Humco Holding Group, Inc 1/26/17

U.S. FOOD & DRUG ADMINISTRATION

Dallas District Office
4040 N. Central Expressway,
Suite 300
Dallas, Texas 75204

January 26, 2017

2017-DAL-WL-09

Warning Letter

UPS OVERNIGHT MAIL

Gregory C. Pulido, Chairman and CEO
Humco Holding Group, Inc.
7400 Alumax Rd.
Texarkana, Texas 75501-0282

Dear Mr. Pulido:

During our June 25, 2015 to July 1, 2015 inspection of your pharmaceutical manufacturing facility, Humco Holding Group, Inc., located in Texarkana, Texas, investigators from the Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 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 products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), 21 U.S.C. 351(a)(2)(B).

The inspection also revealed that your firm manufactures and distributes unapproved new drugs in violation of section 505(a) of the Act [21 U.S.C. § 355(a)]. Additionally, FDA has determined that some of the drugs that you manufacture are also

misbranded in violation of sections 502 and 503 of the Act [21 U.S.C. §§ 352 and 353].

Unapproved New Drug Violations

Based on the information collected during the recent inspection, you manufacture and/or distribute an unapproved new drug in violation of sections 301(d) [21 U.S.C. §§ 331(d)], and 505(a) of the Act [21 U.S.C. § 355(a)].

The following unapproved new drugs were identified on inspection include:

- Humco Cherry Flavored Potassium Chloride Oral Solution 10% (NDC 0395-2300)
- Shohl's Solution (Modified), Sodium Citrate and Citric Acid Oral Solution (NDC 0802-3962)

The above product are drugs within the meaning of section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)], because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and intended to affect the structure or any function of the body of man or other animals. Further, as labeled, these drugs are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling.

Under sections 301(d) and 505(a) of the Act, a new drug may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. There are no FDA-approved applications on file for the drugs listed above. The marketing of these drugs, or other new drugs, without an approved application constitutes a violation of the Act.

Misbranded Drugs Under the FD&C Act

A. Prescription Drug Products

1. Section 502(f)(1)

Your Humco Cherry Flavored Potassium Chloride Oral Solution 10% and Humco Shohl's Solution are misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)].

The Humco Cherry Flavored Potassium Chloride Oral Solution 10% and Humco Shohl's Solution are "prescription drugs" as defined in section 503(b)(1)(A) of the Act [21 U.S.C. § 353(b)(1)(A)], because, in light of their toxicity or potential for harmful effects, the method of their use, or the collateral measures necessary for their use, they are not safe for use except under the supervision of a practitioner licensed by law to administer them.

Because these drugs are not safe for use except under the supervision of a practitioner licensed by law to administer them, adequate directions cannot be written so that a layman can use them safely for their intended uses. Consequently, the

labeling of your firm's unapproved prescription drug product fails to bear adequate directions for their intended uses, causing it to be misbranded under section 502(f)(1) of the Act.

Because your product lacks the required approved applications, they are not exempt under 21 CFR 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these misbranded products therefore violates section 301(a) of the Act [21 U.S.C. § 331(a)].

2. Section 503(b)(4)(A)

Humco Cherry Flavored Potassium Chloride Oral Solution 10%, Humco Shohl's Solution, and Humco Strong Iodine Solution (Lugol's Solution) (NDC 0395-2775) are prescription drugs, and therefore they are required to bear the symbol "Rx only." These three prescription products are misbranded because the products' labels fail to include the "Rx only" symbol that is required under section 503(b)(4)(A) of the Act [21 U.S.C. § 353(b)(4)(A)]). The introduction or delivery for introduction into interstate commerce of these drugs violates section 301(a) of the Act.

3. Section 502(a)

The label collected during the inspection for your Humco's Cherry Flavored Potassium Chloride 10% Oral Solution claims that the product is to be used as "As a flavoring agent and a potassium source in compounding." This label is false or misleading, causing the product to be misbranded under section 502(a) of the Act [21 U.S.C. § 352(a)]. While we note that the 16 fluid ounces presentation for this product is no longer listed with FDA, your firm's response to the FDA 483 stated that your firm plans to continue to market this product in a gallon container.

