Inspections, Compliance, Enforcement, and Criminal Investigations

P.A. Benjamin Manufacturing Co., Ltd. 1/29/13

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-07

January 29, 2013

Mr. Errol L.G. Powell
Chairman
P.A. Benjamin Manufacturing Co., Ltd.
95-97 East Street
Kingston, Jamaica

Dear Mr. Powell:

During our May 5 through 11, 2012**,** inspection of your pharmaceutical manufacturing facility, P.A. Benjamin Manufacturing Co., Ltd., located at 95-97 East Street, Kingston, Jamaica, investigator(s) 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 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.

We have conducted a detailed review of your firm's response of May 24, 2012, and note that it lacks sufficient corrective actions.

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

CGMP VIOLATIONS

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Two examples of this violation include:

a. Lot #JU83 of Infant Gripe Mix failed the pH specification. The range was **(b)(4)** to **(b)(4)**, whereas the result recorded in the batch record was **(b)(4)**.

b. Lot # KM40 of Diphenhydramine Expectorant failed specific gravity and **(b)(4)**. The results for specific gravity and **(b)(4)** were **(b)(4)** and **(b)(4)**, whereas the acceptable ranges were **(b)(4)**-**(b)(4)** and **(b)(4)**-**(b)(4)**, respectively.

You conducted no investigation for these failures, yet you released these lots for distribution. The quality assurance manager stated that the specification failures did not impact the therapeutic activity of the drug products but provided no evidence to support this conclusion. In your response to this letter, provide your investigation into these failures and the action plan regarding failed batches that are within expiry and currently in U.S. distribution.

In addition, please provide a detailed description of the changes and improvements made to your investigation procedures.

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 material, labeling, and drug products (21 CFR 211.22(a)).

Two examples of this violation include:

a. The quality unit (QU) failed to review or approve drug product production batch records before release and distribution of your products. For example, your firm released for distribution lot #JM11 of Infant Gripe Mixture and lot #JS17 of Benjamins Cough and Cold, notwithstanding the fact that your QU did not provide review of multiple corrections of documentation errors.

b. Your quality unit failed to review and approve multiple changes your firm made to the manufacturing processes. For example, during the manufacture of lot # KM 40 of Diphenhydramine Expectorant, your firm added **(b)(4)** to the bulk tank. This step was not in the master batch record and your QU did not review or approve these changes.

In your response to this letter, please include a detailed plan on how your quality unit will provide consistent, adequate review and approval of investigations and production batch records. Include a list of all responsibilities assigned to the quality unit.

3. Your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis (21 CFR 211.84(d)(2)).

For example, your firm released raw materials, including glycerin, **(b)(4)**, **(b)(4)**, and **(b)(4)**, relying only on the certificates of analysis. The performance of identity testing on each incoming ingredient lot is a fundamental part of good manufacturing practice. An incoming lot cannot be accepted based on the identification test result listed on a vendor's certificate of analysis. In particular, glycerin and **(b)(4)** are vulnerable to intentional adulteration and incoming lots should be afforded special quality control scrutiny prior to a lot disposition decision for use in manufacturing. For more guidance, see *Testing for Glycerin for Diethylene Glycol* (May, 2007) at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070347.pdf[1].

In your response to this letter, describe in detail your raw material testing program, including how you will ensure that raw materials used in the manufacture of your drug products will be withheld from use unless the lot has been tested or examined in accordance with the current USP/NF and released for use by the quality control unit. In addition, describe your vendor qualification program and your procedures to periodically verify each vendor's full certificate of analyses.

4. Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile (21 CFR 211.113 (a)).

For example, your firm lacks written approved procedures to prevent microbial contamination

during the manufacturing operations of over-the-counter (OTC) drug products at your facility. Additionally, there was no evidence that your firm tested finished drug products for microbial limits. For example, your firm did not perform total aerobic microbial count (TAMC) and total combined yeast and mold counts (TYMC) to ensure a low bioburden.

In your response to the inspectional observations, you acknowledged a need to develop validated and approved procedures to prevent microbial contamination during manufacturing. However, you did not describe these procedures, nor did you describe your plans for testing microbial quality of raw materials, in-process intermediates, and finished products.

We are concerned about your firm's failure to assure appropriate microbial quality of the drug products shipped to the U.S. market. For example, some of your products are to be given orally to infants and they have not been tested for microbial contamination. Provide a risk assessment of all the drug products that remain within expiration in U.S. distribution, as well as an action plan to ensure that the products released for distribution are free of objectionable contamination.

5. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

For example, your firm failed to validate a cleaning method used for the multi-product manufacturing equipment and utensils. Your firm has no assurance that your current, manual cleaning methods are effective in removing residues of drug products and detergents from the manufacturing equipment and utensils. Additionally, your firm failed to validate the "**(b)(4)**" device used to detect **(b)(4)** traces on the equipment surfaces after cleaning. Finally, your firm failed to implement procedures on the proper use of the device.

In your response, you acknowledged your failure to implement and record the validation of your firm's cleaning processes. Your response is inadequate because it did not include a plan to implement cleaning procedures to ensure that drug product residues and cleaning agents are removed adequately. In your response to this letter, please provide your updated cleaning procedures, protocols for demonstrating that these procedures are effective, and reasonable timelines for executing these protocols. If you choose to continue manufacturing prior to completion of the cleaning validation, submit the acceptance criteria you will use for cleaning verification. You should also include your evaluation of the potential for cross-contamination of products currently in distribution in U.S. due to inadequate cleaning. During our next inspection, we will confirm proper qualification of equipment as well as suitability of test methods.

