Dear Mrs. Qiu Hui:

During our March 24, 2014 through March 28, 2014 inspection of your pharmaceutical manufacturing facility, China Resources Sanjiu (999) Medical and Pharmaceutical Co., Ltd. located at No. 1 Guanqing Road, Shenzhen, China, an investigator from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

Our inspection also revealed that your firm failed to fulfill its registration obligations under Section 510(i)(1) of the Act and its listing obligations under Sections 510(i)(2) and 510(j), which is prohibited under Section 301(p). 21 U.S.C. 360(i)(1) and (2), 360(j), and 331(p).

We have conducted a detailed review of your firm’s response dated April 16, 2014 via an e-mail and note that it lacks sufficient corrective actions.

Our investigator observed specific violations during the inspection, including, but not limited to, the following:

**CGMP VIOLATIONS**

1. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specification for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

Specifically, your firm manufactures Ganmaoling Cold Granule and Ganmaoling Cold Capsule drug products containing three active pharmaceutical ingredients (APIs): acetaminophen, chlorpheniramine maleate, and caffeine. However, you only verify by assay one of the three APIs, acetaminophen, at the time of batch release.

In your response, you indicate that your Ganmaoling Cold Granule and Ganmaoling Cold Capsule drug products are manufactured according to the Chinese National Legal Standard, which only requires an assay test for acetaminophen. If your product is intended for the US market it is required to meet US quality standards and each active ingredient must be tested to verify its labeled strength.
2. 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)).

For example, your firm has not established a release specification and test procedure to determine the level of impurities in the Ganmaoling Cold Granules and Ganmaoling Cold Capsule drug products. You have not determined an impurity profile for these products.

In your response, you state that you are not able to separate the APIs and impurities effectively by HPLC or TLC due to the drug products' complicated formulation and that you need to continue your research to identify a suitable method. Please be advised that if you intend to legally market in the US and apply for a new drug application, you will be required to submit scientifically sound and appropriate specifications and testing methods for purity, impurity, release, and stability.

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

Specifically, your firm does not perform stability testing on chlorpheniramine maleate and caffeine for assay. You lack stability data to support the (b)(4) expiry period assigned to your Ganmaoling Cold Capsules and Ganmaoling Cold Granule drug products.

Please be advised that if you intend to legally market in the US and apply for a new drug application, you will be required to submit an adequate written stability testing program and results to support your determination of appropriate drug product storage conditions and expiration dates.

4. Your firm failed to use equipment constructed in a way that surfaces that contact components, in-process materials, or drug products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirement (21 CFR 211.65(a)).

For example, after (b)(4), the product is (b)(4) through (b)(4). The inspection documented that the (b)(4) material frequently breaks, resulting in (b)(4) particles in the (b)(4). Although you change the (b)(4) every (b)(4) in an attempt to prevent its breakdown, this appears to be an inadequately designed process using an inappropriate piece of equipment. We also note that your firm uses a (b)(4) after (b)(4) to remove any (b)(4) particles that may be introduced into the (b)(4) during the process. However, your firm did not qualify this equipment prior to use, and you are not able to provide documentation to support the consistent performance and operation of this equipment.

Please be advised that if you intend to legally market in the US and apply for a new drug application, you will be required to ensure the safety, identity, quality, and purity of your drug products.

Submitting adequate corrective and preventive actions for the above exceptions does not exempt you from your responsibility to comply with the requirements described below.

DRUG REGISTRATION VIOLATIONS

Your firm failed to fulfill its registration obligations under Section 510(j)(1) of the Act and its listing obligations under Sections 510(j)(2) and 510(j), which is prohibited under Section 301(g). 21 U.S.C. 360(j)(1) and (2), 360(j), and 331(p).

Specifically, our investigator requested to inspect your facility located at 1028 Belhuan Road in Shenzhen, which is listed with FDA for drug product manufacturing. However, your firm management redirected the investigator to the site at No. 1 Guanqing Road in Shenzhen, stating you had moved to this location since 2013. However, during the inspection, it was revealed that the site at No. 1 Guanqing Road in Shenzhen was not registered with the FDA as a drug manufacturing facility for any drug products.

Please note that a drug offered for import into the United States may be refused admission under Section 801(o) of the Act if the importer, owner, or consignee is not able to show that it is manufactured in a registered facility. In addition, if a drug is not listed in accordance with Section 510 of the Act, including if the listing for the drug references a manufacturing establishment that does not maintain a current establishment registration, such drug would appear to be misbranded under Section 502(o) and subject to refusal of admission under Section 801(a)(3), 21 U.S.C. 352(o).

The FDA investigator discussed this issue with you during the inspection and advised you verbally to register this site with the FDA. Your response does not address this issue and the site at No. 1 Guanqing Road in Shenzhen remains not registered. All manufacturers must register annually as required by 21 C.F.R. § 207.40. Information on how to register is available at link [www.fda.gov/edrls](http://www.fda.gov/edrls).

If you continue to produce drugs that are offered for import into the United States, you must complete the required registration and listing. You should provide evidence that you have fulfilled these requirements in your response to this letter.

UNAPPROVED AND MISBRANDED OVER-THE-COUNTER (OTC) DRUGS

In addition to the foregoing violations, we reviewed the OTC drug labeling that we collected. Below is an analysis of the regulatory status of 999 Ganmaoling Cold Capsule, 999 Ganmaoling Cold Packets and 999 Itch Relief Ointment, which includes excerpts of the violative labeling and the specific new drug and misbranding charges. Please note that this is not an all-inclusive description of violative labeling for your OTC drug products.

