WARNING LETTER

Zhuhai Aofute Medical Technology Co., Ltd.
MARCS-CMS 590945 – JANUARY 09, 2020

Delivery Method:
VIA UPS

Product:
Drugs

Recipient:
Mr. Guilin Wu
Chairman
Zhuhai Aofute Medical Technology Co., Ltd.
Room 202, Building 2
No. 33, Yongnan Road
Zhuhai Shi Guangdong Sheng, 519070
China

Issuing Office:
Center for Drug Evaluation and Research
United States

Warning Letter 320-20-18

January 9, 2020

Dear Mr. Wu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhuhai Aofute Medical Technology Co., Ltd., FEI 3013761135, at Room 202, Building 2, No. 33, Yongnan Road, Zhuhai, from July 15 to 18, 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 product is 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 “Magic Spray for Pain Relief.” This product is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and is misbranded under sections 502(c) and (x) of the FD&C Act, 21 U.S.C. 352(c) and (x). Introduction or delivery for introduction of such products into interstate commerce is prohibited under sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a). These violations are described in more detail below.

We have not received a response from your firm detailing corrective actions to our Form FDA 483 observations identified during the inspection.

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)).

Your firm failed to perform critical quality control tests of finished drug products before a batch release decision. For example, our inspection found you lacked identity and strength testing for each batch of your over-the-counter (OTC) finished drug product, “Magic Spray for Pain Relief.”

Complete and appropriate testing of each batch is one of many essential elements necessary to ensure that the drug products you manufacture meet appropriate specifications.

Your staff also stated during the inspection that you did not evaluate the suitability of incoming component (e.g., ingredient) lots, as you lacked appropriate testing including but not limited to identification (21 CFR 211.84).

In response to this letter, provide the following:

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate corrective and preventive action plan (CAPA) effectiveness for your laboratory system.

- A list of chemical and microbial specifications, including test methods, used to analyze each batch of your drug products before a batch disposition decision. Include:
  
  - 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.

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm’s documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
• A comprehensive, independent 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 results from your supplier’s certificates of analysis (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.

• A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.

2. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

You failed to establish an independent and effective quality unit. For example, you failed to adequately perform basic quality unit (QU) responsibilities, including but not limited to:

• Approval or rejection of all components and drug product containers, closures, in-process materials, packaging materials, labeling, and drug products.

• Review of all production and control records.

• Assure establishment of adequate batch records.

• Approval of procedures and specifications impacting on the identity, strength, purity and quality of all drug products.

Notably, you lacked adequate production and laboratory records. Your firm did not demonstrate the appropriate controls to assure drug product batches were manufactured following appropriate written procedures. Because no meaningful production records were available, there is no assurance that, if errors occurred, they were fully investigated before batches were released. Furthermore, your laboratory technician stated that original raw data is routinely discarded.

Your QU was also not independent from the manufacturing unit. For example, during the inspection your Factory Director, responsible for manufacturing operations, was also acting as the Quality Director.

In response to this letter, provide the following:

• 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 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.

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.

3. 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)).

**Inadequate control of manufacturing processes**

Your firm lacks an ongoing program for monitoring process control to ensure stable manufacturing operations. You have not demonstrated that your manufacturing process is capable of consistently producing drugs of uniform character and quality. Specifically, you have not validated your manufacturing process for “Magic Spray” OTC topical liquid spray drug products.

During the inspection, you failed to provide validation protocol records and lacked adequate written production and process control procedures.

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 a remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing, including production operations, meets appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality. Also 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, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
- A timeline for performing appropriate process performance qualification for each of your marketed drug products.
- Include your process performance protocol(s), 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.

**Inadequate control of (b)(4) system**
The (b)(4) used to clean your non-dedicated equipment comes from a system that you have not validated. You did not demonstrate your (b)(4) quality is suitable for pharmaceutical use. Specifically, you have not established that your (b)(4) system is adequately designed, controlled, maintained, and monitored to ensure that it consistently produces (b)(4) that meets the USP monograph for (b)(4) and appropriate microbial limits. Your firm also failed to perform (b)(4) system validation studies. Your firm stated that the (b)(4) system is turned off after each use and run only when (b)(4) is needed.

In response to this letter, provide the following:

- A comprehensive remediation plan for the design, control, and maintenance of the (b)(4) system. Include a (b)(4) system validation report of the studies conducted only after system design and control has been fully remediated. Summarize any improvements made to system design and to the program for ongoing control and maintenance.

- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces water that meets (b)(4), USP monograph specifications and appropriate microbial limits.

**Unapproved New Drug and Misbranding Charges**

"Magic Spray for Pain Relief"

“Magic Spray for Pain Relief” is a “drug” as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because it is intended for the diagnosis, cure, mitigation, treatment, or prevention of disease and/or under section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C), because it is intended to affect the structure or any function of the body.

Specifically, “Magic Spray for Pain Relief” is intended for use as an external analgesic.