6. 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, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

Specifically, your firm has not validated the manufacturing processes for the OTC drug products, Diphenhydramine Elixir, Diphenhydramine Expectorant, and Infant Gripe Mix. In addition, you reprocessed several batches of these products without approval by the Quality Unit and without assessing the impact of the changes on the quality of the product.

In your response, you should include validation plans for the production and process control procedures you use in the manufacture of drug products intended for U.S. distribution. Additionally, include a revised master batch record and procedure for reprocessing batches after quality unit approval.

Validated processes help ensure that your products are manufactured reproducibly, master batch records are adequate, and variability is controlled to prevent batch failures. Additionally, monitoring of process performance and product quality throughout the process validation lifecycle provides opportunities to improve control of your manufacturing processes and the

quality of your products.

The items listed above, as well as other deficiencies found by our investigator, lead us to question the effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is essential that your firm implement a robust quality system. We remind you that you are responsible for ensuring that your firm's drug manufacturing operations comply with applicable requirements, including the CGMP regulations. FDA strongly recommends that your firm's executive management immediately undertake a comprehensive and global assessment of your manufacturing operations to ensure that your systems and processes, and ultimately, the drug products you manufacture, conform to FDA requirements. We also recommend that you hire a qualified consultant to provide your firm's staff with CGMP guidance and training on GMPs and particularly the responsibilities and procedures applicable to the quality unit.

UNAPPROVED NEW DRUG AND MISBRANDING VIOLATIONS

In addition to violating CGMPs, Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, Benjamins Cold and Cough and Benjamins Infants Gripe Mixture are OTC products that violate the unapproved new drug and misbranding provisions of the Act. As described in more detail below, these products are unapproved "new drugs" in violation of section 505(a) of the Act [21 U.S.C. § 355(a)]. In addition , Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough are also all misbranded under 502(f)(2) the Act [21 U.S.C. § 352 (f)(2)] and Benjamins Flu Relief is further misbranded under Section 502(c) of the Act [21 U.S.C: § 352(c)].

According to the labeling for Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough these products 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.

Furthermore, the products are intended for purposes that include as an antihistamine, expectorant, antitussive and/or decongestant and include uses for addressing cough cold symptoms. In order for OTC antihistamine, expectorant, antitussive, decongestant or other related cough cold products 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. Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough are unapproved new drugs because they do not meet this final monograph and are not otherwise covered by an FDA-approved application.

Among the violations for these products, the labeled directions for use for these products do not comply with the directions for use set forth under the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use, 21 CFR Part 341. For example, Benjamins Flu Relief, Benjamins Sinus, and Benjamins Cough and Cold contain dosing directions for children down to one year of age when the final monograph provides that one should consult a doctor for children under two. Furthermore, Benjamins Diphenhydramine Expectorant contains dosing directions for children down to the age of three and Benjamins Diphenhydramine Elixir contains dosing directions down to the age of two years when the final monograph provides that one should consult a doctor for children under six years of age for antihistamine containing drug products.

In addition, Benjamins Diphenhydramine Expectorant and Benjamins Cough and Cold contain active ingredients that do not comply with the final monograph, such as **(b)(4)** and **(b)(4)**. Furthermore, Benjamins Flu Relief and Benjamins Cough and Cold contain indications that do not comply with the final monograph, such as **(b)(4)** and **(b)(4)**, respectively.

Thus, as formulated and labeled, Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough 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 section 505(a) of the Act [21 U.S.C. § 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless it is the subject of an FDA-approved application. Your firm's marketing of Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough without FDA-approved applications violates this provision of the Act.

The products Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough are also all 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. Benjamins Flu Relief and Benjamins Sinus are also misbranded under section 502(f)(2) of the Federal Food, Drug and Cosmetic Act (the Act) because the products' labeling does not comply with FDA's organ specific labeling regulation for acetaminophen containing OTC drug products. Specifically, they do not include the required liver warning information described 21 C.F.R. § 201.326(a)(1)(iv). Please note that this warning is required to be on both outer and immediate container labeling if there is both an outer and immediate container.

Benjamins Flu Relief is also not labeled in accordance with the "Drug Facts" labeling requirements described in 21 C.F.R. § 201.66. Therefore, this product is further misbranded under section 502(c) of the 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.

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 Benjamins Flu Relief, Benjamins Diphenydramine Expectorant, Benjamins Diphenydramine Elixir, Benjamins Sinus, and Benjamins Cold and Cough violates this provision of the Act.

Furthermore, the product Benjamins Infants Gripe Mixture as formulated and labeled is an OTC drug. The product contains a combination of active ingredients and indications that are not covered under FDA's OTC Drug Review, which establishes conditions for general recognition of safety and effectiveness for OTC drugs. Furthermore, we are not aware of a product with your formulation and labeling otherwise being eligible for the OTC Drug Review nor are we aware of any evidence establishing that a product as formulated and labeled as Benjamins Infants Gripe Mixture is generally recognized as safe and effective for the described indications. Therefore, Benjamins Infants Gripe Mixture is a new drug under section 201(p) of the Act [21 U.S.C. § 321 (p)]. Under section 505(a) of the Act [21 U.S.C. § 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless it is the subject of an FDA-approved application.

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 may result in FDA continuing to refuse admission of articles manufactured at Benjamin Manufacturing Co., Ltd., located at 95-97 East Street, Kingston, Jamaica, into the United States. 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 product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3004341688.

Please send your reply to:

Allison A. Aldridge, Ph.D.
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
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Division of International Drug Quality
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Sincerely,
/S/
Steven J. Lynn
Director

Page Last Updated: 02/11/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070347.pdf