CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-539

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-539 SUPPL #

Trade Name Acetadote® Injection Generic Name acetylcysteine

Applicant Name Cumberland Pharmaceuticals, Inc. HFD-180

Approval Date January 23, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X _/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X _/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # MUCOMYST (ACETYL CYSTEINE)

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__**X**_/ NO /_ __/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_**X**__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO/_**X**_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__X_/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CMAX Study CM8801

Investigation #2, Study # HATS database

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_ X _/

Investigation #2 YES /___/ NO /_ X __/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # CMAX CM8801

Investigation # 2 , Study # HATS database

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /_ **X** _/ Explain: The sponsor did not open an IND and the study was not conducted in the U.S.
Investigation #2	
IND # _____ YES /___/	NO /_ **X** _/ Explain: The sponsor did not open an IND and the study was not conducted in the U.S.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /_ **X** _/ Explain The applicant provided support for the analyses only. The applicant did not certify that it or a predecessor in interest provided substantial support for the study.
_____	_____

Investigation #2	!	
YES /___/ Explain _____	!	NO /_ **X**_/ Explain <u>The applicant provided support for the analyses only. The applicant did not certify that it or a predecessor in interest provided substantial support for the study.</u>
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_ **X** _/

If yes, explain: _____

_____

_____

Paul E. Levine, Jr., R.Ph., J.D.

_____

Signature of Preparer Date: 01/23/04
Regulatory Health Project Manager

Robert L. Justice, M.D., M.S.

Signature of Office or Division Director Date: 01/26/04

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Robert Justice
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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-539 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: July 21, 2003 Action Date: January 24, 2003

HFD-180 Trade and generic names/dosage form: Acetadote® (acetylcysteine) Injection

Applicant: Cumberland Pharmaceuticals, Inc. Therapeutic Class: 3P

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: 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

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☑ No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**__1__	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**_16__	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☑ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): __07/24/04_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

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/s/

Robert Justice
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Division Director Summary Review of a New Drug Application

NDA: 21-539
Drug: ACETADOTE® (acetylcysteine) Injection
Applicant: Cumberland Pharmaceuticals, Inc.
Date: January 23, 2004

This application requests approval of ACETADOTE® "to prevent or lessen hepatic injury [redacted] The submission of July 24, 2003, is a response to the not approvable letter of December 30, 2002. The letter contained a number of CMC deficiencies and two major clinical deficiencies. The clinical deficiencies were as follows.

1. [redacted]

2. [redacted]

The applicant chose to submit a meta-analysis, data from the Hunter Area Toxicology Service (HATS), and an update of CMAX Study No. CM8801.

Clinical Review

The Medical Officer Review of this submission was completed on December 30, 2003. Dr. Prizont recommended the following:

1. Approval of Cumberland's intravenous formulation of N-acetylcysteine (ACETADOTE®) [redacted]
2. The INDICATION section of the label should inform that intravenous infusion of N-acetylcysteine has been shown to be effective within an 8-10 hour period of the acetaminophen overdose. No effectiveness has been shown if administered after 10 hours from the overdose.

3. The label should include a WARNING section stating that serious anaphylactoid reactions including death, have been reported in patients with asthma administered with an intravenous N-acetylcysteine dose. This WARNING should also recommend caution with the use of intravenous N-acetylcysteine in individuals with known history of allergies, due to the potential of anaphylactoid reactions.
4. Administration of ACETADOTE® should be contraindicated in individuals with a history or diagnosis of asthma, even if medicated with bronchodilators or corticosteroids.

The recommendation for approval was based on several lines of evidence. The first was the meta-analysis. Although the medical and statistical reviewers (see below) concluded that the meta-analysis was methodologically inadequate, the Group Database portion of the meta-analysis identified seven supportive publications. Dr. Prizont concluded that

> "Statistics notwithstanding, the Group Database revealed a markedly low incidence of hepatotoxicity as defined by a serum ALT/AST <1000 IU/L in patients treated with intravenous NAC within 8-10 hours of the APAP overdose. Two further pieces of evidence, indicates the clinical efficacy of intravenous NAC. First, the 1999 Buckley et al study/meta-analysis of over 900 patients revealed similar efficacy between intravenous NAC administered at the proposed 300 mg/k, and oral NAC administered at 1300 mg/k. The intravenous NAC efficacy was largely observable when NAC treatment was given 8-10 h of the APAP overdose. Secondly, the Hunter database, which compared the intravenous NAC, 300 mg/k to no treatment, confirmed the efficacy of the I.V. NAC when administered within the 8-10 h post-overdose period. In this Hunter database, a small number of overdosed patients treated with the 8-10 h early period with gastric lavage and/or charcoal alone, exhibited similar low incidence of hepatotoxicity."
>
> "The safety profile of the intravenous NAC was supplemented in this second submission with a fatal outcome reported in the literature of 2002. The patient, an asthmatic, developed irreversible bronchospasm and respiratory failure shortly after a loading infusion of 150 mg/k of intravenous NAC administered as the antidote of an APAP overdose. The present submission further corroborated that a proportion close to 1 out of 5 patients given intravenous NAC develop anaphylactoid reaction, mostly mild to moderate in severity."