999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets

According to the labeling for 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets, these products contain acetaminophen, chlorpheniramine, and caffeine as active ingredients and are intended for use as a pain reliever, fever reducer, and antihistamine. Based upon these claims, 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets are drugs within the meaning of Section 201(g)(1)(B) of the Act, 21 U.S.C. § 321(g)(1)(B), because they are intended for use in the diagnosis, treatment, or prevention of disease, and under section 201(g)(1)(C) of the Act [21 U.S.C. § 321(g)(1)(C)] because they are intended to affect the structure or function of the body.

As antihistamines, in order for 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets to be generally recognized as safe and effective and not misbranded, and thus be marketed without an approved NDA, they must meet the requirements of the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use, 21 CFR Part 341, among other requirements. 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets are unapproved new drugs because they do not meet this final monograph.

For example, the products do not meet 21 CFR 341.40 that describes the requirements for permitted combinations of active ingredients. Specifically, 21 CFR 341.40 describes combinations of active ingredients that are permitted provided that each active ingredient is present within its established dosage limits. 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets do not meet this final monograph because adults are to take 200 mg of acetaminophen three times a day. This dosage for acetaminophen is not consistent with the Agency’s proposal in the Internal Analgesic Tentative Final Monograph (53 Fed. Reg. 46204, Nov. 16, 1988) that describes an oral dosage of 325 to 650 mg every 4 hours, 325 to 500 mg every 3 hours, or 650 to 1,000 mg every 6 hours not to exceed 4,000 mg in 24 hours. Therefore, your products...
do not conform to the acceptable dosage for each individual active ingredient because 200 mg of acetaminophen to be taken three times a day has not been proposed in the Tentative Final Monograph (TFM) as a safe and effective dosage nor otherwise covered by the ongoing rulemaking.

Thus, as formulated and labeled, 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets are not generally recognized as safe and effective for the indications described in their labeling, and therefore, are new drugs under section 201(p) of the Act [21 U.S.C. § 321 (p)]. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless a FDA-approved application is in effect for it. Your firm’s marketing of 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets without FDA-approved applications violates this provision of the Act.

The products 999 Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets are also misbranded under 502(f)(2) the Act because the products’ labeling fails to bear all of the required warnings described in the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use, 21 CFR Part 341 for each declared active ingredient. For example, your products fail to disclose the required warning, “May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product,” see 21 CFR 341.72(c)(3).

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the Act [21 U.S.C. § 331(a)]. Therefore, the marketing of Ganmaoling Cold Capsule and 999 Ganmaoling Cold Packets violates this provision of the Act.

999 Itch Relief Ointment

According to the labeling for 999 Itch Relief Ointment the product contains the active ingredients, Dexamethasone Acetate 0.075%, Camphor 1%, and Menthol 1% and is labeled for use as an “[a]nti-allergic, anti-inflammatory, itch relief ointment,” and “[f]or the temporary relief of pain caused by itching and rashes.” Based upon these claims, 999 Itch Relief Ointment is a drug within the meaning of Section 201(g)(1)(B) of the Act, 21 U.S.C. § 321(g)(1)(B), because it is intended for use in the diagnosis, treatment, or prevention of disease, and under section 201(g)(1)(C) of the Act [21 U.S.C. § 321(g)(1)(C)] because it is intended to affect the structure or function of the body.

OTC topical products intended for relief of minor skin irritation or itching are being evaluated under the TFM for OTC External Analgesics in the OTC Drug Review (48 Fed. Reg. 5852, February 8, 1983). Although your product includes OTC external analgesic indications and two external analgesic active ingredients, camphor and menthol, that are addressed under the TFM, your product also contains dexamethasone acetate which is neither an active ingredient covered under the external analgesic rulemaking nor any other OTC drug rulemaking.

In addition, we note your product bears anti-inflammatory claims. The external analgesic rulemaking does not cover general anti-inflammatory claims and descriptive anti-inflammatory claims related to non-serious conditions of minor skin irritations and rashes are only proposed for hydrocortisone and hydrocortisone acetate. Thus, as formulated and labeled, this product is not covered under any OTC monograph that sets forth conditions for general recognition of safety and effectiveness; nor are we aware of a similarly formulated and labeled product otherwise being considered or eligible for consideration under FDA’s OTC Drug Review. Furthermore, we are not aware of evidence to show that 999 Itch Relief Ointment is generally recognized as safe and effective for its labeled uses.

999 Itch Relief Ointment is a new drug under section 201(p) of the Act [21 U.S.C. § 321 (p)]. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless a FDA-approved application is in effect for it.

In light of the foregoing, your firm’s marketing of 999 Itch Relief Ointment without an FDA-approved application violates this provision of the Act.

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 the violations identified above and for preventing their recurrence and the occurrence of other violations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm’s compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations has resulted already in FDA refusing admission of articles manufactured at No. 1 Guanqing Road, Shenzhen, China into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles are subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), 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 Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug products at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 301053926.

Please send your reply to:

Xiaohui Shen
Compliance Officer
White Oak Building 51, Room 4223
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Sincerely,

/S/
Thomas Cosgrove, J.D.
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research