



U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

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Compania Internacional de Comercio, S.A. de C.V. 6/13/12



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-18

06/13/2012

Compañía Internacional de Comercio, S.A. de C.V.
Mr. Takashi Tsuru Kabaya, Director General
Calle Monzón No. 184
Colonia Cerro de la Estrella
Del Iztapalapa
México, D.F.
México 09860

Dear Mr. Kabaya:

During our August 22-25, 2011, inspection of your over-the-counter (OTC) drugs manufacturing facility, Compañía Internacional de Comercio, S.A. de C.V. located at Calle Monzón No. 184, Colonia Cerro de la Estrella, Del Iztapalapa, México D.F., México 09860 investigator(s) from the 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 product(s) 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.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not established appropriate controls designed to assure that laboratory records include all data secured in the course of each test, including graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested [21 CFR 211.194 (a)(4)].

Specifically, the inspection revealed that your firm has not established written procedures to control and account for electronically generated worksheets used by analysts to record analytical test results. Analysts in your QC laboratory print an uncontrolled number of worksheets from computers throughout the QC laboratory without supervision.

For example,

- a) The investigator found a certificate of analysis (COA) for **(b)(4)** oz, lot number **(b)(4)**, dated January 19, 2011, in a trash container in the office used by QC personnel. This COA reported an assay value for **(b)(4)** of **(b)(4)**%. A second COA, dated January 21, 2011, filed with the analytical package for lot **(b)(4)**, reported an assay value of **(b)(4)**%.
- b) An analytical worksheet for **(b)(4)**oz, lot **(b)(4)**, dated January 21, 2011, with no approval signature, was found in a trash container in the office used by QC personnel. This analytical worksheet shows calculations of content uniformity for active ingredient **(b)(4)** of **(b)(4)**%. The COA dated January 21, 2011 filed with the analytical package reports a content uniformity (CU) value of **(b)(4)**%. The CU value in the reference COA represents the analytical testing performed on a single in-process sample after the product has been **(b)(4)**.
- c) The calculations for **(b)(4)** in **(b)(4)** Lot # **(b)(4)** was conducted using two (2) of three (3) injection areas. The FDA investigator's review of the HPLC (# C003) raw data verified the existence of three (3) HPLC chromatograms generated from batch # **(b)(4)**. However, only two (2) injection areas were used in the calculations.

The violation listed under examples 2a and 2b, raises serious concerns regarding the lack of quality oversight and poor CGMP documentation practices at your facility, specifically in the area of the disposition and handling of critical analytical data. In your response, include your remediation plan to ensure that raw data is retained as required, along with the written procedure describing the retention and disposition policy for all laboratory control records. We recommend that you conduct a comprehensive retrospective investigation review of your analytical data and the extent of this practice. Please include a summary of your results and the reason for discarding the analytical data referenced above. Specifically, indicate if the discarded data pertained to lots shipped to the US and your justification for invalidating the data.

Your laboratory records must include a complete record of all data obtained in the course of each test to determine a product's acceptability, including graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process materials, or drug product and lot tested. The complete records, including failing results, are needed to carry out an investigation required under 21 CFR 211 regulations. In response to this letter, provide your comprehensive corrective action plan, with supportive

information, including revised procedures, training records and the additional preventative and systemic actions you will implement to assure integrity of all CGMP records produced by your firm. This plan should also include a retrospective review of the in-process and finished product analytical test results to ensure product quality was not compromised due to your practice of discarding analytical data. You are also responsible for conducting investigations where deficiencies are noted.

In your response to this letter, you should include your plan to implement a robust CGMP training program designed to instruct your employees, including senior management, with CGMP (21 CFR 210 & 211) and other applicable regulatory requirements. CGMP training is essential to facilitate all the skill-sets and knowledge that your employees require in order for your firm to be compliant with good manufacturing practice. Note that training must be conducted by qualified individuals on a continuing basis, and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to their assigned functions.

2. Your firm does not have a written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expiration dates [21C.F.R. 211.166(a)].

For example, during the inspection, the FDA investigator requested information regarding long term stability data and forced degradation studies of (b)(4)oz. and (b)(4) oz and any other OTC products exported to the US market for distribution. However, your firm provided no evidence or documentation of a written program or data to demonstrate the stability of the OTC products manufactured for distribution in the US market. Furthermore, because you have not performed forced degradation studies for any of your OTC products, your firm did not establish that your methods are stability indicating.