The 16 fluid ounce product was labeled as both a flavoring agent for compounding and as a source of potassium, an active ingredient. Labeling this product either in the 16 fluid ounce or gallon container as both an excipient and as an active ingredient is confusing and may result in the inadvertent delivery of therapeutic doses of potassium chloride when the product is used to flavor a drug. Your firm also markets a Cherry Syrup product (NDC 0395-2662) which is labeled as a "Pharmacy Compounding Syrup Vehicle" and is used in compounding as a flavoring agent, raising the likelihood that these two products could be mistaken for one another. As a result, the label for the Humco's Flavored Potassium Chloride 10% Oral Solution's 16 fluid ounces is false or misleading, causing the product to be misbranded under section 502(a) of the Act [21 U.S.C. § 352(a)]. The introduction or delivery for introduction into interstate commerce of this drug therefore violates section 301(a) of the Act [21 U.S.C. § 331(a)] .

We further note that Humco's Lugol's Solution label contains a directions section which uses an apothecary measurement no longer recommended for use by FDA. The directions section states that the "Dosage: Usual Dose; 4-1/2 minims 3 times a day," this section also states "Usual Dose Range: 1-1/2 to 15 minims daily." In FDA's Draft Guidance for Industry entitled: "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" dated April, 2013,[1]the Agency outlines several important recommendations to firms to help avoid

medication errors through product labeling. Specifically, with regard to product strength, the guidance recommends expressing dose in metric units of measure, such as mL, mg and mcg rather than apothecary measurements to avoid miscalculation of medication doses when converting from one unit of measure to another. Minims is a form of measurement no longer in common use and should be updated to reflect a metric unit of measurement to avoid potential errors and safety concerns.

4. Section 502(o)

Section 510 of the Act and 21 CFR 207, subject to certain limited exceptions, require establishment owners and operators (registrants) upon first engaging in the manufacture, preparation, propagation, compounding, or processing of drugs to register their establishments and submit listing information for all drugs in commercial distribution. Any drugs not included in the initial registration must be included with subsequent listing updates, either in June or December; whichever first occurs after the product has initially been marketed. In addition, any changes to a previously listed drug (including labeling) must be reported to the agency in June or December of the same year.

Although in commercial distribution, listing obligations under section 510(j) of the Act were not satisfied for Humco Shohl's Solution (NDC 0802-3962), which is a prohibited act under section 301(p) of the Act [21 U.S.C. 360(j) and 331(p)]. An incomplete drug listing paper form 2657 was submitted to FDA in 1992 but the deficiency in the data was not addressed. Your firm's failure to fulfill its listing obligations misbrands the product under section 502(o) of the Act [21 U.S.C. 352(o)], introduction or delivery for introduction into interstate commerce of a misbranded product is a prohibited act under section 301(a) of the Act [21 U.S.C. 331(a)].

B. Humco's "(b)(4)" Over-the-Counter Drug Product

(b)(4), is a drug within the meaning of section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)], because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and intended to affect the structure or any function of the body of man or other animals.

For the reasons described below, "**(b)(4)**" is misbranded under sections 502(a) and 502(j) of the Act [21 U.S.C. §§ 352(a) and 352(j)] because it is false or misleading and also because it is a danger to health when used in the dosage or manner prescribed, recommended, or suggested in the labeling.

The principal display panel (PDP) for this drug bears an image of a baby **(b)(4)**, however, the directions for use in populations younger than 12 years old direct consumers to "ask a doctor." Using the image of "**(b)(4)**" on the labeling renders the drug product false or misleading because it suggests that this product may be used in infants.

While there is language on the labeling indicating that children or teenagers recovering from chickenpox or other ailments should not take **(b)(4)**, the precaution is not sufficient to prevent administration to infants given its potentially deadly

complications. **(b)(4)**, a **(b)(4)** infant developed salicylate toxicity requiring hospitalization in the pediatric intensive care unit (PICU) as a result of continued administration of **(b)(4)**.[2] The parents reported that they had chosen **(b)(4)** based on the picture of a baby on the front of the package.

Carton labels and product names should communicate information that is critical to the safe use of the medicine. For example, an image of a child on the PDP should be representative of the age group identified under "Directions" in the Drug Facts label (e.g., a product labeled for use in children twelve years of age or older should not show a picture of an infant on the PDP). The product logo, "**(b)(4)**," and the photograph depicting a baby, impede the safe use of "**(b)(4)**." For these reasons, this product is also misbranded under section 502(j) of the Act [21 U.S.C. § 352(j)] because it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling. The introduction or delivery for introduction into interstate commerce of this drug therefore violates section 301(a) of the Act [21 U.S.C. § 331(a)].

Good Manufacturing Practice Deviations

We have completed a review of your written responses dated July 21, 2015 and August 31, 2015 to the FDA 483 and we acknowledge your promised corrective actions to correct the observations identified during the inspection of your firms. As your facilities work on corrective actions, please continue to update this office and provide associated records to support the completion of your corrective actions.

