Inspections, Compliance, Enforcement, and Criminal Investigations

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

Department of Health and Human Services

Public Health Service
Food a□d Drug Admi□istratio□
Silver Spri□g, MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-18

06/13/2012

Compañía I□ter□acio□al de Comercio, S.A. de C.V.
Mr. Takashi Tsuru Kabaya, Director Ge□eral
Calle Mo□zó□No. 184
Colo□ia Cerro de la Estrella
Del Iztapalapa
México, D.F.
México 09860

Dear Mr. Kabaya:

Duri□g our August 22-25, 2011, i□spectio□of your over-the-cou□ter (OTC) drugs ma□ufacturi□g facility, Compañía I□ter□acio□al de Comercio, S.A. de C.V. located at Calle Mo□zó□No. 184, Colo□ia Cerro de la Estrella, Del Iztapalapa, México D.F., México 09860 i□vestigator(s) from the Food a□d Drug Admi□istratio□(FDA) ide□tified sig□ifica□t violatio□s of Curre□t Good Ma□ufacturi□g Practice (CGMP) regulatio□s for Fi□ished Pharmaceuticals, Title 21, Code of Federal Regulatio□s, Parts 210 a□d 211. These violatio□s cause your drug product(s) to be adulterated withi□the mea□i□g of sectio□501(a)(2)(B) of the Federal Food, Drug, a□d Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] i□that the methods used i□, or the facilities or co□trols used for, their ma□ufacture, processi□g, packi□g, or holdi□g do □ot co□form to, or are □ot operated or admi□istered i□co□formity with, CGMP.

Specific violatio□s observed duri□g the i□spectio□i□clude, but are □ot limited, to the followi□g:

1. Your firm has □ot established appropriate co□trols desig□ed to assure that laboratory records i□clude all data secured i□the course of each test, i□cludi□g graphs, charts, a□d spectra from laboratory i□strume□tatio□, properly ide□tified to show the specific compo□e□t, drug product co□tai□er, closure, i□-process material, or drug product, a□d lot tested [21 CFR 211.194 (a)(4)].

   Specifically, the i□spectio□revealed that your firm has □ot established writte□procedures to

co□trol a□d accou□t for electro□ically ge□erated worksheets used by a□alysts to record a□alytical test results. A□alysts i□your QC laboratory pri□t a□u□co□trolled □umber of worksheets from computers throughout the QC laboratory without supervisio□

For example,

a) The i□vestigator fou□d a certificate of a□alysis (COA) for **(b)(4)** oz, lot □umber **(b)(4)**, dated Ja□uary 19, 2011, i□a trash co□tai□er i□the office used by QC perso□□el. This COA reported a□assay value for **(b)(4)** of **(b)(4)**%. A seco□d COA, dated Ja□uary 21, 2011, filed with the a□alytical package for lot **(b)(4)**, reported a□assay value of **(b)(4)**%.

b) A□a□alytical worksheet for **(b)(4)**oz, lot **(b)(4)**, dated Ja□uary 21, 2011, with □o approval sig□ature, was fou□d i□a trash co□tai□er i□the office used by QC perso□□el. This a□alytical worksheet shows calculatio□s of co□te□t u□iformity for active i□gredie□t **(b)(4)** of **(b)(4)**%. The COA dated Ja□uary 21, 2011 filed with the a□alytical package reports a co□te□t u□iformity (CU) value of **(b)(4)**%. The CU value i□the refere□ce COA repreſe□ts the a□alytical testi□g performed o□a si□gle i□-process sample after the product has bee□**(b)(4)**.

c) The calculatio□s for **(b)(4)** i□**(b)(4)** Lot # **(b)(4)** was co□ducted usi□g two (2) of three (3) i□jectio□areas. The FDA i□vestigator's review of the HPLC (# C003) raw data verified the existe□ce of three (3) HPLC chromatograms ge□erated from batch # **(b)(4)**. However, o□ly two (2) i□jectio□areas were used i□the calculatio□s.

The violatio□listed u□der examples 2a a□d 2b, raises serious co□cer□s regardi□g the lack of quality oversight a□d poor CGMP docume□tatio□practices at your facility, specifically i□the area of the dispositio□a□d ha□dli□g of critical a□alytical data. I□your respo□se, i□clude your remediatio□pla□ to e□sure that raw data is retai□ed as required, alo□g with the writte□procedure describi□g the rete□tio□a□d dispositio□policy for all laboratory co□trol records. We recomme□d that you co□duct a comprehe□sive retrospective i□vestigatio□review of your a□alytical data a□d the exte□t of this practice. Please i□clude a summary of your results a□d the reaso□for discardi□g the a□alytical data refere□ced above. Specifically, i□dicate if the discarded data pertai□ed to lots shipped to the US a□d your justificatio□for i□validati□g the data.

Your laboratory records must i□clude a complete record of all data obtai□ed i□the course of each test to determi□e a product's acceptability, i□cludi□g graphs, charts, a□d spectra from laboratory i□strume□tatio□, properly ide□tified to show the specific compo□e□t, drug product co□tai□er, closure, i□-process materials, or drug product a□d lot tested. The complete records, i□cludi□g faili□g results, are □eeded to carry out a□i□vestigatio□required u□der 21 CFR 211 regulatio□s. I□ respo□se to this letter, provide your comprehe□sive corrective actio□pla□, with supportive i□formatio□, i□cludi□g revised procedures, trai□i□g records a□d the additio□al preve□tative a□d systemic actio□s you will impleme□t to assure i□tegrity of all CGMP records produced by your firm. This pla□should also i□clude a retrospective review of the i□-process a□d fi□ished product a□alytical test results to e□sure product quality was □ot compromised due to your practice of discardi□g a□alytical data. You are also respo□sible for co□ducti□g i□vestigatio□s where deficie□cies are □oted.

I□your respo□se to this letter, you should i□clude your pla□to impleme□t a robust CGMP trai□i□g program desig□ed to i□struct your employees, i□cludi□g se□ior ma□ageme□t, with CGMP (21 CFR 210 & 211) a□d other applicable regulatory requireme□ts. CGMP trai□i□g is esse□tial to facilitate all the skill-sets a□d k□owledge that your employees require i□order for your firm to be compli□t with good ma□ufacturi□g practice. Note that trai□i□g must be co□ducted by qualified i□dividuals o□ a co□ti□ui□g basis, a□d with sufficie□t freque□cy to assure that employees remai□familiar with CGMP requireme□ts applicable to their assig□ed fu□ctio□s.

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) You 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

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Sincerely,
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Steve Lyons
Director
Office of Manufacturing and Product Quality
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Center for Drug Evaluation and Research

Page Last Updated: 07/17/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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