DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-539

Cumberland Pharmaceuticals, Inc.
Attention: Amy Rock, Ph.D.
Regulatory Affairs
209 10th Avenue South, Suite 332
Nashville, Tennessee 37203

Dear Dr. Rock:

Please refer to your new drug application (NDA) dated June 27, 2002, received July 1, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetadote® (acetylcysteine) Injection.

We acknowledge receipt of your submissions dated July 21, October 24, and November 19, 2003; and January 21, 22, and 23, 2004. Your submission of July 21, 2003, constituted a complete response to our December 30, 2002, Not Approvable letter.

This new drug application provides for the use of Acetadote® (acetylcysteine) Injection, administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, to prevent or lessen hepatic injury.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and immediate container and carton labels submitted January 23, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-539**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 1 month to 16 years until July 24, 2004.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the use of Acetadote® (acetylcysteine) Injection, administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, to prevent or lessen hepatic injury in pediatric patients ages 1 month to 16 years.

   Final Report Submission: July 24, 2004

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitments".

We remind you of your postmarketing study commitments in your submission dated January 22, 2004. These commitments are listed below.

1. Commit to further evaluate the incidence of anaphylactoid reactions after administration of Acetadote® (acetylcysteine) Injection.

   Final Report Submission: by April 24, 2004

   If the incidence is similar to that observed in the Safety Study (Infusion Rate Study) provided in your submission dated July 21, 2003, then you commit to assessing the feasibility of a trial designed to evaluate the effectiveness of prophylactic pre-treatment with antihistamines. If both the FDA and Cumberland determine that a trial design is feasible, you commit to conducting an adequate study to evaluate the effectiveness of prophylactic pre-treatment with antihistamines. Submission dates for this study shall be determined upon agreement that the trial design is feasible.

2. Commit to evaluate the potential benefit of Edetate disodium on the stability of the drug product. The study shall include a comparison of the current concentration of Edetate to a formulation with a lower concentration and no concentration of Edetate. Generate stability data from the new proposed formulations including compatibility stability with infusion bags.

   Protocol Submission: by April 24, 2004
   Study Start: by July 24, 2004
   Final Report Submission: by January 24, 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected

summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**"

In addition, if applicable, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-443-8347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

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

/s/

Robert Justice

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