water **(b)(4)** as a component to manufacture your drug products. Your firm failed to routinely monitor your **(b)(4)** system for all required quality attributes to ensure it consistently produced water suitable for its intended use. You stated to our investigator that sampling at **(b)(4)** point-of-use (POU) ports were performed on a random basis. You could not provide evidence that two of your POU ports had ever been tested. Furthermore, evidence showed the other **(b)(4)** POU ports were monitored only twice in 2019. Without routine water monitoring, you cannot ensure that your water meets minimum microbiological and chemical standards suitable for the manufacture of your drug products.

In addition, our inspection revealed at least two instances of high microbial counts (370 CFU/mL and 446 CFU/mL) from your POU ports. You stated that your microbial specification for **(b)(4)** at the POU is **(b)(4)** CFU/mL. This is above the appropriate limits for water intended for pharmaceutical manufacturing.

In response to this letter provide the following:

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. The assessment should be retrospective to ensure that products on the market were adequately tested for their quality attributes. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot 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 that are 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.
- Your plan of action to complete validation (or verification, for compendial methods) for all laboratory methods used together with raw material and drug product testing. In addition, include improved Standard Operating Procedures (SOPs) that require appropriate validation or verification to ensure adequate change management when methods are modified.
- A comprehensive, independent assessment of your water system design, control, and maintenance.
- A thorough corrective action and preventive action (CAPA) plan to fully remediate and validate a suitable water system.
- An effective program for ongoing control, maintenance, and monitoring to ensure the remediated system consistently produces water that meets **(b)(4)**, USP monograph specifications and appropriate microbial limits. Regarding the latter, a total count limit lower than 100 CFU/ml would be appropriate for products produced by your firm.
- The current action/alert limits for total counts and objectionable organisms used for your **(b)(4)** system. Ensure that the total count limits for your **(b)(4)** are appropriately stringent considering the intended use of each of the antiseptic drug products produced by your firm.
- A summary of your program for qualifying and overseeing contract facilities that test your raw materials, water, and the drug products you manufacture.

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

Your firm does not have adequate stability data to show that the chemical and microbiological properties of your drug products remain acceptable throughout the claimed expiry period of three years. You stated that you relied on a study to support your labeled three-year expiry; however, you were unable to provide the study when requested during the inspection. Without appropriate stability data, you cannot ensure your drug products meet established specifications and all pre-determined quality criteria throughout the drug product assigned shelf-life.

In response to this letter provide the following:

- 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:
    - Stability-indicating methods;
    - Stability studies for each drug product in its marketed container-closure system before distribution is permitted;
    - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and,
    - 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.

Misbranding Violations

"Age Blocker" and "Estro-Lift Day Therapy" are drugs as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because they are intended for the diagnosis, cure, mitigation, treatment, or prevention of disease and/or as defined by section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C), because they are intended to affect the structure or any function of the body. Specifically, "Age Blocker" and "Estro-Lift Day Therapy" are intended for use as sunscreen drug products.

Examples of claims observed on the products' labels that provide evidence of their intended uses (as defined by 21 CFR 201.128) include, but may not be limited to, the following:

"Age Blocker" Label Claims

"Helps Prevent Sunburn . . . Sunscreen SPF 30 . . . Anti-Aging Moisturizer and Sunblock in One"

"Estro-Lift Day Therapy" Label Claims

"Helps Prevent Sunburn . . . Sunscreen SPF 30"

The labeling for such drugs, like all OTC drugs, must comply with all of the requirements of section 502 of the FD&C Act and all pertinent regulations found in Title 21 of the Code of Federal Regulations. However, your products do not meet these requirements for the reasons described below.

"Age Blocker" and "Estro-Lift Day Therapy" are not labeled in accordance with the "Drug Facts" labeling requirements described in 21 CFR 201.66 because the products' labels fail to include required information. Specifically, the products' labels fail to include the statement, "[bullet] protect the product in this container from excessive heat and direct sun" under the header "Other information," as required by 21 CFR 201.327(f). Therefore, this product is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c), because the information that is required to appear on the labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

"Age Blocker" is further misbranded under section 502(a) of the FD&C Act, 21 U.S.C. 352(a). Specifically, the product label states, "Anti-Aging Moisturizer and Sunblock in One." According to 21 CFR 201.327(g), the claim "Sunblock" is a false and/or misleading claim that renders the product misbranded under section 502(a) of the FD&C Act, 21 U.S.C. 352(a).

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

Drug Production Suspended

You committed in a statement provided to the investigator to cease manufacturing drug products and to deregister your facility as a drug manufacturer. If you plan to resume manufacturing or distributing drugs manufactured on your behalf by a contract manufacturer, notify this office before resuming your operations

Use of Contract Manufacturers

You stated that you would outsource the production of your OTC drugs to a third-party facility in the future. In response to this letter, provide information regarding the selection of the contract manufacturer you intend to use to manufacture your drug products.

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.

If you plan to engage in the use of contract facilities, you are responsible for the quality of your drugs regardless of agreements in place with your contract facilities. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at https://www.fda.gov/media/86193/download (https://www.fda.gov/media/86193/download).

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. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Your written notification should refer to the Warning Letter Number above (Case # 607476). 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 any issues in this letter, please contact Mark Rivero, Compliance Officer, at 504-846-6103 or mark.rivero@fda.hhs.gov.

Sincerely,

/S/

Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations,
Division II

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