Statistical Review

The statistical review by Lisa Kammerman, Ph.D., was completed on January 7, 2004. Dr. Kammerman's conclusions are as follows.

> "The results submitted do not support the efficacy of IV NAC. CMAX Study CM8801 was the only prospectively randomized trial comparing the treatment of interest with a concurrent control. Unfortunately, because the study was stopped after 180 patients, there were not sufficient numbers of patients in the two

treatment arms to allow a non-inferiority comparison of the rates of anaphylactoid reactions. The incidence of anaphylactoid reactions among the 180 patients was 17%; 18% for the 15-minute treatment group and 14% for the 60-minute treatment group."

"The HATS database and the journal articles used in the applicant's meta-analysis to evaluate the efficacy of the IV formulation do not satisfy the standards for approval. The analysis of the HATS database was limited to those patients who had a liver function test. Overall 20% had a test; 38.3% of those who received NAC treatment within 8 hours of ingestion of acetaminophen had a liver function test compared with 8.4% who were treated without NAC and 13.9% who received no treatment. None of the journal articles used the dose and regimen sought by the applicant."

DSI Inspection

A DSI inspection was not requested since the application is primarily supported by literature, the HATS database, and the Australian safety study.

Chemistry Review

The chemistry review by Ali Al-Hakim, Ph.D., was completed on January 9, 2004. Dr. Al-Hakim recommended approval with one phase 4 commitment:

"Conduct a study regarding the impact of decreasing or removing Edetate from the drug product formulation on:
a) stability program
b) compatibility protocol using infusing bags"

Microbiology Review

The microbiology review by David Hussong was completed on December 16, 2003. The review recommended approval of the application.

Facilities Inspection

The facilities inspections were found to be acceptable on July 30, 2002 and August 5, 2002.

Clinical Pharmacology and Biopharmaceutics Review

The clinical pharmacology and biopharmaceutics review was completed by Tien-Mien Chen, Ph.D., on November 8, 2002. Dr. Chen stated that "NDA 21-539 for Acetadote Injection is acceptable from the viewpoint of OCPBDPEII provided a satisfactory agreement can be reach with respect to the language in the package insert (PI)." Dr. Chen's recommendations have been included in the Division's revised draft PI.

Pharmacology/Toxicology Review

The pharmacology/toxicology review by Ke Zhang, Ph.D. was completed on November 29, 2002. Dr. Zhang recommended approval from a preclinical standpoint with labeling revisions.

Discussion

This is a 505(b)(2) application that is supported by literature, the HATS database, and the CMAX Study CM8801. One of the key publications supporting the effectiveness of treatment of severe acetaminophen poisoning with intravenous acetylcysteine is the study by Prescott (Arch Intern Med 1981:141:386-389). One hundred patients were treated with IV acetylcysteine. All patients had plasma acetaminophen concentrations above a line joining plots of 200 µg/mL at 4 hours and 30 µg/mL at 15 hours on a semilogarithmic graph. High-risk patients were defined as having values above a parallel line joining 300 µg/mL at 4 hours and 45 µg/mL at 15 hours. Comparisons were made to 57 patients receiving supportive therapy only (control group) and 60 patients receiving IV cysteamine or methionine. The treatment groups were reported to be comparable with respect to age, sex, and severity of poisoning. Liver function tests were performed daily and severe liver damage was defined as an AST or ALT greater than 1,000 IU/L.

One of 62 (2%) patients receiving acetylcysteine I.V. within 10 hours developed severe liver damage compared to 20 of 38 (53%) patients receiving acetylcysteine within 10 to 24 hours and to 33 of 57 (58%) patients receiving supportive therapy. The differences were more marked in the high-risk patients. One of 33 (3%) high-risk patients receiving acetylcysteine within 10 hours developed severe liver damage compared to 18 of 27 (67%) patients receiving acetylcysteine within 10-24 hours and to 25 of 28 (89%) of patients receiving supportive therapy. There were no deaths from hepatic failure in high-risk patients receiving acetylcysteine within 10 hours, 2 (5%) deaths in patients receiving acetylcysteine within 10-24 hours, and 3 (5%) deaths in patients receiving supportive therapy.

The author states that "... the results show that acetylcysteine is effective in preventing hepatic and renal damage as well as death after acetaminophen overdose when given eight to ten hours after injection... There was no evidence of any protection after 15 hours; treatment after this time is pointless." The author also points out a major problem with administering acetylcysteine orally. "In our experience of treating almost 2,000 cases of acetaminophen overdose, early nausea and vomiting is an almost constant feature of severe poisoning. In this survey, 77% of our patients vomited; oral therapy was therefore clearly impracticable in most. Vomiting was reported to occur consistently in all patients treated with oral acetylcysteine in another study. Although it is conceivable that enough antidote might still be absorbed, reliance on oral therapy seems and unjustifiable risk in a potentially fatal condition when time is running out and effective IV therapy is available."

Although the submitted meta-analysis was flawed as pointed out in the statistical review, it included publications that reported on the use of I.V. or oral acetylcysteine. These studies are listed in Table 3 on page 22 of Dr. Prizont's review. The table includes the proportion of patients with hepatotoxicity in combined probable and high-risk groups. In three studies, the incidence of hepatotoxicity in patients receiving acetylcysteine orally (1330 mg/kg over 72 hours) within 10 hours of overdose ranged from 6% to 16%. In two studies, the incidence of hepatotoxicity in patients receiving acetylcysteine intravenously (300 mg/kg over 20 hours) within 10 hours of overdose ranged from 2% to 4%. In a third study acetylcysteine 980 mg/kg was administered intravenously over 48 hours. In patients receiving treatment within 10 hours of overdose the incidence of hepatotoxicity was 10%. For patients receiving treatment from 10-24 hours of overdose, the incidence of hepatotoxicity in these studies was 26% to 45% after oral administration and 8% to 53% after I.V. administration.

The results of the safety study and the HATS observational study are summarized in the following excerpts of the final package insert.

> Safety Study (CMAX Study CM8801): "A randomized, open-label, multi-center clinical study was conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the I.V. acetylcysteine loading dose. One hundred nine subjects were randomized to a 15 minute infusion rate and seventy-one subjects were randomized to a 60 minute infusion rate. The loading dose was 150 mg/kg followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. Of the 180 patients, 27% were male and 73% were female. Ages ranged from 15 to 83 years, with the mean age being 29.9 years (+13.0)."
>
> "Within the first 2 hours following I.V. acetylcysteine administration, 17% developed an anaphylactoid reaction (18% in the 15-minute treatment group; 14% in the 60-minute treatment group). (See WARNINGS). A subgroup of 58 subjects (33 in the 15-minute treatment group; 25 in the 60-minute group) were treated within 8 hours of acetaminophen ingestion. No hepatotoxicity occurred within this subgroup; however with 95% confidence, the true hepatotoxicity rates could range from 0% to 9% for the 15-minute treatment group and from 0% to 12% for the 60-minute treatment group."
>
> Observational Study: "An open-label, observational database contained information on 1749 patients who sought treatment for acetaminophen overdose over a 16-year period. Of the 1749 patients, 65% were female, 34% were male, and <1% was transgender. Ages ranged from 2 months to 96 years, with 71.4% of the patients falling in the 16-40 year old age bracket. A total of 399 patients received acetylcysteine treatment. A post-hoc analysis identified 56 patients who (1) were at high or probable risk for hepatotoxicity (APAP >150 mg/L at the four hours line according to the Australian nomogram) and (2) had a liver function test. Of the 53 patients who were treated with I.V. acetylcysteine (300 mg/kg I.V. acetylcysteine administered over 20-21 hours) within 8 hours, two (4%)

developed hepatotoxicity (AST or ALT>1000 U/L). Twenty-one of 48 (44%) patients treated with acetylcysteine after 15 hours developed hepatotoxicity. The actual number of hepatotoxicity outcomes may be higher than what is reported here. For patients with multiple admissions for acetaminophen overdose, only the first overdose treated with I.V. acetylcysteine was examined. Hepatotoxicity may have occurred in subsequent admissions."

Since an oral formulation of acetylcysteine is approved for this indication, the ideal study would be a randomized, controlled trial comparing the safety and efficacy of intravenously and orally administered acetylcysteine. However, such a study is unlikely to ever be conducted. It would be difficult to conduct because a large number of centers would be required given the relative rarity of acetaminophen overdoses at an individual center. In addition, there is likely to be little investigator interest. Informed consent would be difficult because I.V. administration ensures that the drug is administered despite the nausea and vomiting associated with both the overdose and acetylcysteine administration.

The data in this submission provide substantial evidence that I.V. acetylcysteine is as effective as oral administration and is more effective than the supportive care administered in the Prescott study. The safety study suggests that the incidence of anaphylactoid reactions is relatively high, although the reaction was severe in only 1% of patients. The applicant should be asked to determine the feasibility of studying prophylactic treatment with an antihistamine regimen. Such a trial may also be difficult for the reasons stated above. The death in one patient with asthma warrants a warning but not a contraindication. There is insufficient data at this time in patients with asthma to state that acetylcysteine is contraindicated.

Recommended Regulatory Action

The application should be approved with the above phase 4 chemistry commitment and with a commitment to evaluate the need for and feasibility of a study of prophylactic treatment of anaphylactoid reactions.

{see appended electronic signature page}

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

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/s/

Robert Justice
1/23/04 06:46:51 PM
MEDICAL OFFICER

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CUMBERLAND
PHARMACEUTICALS

January 21, 2004

Robert Justice M.D., Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Center for Drug Evaluation and Research
Food and Drug Administration
Division Document, Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Attention: Paul Levine, Jr., R.Ph., J.D., Regulatory Project Manager

RE: NDA 21-539
ACETADOTE™ (Acetylcysteine Injection)
Response to FDA Request for Information

Dear Dr. Justice:

Reference is made to the January 21, 2004 teleconference between the FDA's review team and Cumberland Pharmaceuticals Inc. (Cumberland). In response to the Agency's comments, Cumberland is submitting the following labeling text and phase IV commitments to NDA 21-539.

Observational Study (Demographics – to be inserted after the first sentence)
Of the 1749 patients, 65% were female, 34% were male, and <1% was transgender. Ages ranged from 2 months to 96 years, with 71.4% of the patients falling in the 16-40 year old age bracket. A total of 399 patients received NAC (acetylcysteine) treatment.

Safety Study (Demographics – to be inserted after the first sentence)
Of the 180 patients, 27% were male and 73% were female. Ages ranged from 15 to 83 years, with the mean age being 29.9 years (±13.0).

Phase IV Commitments
As part of a post-approval commitment for Acetadote®, Cumberland Pharmaceuticals will investigate the feasibility of conducting a phase 4 clinical study to investigate the benefit of prophylactic treatments (e.g. antihistamines, steroids, etc) in reducing the incidence of anaphylactoid reactions to acetylcysteine administration. Cumberland will also investigate the published literature to see if there is available data. As an additional, post-approval commitment, Cumberland will evaluate the potential benefit of Edetate disodium, currently in the formulation, on the stability of the drug product. This study will include a comparison of the current concentration of edetate to a lower concentration and/or a formulation containing no edetate. The design of the study will be agreed upon by Cumberland and the FDA prior to initiation.

– ē 6 mos

If you require clarification on any of the information provided please feel free to contact me by telephone (615) 255-0068 or by fax (615) 255-0094.

Sincerely,

Amy D. Rock, PhD
Regulatory Affairs

CUMBERLAND PHARMACEUTICALS INC.
2525 West End Avenue, Suite 950 • Nashville, Tennessee 37203 • Telephone: (615) 255-0068 • Facsimile: (615) 255-0094
www.cumberlandpharma.com

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 further refer to your submissions dated July 25; October 15, 17, and 28; November 4, 18, and 27; December 2, and 20, 2002; and July 21, 2003. Your submission of July 21, 2003, constituted a complete response to our December 30, 2002, Not Approvable letter.

We are reviewing the Microbiology sections of your submissions and have the following comments and information requests. We need your prompt written response in order to complete our evaluation of your NDA.

1. Please confirm that the materials submitted for the manufacturing process are correct for this NDA. The summary of the manufacturing process (page 26 of the amendment) was prepared for a different product, [redacted] and the manufacturing records (e.g., page 75 of the amendment) report the product name as [redacted]

2. In reference to the facility drawing (amendment, page 231) showing the manufacturing area:
   a. Provide a more detailed presentation of the critical zone and its environmental buffer zones, with particular reference to the fill line and its air classification. This should include the [redacted] and [redacted]
   b. Provide details concerning air pressure differentials and flow.
   c. Indicate how the bulk solution enters the fill area and the fill machine (i.e., through batch specific [redacted]). Please include descriptions of how and where connections are made.
   d. Note that the street address of the building housing room [redacted] was not provided.

3. In reference to the descriptions of the [redacted] and [redacted] (SOP [redacted], amendment page 346).

a. Describe the process and validation of endotoxin destruction by the [redacted]. In the report (VAL.MF01, dated 21-JUN-2002), the protocol (section [redacted] "Filling Systems, Room [redacted] Vial Filling," subsection 2. '[redacted]') explains that the [redacted] amendment, p. 438).

b. Provide data and methods in support of this process. These studies should describe the operating parameters ([redacted]) and results of thermal studies. Challenge studies should be described, including the inoculation of vials with known amounts of endotoxin and the assay of those vials before and after the process. The [redacted] parameters used for validation studies should be described in relation to the parameters used during production.

c. Clarify the units in the table presented in step [redacted] (amendment page 349) with the [redacted] capacities. Indicate what the [redacted] headings refer to.

4. In reference to the procedures for media fills, as found in SOP [redacted]

a. The filled containers in step [redacted] (amendment page 452), should be [redacted] or [redacted]

b. Explain the acceptance criterion. In step [redacted] (amendment, page 454) the acceptance criterion is, "The contamination rate is [redacted] as calculated from Appendix 1." However, the calculations in Appendix 1 do not include a formula for calculating [redacted] percent contamination. Is a formula necessary to calculate [redacted] percent?

5. In reference to the sterility test SOP [redacted] in the original submission, volume 1.7, page 8. [redacted] vials are collected for testing, including the [redacted] and [redacted]. Is there a procedure for selecting the remaining [redacted]

6. Please explain the discrepancy between the product endotoxins limit shown on the certificate of analysis (pages 120 and 169 of the amendment) and the dosage and administration found on the label, page 17 of the amendment. We calculate the maximum endotoxins content based on the maximum dosage of 150 mg/kg per hour, and estimate the limit should be [redacted]. The certificates of analysis suggest an acceptance criterion of 32 EU/mL.

7. Provide the stability schedule for endotoxins testing and indicate the acceptance criterion. Our 1994 guidance *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (http://www.fda.gov/cder/guidance/cmc2.pdf), part V.C., discusses "Maintenance of Microbiological Control and Quality: Stability Considerations" regarding endotoxins. The guidance indicates, "For drug products purporting to be pyrogen free, it is recommended that pyrogen or endotoxin tests be carried out at the beginning and end of the stability period as part of the approved stability study protocol."

8. Include an acceptance criterion for the minimum titer of the challenge suspension used in the the microbial ingress assay for the container and closure integrity test described in SOP, ——— , on page 564 of the amendment. Also, we recommend, the SOP should describe ———————————————————

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
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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, TN 37203

Dear Dr. Rock:

Please refer to the meeting between representatives of your firm and FDA on May 9, 2003. The purpose of the meeting was to gain the Agency's input and concurrence into the statistical analysis plans submitted in response to the December 30, 2002 NA letter..

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Brian Strongin
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 9, 2003

TIME: 3:00PM

LOCATION: Parklawn Building, 6B-45 Conference Room

APPLICATION: NDA 21-539; ACETADOTE™ (acetylcysteine injection)

TYPE OF MEETING: Type C Meeting; Discussion of the Statistical Analysis Plan for the NDA

MEETING CHAIR: Tom Permutt, Ph.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Robert Justice, M.D., M.S.	Director	Division of Gastrointestinal and Coagulation Drug Products, HFD-180
2. Joyce Korvick, M.D.	Deputy Director	Division of Gastrointestinal and Coagulation Drug Products, HFD-180
3. Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader, GI Drugs	Division of Gastrointestinal and Coagulation Drug Products, HFD-180
4. Robert Prizont, M.D.	Medical Officer	Division of Gastrointestinal and Coagulation Drug Products, HFD-180
5. Tom Permutt, Ph.D.	Team Leader, Biometrics	Division of Biometrics II, HFD-715
6. Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager	Division of Gastrointestinal and Coagulation Drug Products, HFD-180

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. A.J. Kazimi	Chief Executive Officer	Cumberland Pharmaceuticals
2. Leo Pavliv, R.Ph.	Vice President, Regulatory Affairs and Pharmaceutical Development	Cumberland Pharmaceuticals
3. Amy Rock, Ph.D.	Regulatory Affairs	Cumberland Pharmaceuticals
[redacted]		
5. Richard Dart, M.D.	Director	Rocky Mountain Poison And Drug Center
6. Greg Bogdan, Ph.D.	Toxicologist	Rocky Mountain Poison And Drug Center
7. Jody Green, Ph.D.	Toxicologist	Rocky Mountain Poison And Drug Center

BACKGROUND:

NDA 21-539 for ACETADOTE® was submitted June 27, 2002 for the IV treatment of [redacted]. A Not Approvable (NA) action was taken December 30, 2002. The NA letter cited chemistry, manufacturing, and controls (CMC) and clinical deficiencies including a lack of substantial evidence of safety and efficacy from adequate and well-controlled studies and a concern for severe anaphylactoid adverse events. A recommendation was included to either, "... design and conduct randomized, controlled trials using oral acetylcysteine as the active control..." or "...conduct a meta-analysis of the literature that compares the safety and efficacy of acetylcysteine administered by the intravenous [redacted] Cumberland submitted a draft statistical analysis plan to NDA 21-539 in a correspondence dated February 6, 2003. The Agency responded with comments and recommendations in an advice letter dated April 17, 2003.

MEETING OBJECTIVES:

To gain the Agency's input and concurrence into the statistical analysis plans submitted in response to the December 30, 2002 NA letter

DISCUSSION POINTS:

Since Cumberland Pharmaceuticals made no presentation, the discussion proceeded immediately to their questions. The questions are italicized below followed by the Division's response in bold.

1. *After a more detailed review of all of the available literature, it became apparent that the initial literature meta-analysis statistical plan submitted on 06 February 2003 required modifications to be more consistent with the type of information in the literature and to more appropriately address FDA's 30th December 2002 action letter and teleconference. A revised analysis plan was submitted to FDA on 04 April 2002. The plan was largely modified to demonstrate efficacy and safety of IV NAC as compared to oral NAC treatment, as suggested by the Agency regarding a trial design in the 30 December 2002 action letter. Specifically, Cumberland has removed the analysis comparing (1) oral NAC treatment versus no treatment and (2) IV NAC treatment versus no treatment. Further, a more detailed description of the criteria for efficacy and safety analyses has been included. Based on these modifications, does FDA agree that this revised analysis plan of the literature is also appropriate to address the deficiencies listed in the 30 December 2002 Not Approvable Letter?*

   We reiterate our comments in item #1 of our April 17, 2003 letter. In addition, we believe that an analysis comparing acetylcysteine administered both intravenously ——— to placebo/no treatment should be submitted. If possible, also submit a comparison between patients treated promptly versus patients whose treatment was delayed.

   (NOTE: In response to the Division's question, Cumberland explained that they have been able to locate in the literature only one acceptable study of NAC versus placebo. They will use this study to provide an analysis of IV NAC versus placebo as part of the meta-analysis. They added that they would attempt to include a comparison of patients treated promptly versus those whose treatment had been delayed.)

2. *The CMAX study was initially designed as a multi-center, randomized prospective trial by ——— Australia to determine if there was a difference in safety or efficacy between two different treatment regimens of IV NAC (15 minute vs. 60 loading doses). Cumberland obtained the right to use the data generated by this study in support of NDA-21-539. ——— serves as the external monitor for this study. Based on the limited number of patients in the study and the variability in the treatment population, it is highly unlikely any statistical significance will be seen as either superiority or non-inferiority. It is not Cumberland's intent to draw a positive conclusion from the lack of a difference between treatment groups. However, statistical analyses can be performed to look for both superiority and non-inferiority. Does FDA agree that the use of the CMAX information appears appropriate for the submission in the complete response letter?*

   Yes, it is appropriate to submit these data.

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3. *As part of an ongoing review of the information contained in the HATS database, it became apparent that the initial statistical plan submitted on 06 February 2003 also required modifications due to available information in the database. A revised HATS analysis plan was submitted to FDA on 04 April 2002. Due to the limitations associated with this database and the fact that the only medically accepted treatment protocol in Australia employs solely IV NAC treatment, the plan was revised to report only safety data. It is not Cumberland's intent to state that the data demonstrate effectiveness of prompt treatment versus delayed treatment. Does FDA agree that the use of the information from the HATS database appears appropriate for the submission in the complete response letter?*

   Yes, please submit these data, including outcomes. In addition, to the planned analysis, please provide an analysis of early versus delayed treatment. If feasible, data from The Rocky Mountain Poison Control Center that includes acetylcysteine oral and intravenous treatments should also be submitted.

   (NOTE: Cumberland responded that it is not feasible to submit data collected at the Rocky Mountain Poison Control Center.)

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

1. Cumberland explained that they have been able to locate only one acceptable study in the literature of NAC versus placebo. They will use this study to provide an analysis of IV NAC versus placebo as part of the meta-analysis.

2. Cumberland will attempt to include in the meta-analysis a comparison of patients treated promptly versus those whose treatment has been delayed.

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/s/

Brian Strongin
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MEMORANDUM OF TELECON

DATE: December 30, 2002

APPLICATION NUMBER: NDA 21-539; ACETADOTE® (acetylcysteine injection)

BETWEEN:

Attendee	Title	Company
A.J. Kazimi	CEO	Cumberland Pharmaceuticals, Inc.
Amy Rock, Ph.D.	Regulatory Affairs	Cumberland Pharmaceuticals, Inc.
Leo Pavliv, Pharm D.	Director of Development	Cumberland Pharmaceuticals
Richard C. Dart, M.D., Ph.D.	Consultant	Rocky Mountain Poison and Drug Center
[		]
[		]

Phone: (615) 255-0068

AND

The Division of GI and Coagulation Drug Product Attendee	Title
Robert Justice, M.D., M.S.	Director
Joyce Korvick, M.D.	Deputy Director
Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager

Phone: (301) 827-7310

SUBJECT: Cumberland's Response to the Not Approvable Letter

Background

NDA 21-539 for ACETADOTE® was submitted June 27, 2002 as a 505(b)(2) application for the IV treatment of moderate to severe ———————. This application was classified as a priority NDA with a user fee due date of January 1, 2003. A Not Approvable (NA) action was taken December 30, 2002. The NA letter cited chemistry, manufacturing, and controls (CMC) and clinical deficiencies including a lack of substantial evidence of safety and efficacy from adequate and well-controlled studies and a concern for severe anaphylactoid adverse events. A

recommendation was included to either, "... design and conduct randomized, controlled trials using oral acetylcysteine as the active control..." or "...conduct a meta-analysis of the literature that compares the safety and efficacy of acetylcysteine administered by the intravenous and—— ——. In addition, a request was included to, "...submit a study report and complete data for CMAX Study No. CM8801 that includes the 212 patients that have been randomized to date." Cumberland's response to the NA letter was the subject of today's call. [NOTE: An efficacy supplement to NDA 13-601 for Mucomyst (acetylcysteine 20%) and Mucomyst-10 (acetylcysteine solution 10%) was approved January 31, 1985 providing for oral use as an antidote for acetaminophen overdosage.]

Today's Call

Dr. l —— opened by stating that Cumberland had received the faxed NA letter and expressed an interest in the meta-analysis option. Dr. Justice responded that a comprehensive meta-analysis was necessary. He suggested Cumberland evaluate the article by Buckley et al. entitled, *Oral or intravenous N-acetylcysteine: Which is the treatment of choice for acetaminophen (Paraacetamol) poisoning? Clinical Toxicology, 37:759 – 767, 1999.* The major deficiency of this article is that small studies were excluded. He suggested that Cumberland make their best case that the safety and efficacy or both i.v. and oral acetylcysteine are equivalent. He added that Cumberland should evaluate the literature with the goal of choosing the best dosage regimen and justify their choice.

In response to Cumberland's question, Dr. Justice stated that the article by Keays et al. entitled, *Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303: 1926-1929, 1991*, does not provide primary support for efficacy and is supportive of other data and information only.

In response to Cumberland's question, Dr. Justice stated that CMAX Study No. CM8801, although not designed to show efficacy, does provide uncontrolled safety and efficacy data that may be integrated with the literature submitted including the meta-analysis. He added that the additional patients enrolled since NDA 21-539 was submitted would provide useful data.

Regarding the concern expressed in the NA letter for severe anaphylactoid adverse events, Dr. Justice stated that Cumberland should provide a comparison by infusion rate and between the i.v. and oral routes of administration.

Dr. Justice recommended using the meta-analysis as a source of information regarding safety and efficacy of i.v. acetylcysteine in pediatrics, geriatrics, alcoholics, and patients with ethanol-induced cirrhosis.

In response to Cumberland's question, Dr. Justice recommended against submitting pre-clinical data as evidence of efficacy.