Please include in the response to this letter documentation to support the current expiration dates assigned to the products currently on the market, as well as a commitment to ensure that all products are tested according to an approved stability program. For any ongoing stability studies which may be ongoing at your firm, please provide detailed information about the program and a copy of your stability protocol. Please include the following: products, lot numbers, date stability study started, stability interval, tests performed, storage conditions (temperature/ humidity), and testing site. Please also include assurance that your analytical methods are stability indicating and validated (or verified, if the method is USP).

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience or any combination of thereof, to enable that person to perform the assigned functions [21CFR 211.25 (a) and (b)].

For example, the inspection revealed that a chemist from your Quality Control Laboratory was observed weighing a sample and standard to perform (b)(4) Assay in (b)(4). The analyst failed to follow the requirements of the Analytical Method # CCA-TEC-111, in that he did not use (b)(4) as required by the method. Furthermore, although three HPLC chromatograms were generated from (b)(4) batch # (b)(4) the chemist only reported two injection areas to produce the result (according to review of electronic data from testing of (b)(4) assay).

It was also noted during the inspection that personnel from Quality Control Laboratory who performed sampling of (b)(4) lot # (b)(4)((b)(4) drums) raw material failed to follow the requirements of SOP # CCA-TEC-008, Sampling of Raw Material, in that QC personnel did not sample the correct number of raw material containers as required by your procedure. Other examples of violative CGMP practices include lack of CGMP training documentation; written procedures; sufficient laboratory records; and) adequately qualified senior management (e.g., General Manager of Operations and Head of Production) with respect to knowledge of, and training in, 21 CFR 210 and 211 as required by FDA for firms manufacturing drugs for the US market. Furthermore, your firm does not have a written training program designed to instruct your employees and management in the FDA Current Good Manufacturing Practices (CGMP).

4. Your quality control laboratory has not followed written procedures for testing and laboratory controls designed to assure that the drug products you tested have the identity, strength, quality and purity they purport or are represented to possess [21 C.F.R. 211.160 (a)].

For example,

a) Your firm's procedure, SOP CCA-TEC-152, Análisis de Materia Prima (Raw Material Testing), requires your quality control unit to test all incoming raw materials prior to releasing them. However, the release of (b)(4) raw material, lot # (b)(4) on September 21, 2010 was based on the analytical results from another lot ((b)(4) raw material lot # (b)(4) dated August 19, 2010). Thus, it appears you released the active pharmaceutical ingredient lot # (b)(4) without testing it as required by your SOP.

b) You did not perform sampling of (b)(4) raw material lot # (b)(4) as required by your firm's SOP CCA-TEC-008, Muestreo de Materia Prima (Raw Material Sampling). (b)(4) lot # (b)(4) consisted of (b)(4) ((b)(4)) drums but you only sampled two (2) drums. Your SOP requires the application of the (b)(4) formula to determine the number of containers to be sampled if more than (b)(4) ((b)(4)) containers are received.

c) Your firm's (b)(4) assay analytical method and procedures for (b)(4) oz, CCA-TEC-111 requires the use of (b)(4) glassware. However, your analyst was observed performing the (b)(4) assay for (b)(4) in (b)(4), (b)(4) glassware instead.

In your response, please conduct a thorough review of all records regarding sampling, testing, and material release for products on the market that are within expiry. Please provide your proposed action plan for all instances in which you find deficiencies. Your response should also include additional measures to be taken by your firm to ensure proper testing in the future.

5. Your firm has not established and documented the accuracy, reliability and performance of your computer systems employed in the release of drug products [21 C.F.R. 211.68 (a)]

For example, your firm did not verify the accuracy of Excel spreadsheets used to calculate product assay analytical results, for all products manufactured for the US market, in order to verify the accuracy of the results obtained.

In response to this letter, provide corrective actions with supportive documentation, including training records, revised procedures, and preventive actions to address this issue. Your corrective actions should also include a comprehensive retrospective review of in-process and finished product test results to ensure that all products produced and released by your quality unit meet specifications.

The violations cited in this letter are not intended to be an all-inclusive statement 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. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations. Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, you will remain on Import Alert and FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. 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 Current Good Manufacturing Practice 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 violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI # 3002775853.

If you have questions or concerns regarding this letter, contact Cesar E. Matto, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-5339
Fax: (301) 847-8741

Sincerely,
/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
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