

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022424Orig1s000

OTHER ACTION LETTERS



NDA 22424

COMPLETE RESPONSE

Tiber Laboratories
c/o Mikart, Inc.
1750 Chattahoochee Avenue
Atlanta, Georgia 30318

Attention: Jason Waldroup
Director, Regulatory Affairs

Dear Mr. Waldroup:

Please refer to your New Drug Application (NDA) dated November 24, 2010, received November 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for hydrocodone and guaifenesin oral solution, 2.5mg/200mg per 5 ml.

We acknowledge receipt of your amendments dated January 06, February 23, March 14, May 16 and May 31, and June 23, 2011.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. An audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site (refer to our information request letter dated September 13, 2011). Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of your hydrocodone and guaifenesin oral solution. The additional clinical pharmacology studies that you submitted on June 23, 2011, to support this application (studies S11-028 a single-dose bioavailability study and S11-0029 a single-dose crossover food effect study) show that the guaifenesin component of your oral solution product is not bioequivalent to the reference guaifenesin product (b) (4)

This deficiency may be addressed by doing the following:

- a) Assess the design of your relative bioavailability study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study to evaluate the bioavailability of your proposed hydrocodone 2.5 mg/guaifenesin 200 mg per 5 mL oral solution combination product compared to the individual reference products, using the bioequivalence goal post of 80–125%.

OR

- b) Evaluate whether there is a formulation effect with your proposed combination product and reformulate the product if necessary. If you reformulate the product you must provide complete CMC information for the new product, repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products, using the bioequivalence goal post of 80 – 125%. You may also need to repeat the food effect study if the product is reformulated.

OR

- c) Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.

2. Further, your proposed drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism considered objectionable in non-sterile aqueous drug products.

This deficiency may be addressed by doing the following:

- a) Incorporate testing and acceptance criteria for the bacteria, *Burkholderia cepacia*, into the release specification for your proposed hydrocodone and guaifenesin combination product.
- b) Provide test method(s) for *Burkholderia cepacia* and the relevant method validations. The test method(s) validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

Additional Comments:

- A. To control the objectionable microorganism *Burkholderia cepacia*, we recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- B. Update the revised acceptance limits for impurities and Total Combined Mold/Yeast Count in the stability data summary table in your next stability data update.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
09/28/2011