Examples of claims observed on the product label and labeling, that provide evidence of the intended uses (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

*Statements that appear on the product label*

“Magic Spray for Gout & Sciatica”

*Statements that appear on the product labeling*


OTC drug products intended for use as external analgesic drug products, such as “Magic Spray for Pain Relief” are being evaluated as part of the OTC Drug Review. External analgesic products have been proposed to be classified as generally recognized as safe and effective and not misbranded under the Tentative Final Monograph (TFM) for External Analgesic Drug Products for Over-the-Counter Human Use (External Analgesic TFM) (48 Federal Register (FR) 5852, February 8, 1983) if they meet each condition in the TFM and each general condition in 21 CFR 330.1.

It is important to note that the TFM covers two types of external analgesic drug products, counterirritants and analgesics/anesthetics/antipruritics, each having its own proposed allowable active ingredients, dosage strengths, and indications for use (48 FR 5852 at 5867 and 5868, February 8, 1983).
Pending the promulgation of a final rule, FDA generally does not intend to pursue regulatory action against products marketed in accordance with the conditions proposed in the TFM and each general condition in 21 CFR 330.1 unless a particular product poses a public health concern. Such marketing, however, is subject to the risk that a final rule may require reformulation and/or relabeling or FDA approval through the “new drug” procedures of the FD&C Act (Section 505). However, “Magic Spray for Pain Relief” does not meet these conditions for the reasons explained below.

The formulation and labeling for “Magic Spray for Pain Relief” is not consistent with the conditions proposed in the External Analgesic TFM. Specifically, since the product labeling does not distinguish between active and inactive ingredients, this causes all of the labeled ingredients (musk, carthamus tinctorius, menthol, borneol, rehmannia glutinosa, methyl salicylate, panax notoginseng and alcohol) to be represented as active ingredients. This combination of active ingredients is not proposed in the External Analgesic TFM.

Further, the product labeling includes indications related to the cure, mitigation, treatment, or prevention of gout, sciatica, rheumatic pain and improvement in blood circulation that are not proposed under this rulemaking, or any rulemaking being considered under the OTC Drug Review. According to its labeling, the product also combines analgesic/anesthetic/antipruritic active ingredients and indications, such as the temporary relief of pain and/or itching associated with insect bites, with counterirritant active ingredients and indications, such as the temporary relief of joint and muscle pain. Analgesic/anesthetic/antipruritic in combination with counterirritants are not proposed under the External Analgesic TFM (48 FR 5852 at 5868, February 8, 1983). A product formulated and labeled, such as “Magic Spray for Pain Relief,” is not proposed under the TFM.

Furthermore, we are not aware of any adequate and well controlled clinical trials in the published literature that support a determination that “Magic Spray for Pain Relief” is generally recognized as safe and effective for its labeled indications. Additionally, we are not aware of a similar OTC product, as formulated and labeled, that was available in the United States market on or before the inception of the OTC Drug Review.

“Magic Spray for Pain Relief,” as formulated and labeled, is therefore a new drug within the meaning of section 201(p) of the FD&C Act because it is not generally recognized among scientific experts as safe and effective for the drug uses described in its labeling. “New drugs” may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FD&C Act is in effect for the drug. “Magic Spray for Pain Relief” is not the subject of an approved new drug application; therefore, marketing this product in the United States is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d) and violates section 505 of the FD&C Act.

“Magic Spray for Pain Relief” is also misbranded because it is not labeled in accordance with the Drug Facts labeling requirements described in 21 CFR 201.66. Specifically, it does not include a Drug Facts panel. Therefore, this product is misbranded under section 502(c) of the FD&C Act, 21 U.S.C. 352(c), in that 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.

Lastly, “Magic Spray for Pain Relief” is misbranded under section 502(x) of the FD&C Act, 21 U.S.C. 352(x), because the product labeling fails to disclose a domestic address or domestic telephone number through which the responsible person may receive a report of a serious adverse event with such drug. Please note that section 201(k) of the FD&C Act, 21 U.S.C. 321(k), states that “[t]he term ‘label’ means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under the authority of the FD&C Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such . . . also appears on the outside container . . . .”
Therefore, the domestic address or domestic telephone number must appear on the immediate container label and on the outside container label if one exists.

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). Therefore, the marketing of “Magic Spray for Pain Relief” violates this provision of the FD&C Act.

**Data Integrity Remediation**

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA’s guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at [https://www.fda.gov/media/119267/download](https://www.fda.gov/media/119267/download).

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

**CGMP Consultant Recommended**

Based on the nature of the violations we identified at your firm, if your firm intends to resume manufacturing drugs for the U.S. market, 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 consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm’s compliance status with FDA.

If you intend to resume manufacturing and shipping drugs to the United States, you should provide comprehensive corrective actions which include systemic remediation as well as a global assessment and remediation of all six systems of your manufacturing operations.

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.

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

FDA placed your firm on Import Alert 66-40 on November 13, 2019.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Zhuhai Aofute Medical Technology Co., Ltd., at Room 202, Building 2, No. 33, Yongnan Road into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

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.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Chhaya Shetty

Microbiologist

U.S. Food and Drug Administration

White Oak Building 51, Room 4235

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3013761135.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance