



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office

94569d

60 8th Street, N.E.
Atlanta, Georgia 30309

March 12, 2004

VIA FEDERAL EXPRESS

WARNING LETTER

(04-ATL-6)

Craig Collard, President
Carolina Pharmaceuticals, Inc.
8000 Regency Parkway
Suite 430
Cary, NC 27511

Dear Mr. Collard:

This letter pertains to your marketing and distribution of the drug products "Humibid L.A." and "Humibid DM." Humibid L.A. tablets contain a combination of 600 mg of guaifenesin and 300 mg of potassium guaiacolsulfonate. Humibid DM capsules contain a combination of 400 mg guaifenesin, 200 mg potassium guaiacolsulfonate, and 50 mg dextromethorphan.

On July 12, 2002, the Food and Drug Administration (FDA) approved an application for a single-ingredient guaifenesin 600-mg extended-release drug product. Following this approval, FDA reviewed the marketing status of all strengths of single-ingredient guaifenesin extended-release drug products and determined that those products should no longer be marketed in light of the existence of an approved product. On October 11, 2002, the agency sent warning letters to approximately sixty-six manufacturers and distributors regarding the marketing of unapproved single-ingredient guaifenesin extended-release products. The warning letters stated the agency's position that single-ingredient guaifenesin extended-release products are new drugs and require an approved new drug application for legal marketing under the Federal Food, Drug, and Cosmetic Act (the Act).

In November of 2002, a number of warning letter recipients filed a Citizen Petition asking FDA to reconsider its issuance of the warning letters and, instead, to adopt an alternative approach that "allows firms marketing affected products to continue to market their products while taking appropriate steps to comply with the regulatory procedures called for by the Agency." FDA met with the petitioners and various industry counsel and representatives later that month and stated

that it would not stay implementation of the warning letters. The agency said, however, that it would consider a grace period of enforcement discretion for distribution of unapproved single-ingredient guaifenesin extended-release products.

The agency subsequently decided on the length and terms of that grace period. These conditions were relayed through a letter dated February 25, 2003, to the recipients of the October 11, 2002, Warning Letter. The terms and conditions of the grace period relayed in that letter were as follows:

- The warning letter recipients were to stop manufacturing unapproved single-ingredient guaifenesin extended-release products no later than May 21, 2003, and were not to resume manufacturing until FDA approval of an application covering the particular products; and
- Distribution of unapproved single-ingredient guaifenesin extended-release products would continue until October 23, 2003. Distribution of single-ingredient guaifenesin extended release products would not resume after that date unless and until FDA approval of an application for the single-ingredient guaifenesin extended-release products.

FDA set those deadlines so that, with reasonable advance inventory planning by retailers, there would be no further sales of such products past November 2003.

In August 2003, after FDA sent the above-referenced warning letters and as the agency's enforcement grace period was drawing to a close, your firm purchased the trade name "Humibid." Previously, Humibid was sold as a single-ingredient guaifenesin extended-release product. Your firm announced that it would launch two reformulated versions of Humibid: Humibid L.A. and Humibid DM.

The claims made for these products cause them to fall within the definition of "drug" set forth at section 201(g) of the Act. Regarding Humibid L.A., FDA is unaware of substantial scientific evidence showing that a drug containing 600 mg guaifenesin and 300 mg potassium guaiacolsulfonate is generally recognized by qualified experts as safe and effective for its labeled indications. Similarly, FDA is unaware of substantial scientific evidence showing that a drug like Humibid DM, which contains 400 mg guaifenesin with 200 mg potassium guaiacolsulfonate and 50 mg dextromethorphan hydrobromide, is generally recognized by qualified experts as safe and effective for its labeled indications. Accordingly, both products fall within the definition of "new drug" set forth at section 201(p) of the Act.

In addition, FDA has, through rule making procedures, accorded new drug status to certain drugs (21 CFR § 310.502). Included among these are extended-release dosage forms (21 CFR § 310.502(a)(14)). Humibid L.A.'s labeling describes it as a sustained-release formulation and Humibid DM's labeling describes it as providing a prolonged and an immediate release effect. FDA regards both sustained and prolonged release formulations as extended release dosage forms. Thus, Humibid L.A. and Humibid DM are new drugs within the meaning of section 201(p) of the Act pursuant to the rule governing these dosage forms.

These products are also new drugs because they contain potassium guaiacolsulfonate. This ingredient was included in the review underlying FDA's development of over-the-counter (OTC) drug monographs. The panel reviewing potassium guaiacolsulfonate found it to be not effective, 41 Fed. Reg. 38367 (Sep. 9, 1976). FDA found the drug ineffective in its tentative final and final monographs for OTC expectorant drug products. The ingredient is currently considered a new drug and is listed in 21 CFR § 310.545(a)(6)(iii) as a non-monograph OTC ingredient.

Section 505(a) of the Act requires that any new drug be the subject of an FDA-approved new drug application before its introduction into interstate commerce. There are no approved applications on file with FDA for Humibid L.A. or Humibid DM. The marketing of these products without approved new drug applications therefore violates Section 505(a) of the Act.

The violations described in this letter are not meant to be all-inclusive. It is your responsibility to ensure that all drug products manufactured and distributed by your firm comply with the Act.

We request that you take immediate action to correct the above-referenced violations. Please respond in writing to this office within fifteen working days of receipt of this letter, describing the specific actions that you will take, or have taken, to correct the violations. Your response should include an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen working days, state the reason for the delay and the time within which corrections will be complete.

Failure to correct the referenced violations may result in regulatory action without further notice, including seizure and/or injunction. In addition, Federal agencies are advised of the issuance of all Warning Letters pertaining to drugs and devices so that they may take this information into account when considering the award of contracts.

We also note that your products use trade names associated with previously marketed products containing different formulations. These associations may confuse drug prescribers and dispensers, who are unaware that Humibid products have been reformulated. Such confusion may result in your products being mis-prescribed, thereby risking dangerous drug interactions and overdoses. To address our concerns in this regard, please let us know of the steps that you have taken to advise both prescribers and dispensers of the changes to your products.

Your response to this letter should be directed to the attention of Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,



Mary Woleske, Director
Atlanta District