Cumberland responded that they would submit a plan for the Division's review and comment.

The call was then concluded.

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/s/

Brian Strongin
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-539

12/30/02

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 25, October 15, October 28, November 4, November 18, November 27, December 2, and December 20, 2002.

We also acknowledge receipt of your submissions dated October 17 and December 20, 2002. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies in this letter.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

2. We have concerns regarding the potential for sometimes severe anaphylactoid adverse events to occur in patients that have received intravenous acetylcysteine. The rates of anaphylactoid adverse events after intravenous and after oral administration should be compared.

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 12 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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 Brian Strongin, R.Ph., M.B.A. at (301) 827-7310.

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

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/s/

Robert Justice
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Division Director Comments on a New Drug Application

NDA: 21-539
Drug: Acetadote® (Acetylcysteine Injection)
Sponsor: Cumberland Pharmaceuticals Inc.
Date: December 30, 2002

The submission is a new drug application for Acetadote®, a sterile solution of N-acetylcysteine (NAC), for the indication of [redacted] The proposed regimen involves IV administration over 21 hours. An oral formulation of N-acetylcysteine was first approved in 1984 and is administered over 72 hours. Six "primary" studies were submitted in support of this application: five are literature references and one is an interim analysis of a study (CM8801) with supporting documentation and primary data. The only documentation provided in support of the five literature references is a protocol for the Perry and Smilkstein studies. Details of these studies are provided in Dr. Prizont's review.

1. The Keays study (BMJ 1991) was a single center, open-label, randomized, controlled trial in patients with fulminant hepatic failure from acetaminophen overdose. Twenty-five patients were randomized to IV NAC and 25 to "conventional intensive liver care." Survival was 48% in the NAC group and 20% in the control group ($p=0.037$). Although this study does provide evidence that IV NAC is superior to control in the treatment of fulminant hepatic failure from acetaminophen overdose, it was not conducted in the prevention population and does not provide a comparison to orally-administered NAC. Because of the longer duration of administration, it is possible that the oral regimen could be superior.

2. The Perry study (J Pediatr 1998) was a multicenter, open-label, historically-controlled comparison of IV vs. oral administration in pediatric patients with acetaminophen overdose. Twenty-five patients received NAC IV and 29 historical controls received the drug orally. The 52-hour IV NAC regimen was reported to be as effective as a 72-hour oral regimen. Deficiencies of this study include the comparison to a historical control group and a conclusion of non-inferiority which was not based on a non-inferiority analysis.

3. The Prescott study (Arch Intern Med 1981) was a single center, open-label, historically-controlled study of IV NAC vs. supportive care vs. cysteamine or methionine in adults with acetaminophen overdose. One hundred patients received NAC, 57 received supportive therapy, and 60 received cysteamine or methionine. The applicant concluded that "iv administered NAC was considered the safest and most effective treatment for APAP poisoning, especially if administered within 10 hours of APAP ingestion." Deficiencies of this study include the comparison to historical controls and the absence of an oral NAC control arm.

4. The Smilkstein study (Ann Emerg Med 1991) was an open-label, multicenter, historically-controlled trial in children and adults presenting with an acetaminophen overdose. One hundred seventy-nine patients received IV NAC. The authors concluded that "This 48-hour IV NAC treatment protocol is safe and, based on available data is as efficacious as other NAC regimens when started within ten hours of acetaminophen overdose." Deficiencies of this study include the comparison to historical controls and inadequate information to evaluate their adequacy.

5. The Oh study (Med J Aust 1980) was an open-label, single-center, uncontrolled trial in patients with an acetaminophen overdose. Eleven patients received IV NAC and all recovered. Deficiencies of this study include small sample size and absence of a control arm.

6. The CMAX study (CM8801) is an ongoing, open-label, multicenter, randomized trial comparing administration of the loading dose of NAC IV over 60 minutes vs. over 15 minutes. The primary objective the study was to compare the safety of the two regimens. Data on an interim analysis of the trial were submitted. Ninety-six of the planned 500 patients were randomized, 61 to the 15-minute treatment arm and 35 to the 60-minute treatment arm. The rates of hepatotoxicity were 5% (3/61) in the 15-minute loading dose group and 12% (4/34) in the 60-minute group. Given the small sample size, the difference in the rates was not statistically significant. NAC therapy is thought to be more effective when administered within 8 hours of an overdose. Only 29 patients (11 in the 60-minute group) received NAC within 8 hours. There was no difference in efficacy between the treatment groups in this subset of patients.

   This study also does not include a comparison to orally administered NAC. However, it does provide documentation and primary data in support of the relative safety and efficacy of the two IV regimens. The sponsor's submission of December 20, 2002 states that a total of 212 patients have been randomized to date.

Conclusion: There is a lack of substantial evidence from adequate and well-controlled trials that ACETADOTE® will have the effect it purports to have under the conditions of use described in its proposed labeling.

Robert L. Justice, M.D., M.S.