Should we observe the deficiencies identified on the above mentioned FDA 483, or similar deficiencies in the future; regulatory action (e.g., seizure, injunction, and civil money penalties) may be taken without further notice.

Our investigators observed specific violations, including, but not limited to, the following:

1. Your firm failed to establish 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)).

Failure to Validate Drug Manufacturing Processes

You have not validated the manufacturing processes for **(b)(4)** drug products you manufacture, including, but not limited to, Lugol's Solution, Shohl's Solution, Potassium Chloride, and **(b)(4)**. You were previously cited for failing to validate manufacturing processes at the conclusion of our 2012 inspection of your facility.

Your July 21, 2015 response states that you have traditionally validated your processes through "historical review" and **(b)(4)** product reviews. You have not shown how these "historical reviews" support the validity of your manufacturing processes, nor have you provided documented retrospective or continuous verification activities for approximately **(b)(4)** of your drug manufacturing processes.

In response to this letter provide details, including timeframes, on how you will validate manufacturing processes for all of your drugs.

FDA's guidance document on *Process Validation: General Principles and Practices* may help you understand our current thinking on approaches to process validation. The guidance is available at UCM070336.pdfhttp://www.fda.gov/downloads/Drugs/Guidances/.

Failure to Validate Purified Water System

You have not validated the purified water system that you have been using for at least three years to manufacture products that are ingested, inhaled, or applied topically. Some of these products are indicated to treat irritated tissues or wounds that may be more vulnerable to infection. Although you partially documented the results of validation activities you conducted in 2013 following relocation of your water system in a report dated April 28, 2014, your report does not include the results of microbiological tests, **(b)(4)** tests, or **(b)(4)** tests that you performed during your validation activities. The same report states the microbial load of your purified water system steadily increased following the **(b)(4)**-day validation period in May, 2013, and that additional maintenance activity was required to address the increased microbiological load. You failed to validate the purified water system after completing the required maintenance activities.

Additionally, on multiple occasions, components of the water system failed. At least one of these incidents resulted in the water system operating without **(b)(4)**. For example, on February 26, 2015, the **(b)(4)** of the **(b)(4)** failed and the system was**(b)(4)** until the **(b)(4)** was rebuilt on March 4, 2015. You did not conduct an investigation to evaluate the effects of this or other failures on the quality of the products you manufactured and released for distribution during this time.

Your August 31, 2015, response states you have contracted with a third party company to conduct a full validation of your water system. In response to this letter, provide the validation protocol and the final validation report.

2. 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).

You received a complaint from a customer that Mecuroclear lot 542639 was contaminated with Gram negative bacteria commonly found in water, *Burkholderia sp.,* and unspecified yeast and mold. This product is intended to be used as a first aid antiseptic to prevent infection in wounds. During the inspection, you provided a retrospectively written document that outlined the narrow and limited investigation you conducted into this complaint. Your investigation report failed to:

• evaluate whether Mecuroclear lot 542639 was contaminated with all of the microorganisms reported in the complaint;
• include the results of all microbiological tests conducted;
• identify a clear assignable cause; or
• evaluate whether other lots or products were affected by the problem.

Your response states you will modify your recall and investigation procedures to require investigations even when products are discontinued. However, you have not addressed how you will ensure investigations extend to other lots or products that may have been affected by the same problem. Provide details on how your recall and investigation procedures will ensure that investigations are thorough and extend to other potentially affected lots of the drug product and other drug products. Additionally, provide microbiological testing results for products currently on the market to ensure that they are free of contamination.

Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant with appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that the drugs you manufacture have their appropriate identity, strength, quality, and purity.

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. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter, including immediately discontinuing the manufacture and distribution of the unapproved drugs at your facility. Failure to promptly correct these violations may result in legal action without further notice including seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary to verify corrective actions have been completed.

If, as a result of receiving this Warning Letter or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients and/or finished products produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances in your drug manufacture under 21 U.S.C. 356C(a)(1) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

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. Additionally, your response should state if you no longer manufacture or distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your firm's response should be sent to: Jeff R. Wooley, Compliance Officer, Dallas District Office, Food and Drug Administration, 4040 N. Central Expressway, Suite 300, Dallas, Texas 75204. If you have any questions about the contents of this letter, please contact: Mr. Wooley at (214) 253-5251.

The specific violations noted in this letter and in the Inspectional Observations, FDA 483, issued at the close of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality management systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and bring the products into compliance.

Sincerely,
/S/
Gerald Bromley, Jr.
Acting Dallas District Director

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[1] See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

[2] **(b)(4)** Salicylate toxicity **(b)(4)**.