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Robert Justice
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MEDICAL OFFICER

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MEMORANDUM OF TELECON

DATE: December 19, 2002

APPLICATION NUMBER: NDA 21-539; ACETADOTE® (acetylcysteine injection)

BETWEEN:

Attendee	Title	Company
A.J. Kazimi	CEO	Cumberland Pharmaceuticals, Inc.
Amy Rock, Ph.D.	Regulatory Affairs	Cumberland Pharmaceuticals, Inc.
Richard C. Dart, M.D., Ph.D.	Consultant	Rocky Mountain Poison and Drug Center
[		]
[		]

Phone: (615) 255-0068

AND

The Division of GI and Coagulation Drug Product Attendee	Title
Robert Justice, M.D., M.S.	Director
Joyce Korvick, M.D.	Deputy Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader, GI Drugs
Robert Prizont, M.D.	Medical Officer
Tom Permutt, Ph.D.	Team Leader, Biometrics
Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager

Phone: (301) 827-7310

SUBJECT: Clinical Deficiencies

Background

NDA 21-539 for ACETADOTE® was submitted June 27, 2002 as a 505(b)(2) application for the IV treatment of moderate to severe acetaminophen overdose. This application was classified as a priority NDA with a user fee due date of January 1, 2003. The clinical deficiencies were

discussed in today's call. [NOTE: An efficacy supplement to NDA 13-601 for Mucomyst (acetylcysteine 20%) and Mucomyst-10 (acetylcysteine solution 10%) was approved January 31, 1985 providing for oral use as an antidote for acetaminophen overdosage.]

Today's Call

Dr. Justice opened by explaining that all reviews had not been completed and that the Division would like to discuss clinical issues that had arisen to that point. He explained that the lack of source documentation for the literature submitted in support of efficacy and safety was an overarching issue. Although protocols for two studies had been submitted, no other source documents had been obtained.

He then summarized the principle deficiencies of the six primary studies as follows:

R. Keays et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303: 1926 –1029, 1991

This study was conducted in patients with fulminant hepatic failure from acetaminophen overdose, not in patients for whom acetylcysteine was administered for the prevention of hepatic failure due to acetaminophen overdose. In addition, patients experienced a high mortality rate, 52% for acetylcysteine v. 80% for placebo and no comparison was made to oral acetylcysteine.

H.E. Perry et al. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. J. Pediatr 132: 149-152, 1998

The application did not include enough information about the historical control group to evaluate its adequacy, the study was non-randomized, and the author's conclusions of non-inferiority were not based on a statistical analysis.

M.J. Smilkstein et al. Acetaminophen overdose: a 48 h intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 20: 1058 – 1053, 1991

The deficiencies listed above for the Perry et al study apply here also.

T.E. Oh and Gillian M. Shenfield. Intravenous N-acetylcysteine for paracetamol poisoning. Med J. Aust 1: 664 – 665, 1980

This study involved a very small sample size (eleven patients) and was uncontrolled.

L.F. Prescott. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. Ann Intern Med 141:386-289, 1981

The application did not include enough information about the historical control group to evaluate its adequacy.

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The call was then concluded.

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Brian Strongin
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 17, 2002

TO: Robert Justice, MD
Director
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical team Leader (GI Drugs)
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

SUBJECT: **Recommendations for Regulatory Action**
Original NDA 21-539 Acetadote® (N-Acetyl-cysteine injection)
Sterile Injection Solution (20%; 10 and 30 ml vials)
Drug Class: /
Indication:

Sponsor: Cumberland Pharmaceuticals Inc..
Nashville, TN

1. INTRODUCTION

N-Acetyl-cysteine (N-Ac-cyst) is an antidote for acetaminophen overdose. Pre-clinical studies have shown that co-administration of N-ac-cyst with acetaminophen increases hepatic glutathione concentration, decreases the amount of covalent binding of a toxic metabolite of acetaminophen to hepatic protein, and prevents acetaminophen-induced liver toxicity. Currently, Mucomyst (N-ac-cyst oral 10 and 20%) is approved as an oral antidote to prevent or lessen hepatic injury, which may occur following the injection of potentially hepatotoxic quantities of acetaminophen. Under NDA 21-539, the sponsor is seeking approval of Acetadote Injection (N-ac-cyst, 200 mg/ml or 20%)

The following dosing regimen is proposed:

Loading dose: 150 mg/kg in 200 ml of 5% dextrose, i.v. infusion over

Maintenance dose: 50 mg/kg in 500 ml of 5% dextrose, i.v. infusion over 4h followed by 100 mg/kg in 1000 ml of 5% dextrose over 16h.

This secondary review formulates an overall recommendation on approvability based on the regulatory recommendations from individual review disciplines.

II. CONCLUSIONS/RECOMMENDATIONS FROM INDIVIDUAL DISCIPLINES

A. CHEMISTRY AND MANUFACTURING CONTROLS (Dr. Ali Al-Hakim)

As summarized in Dr. Al-Hakim's review, the main chemistry, manufacturing and control deficiencies related to Acetadote are unsatisfactory stability protocol and data, manufacturing process of the drug substance, specifications of the drug substance and the drug product, and inclusion of EDTA in the formulation of the drug product. These, as well as labeling and packaging deficiencies are all approvability issues, communicated to the sponsor during a telephone conference on December 16, 2002. The sponsor has promised to respond to these deficiencies by next week.

B. PHARMACOLOGY/TOXICOLOGY (Dr. Ke Zhang)

There are no nonclinical safety issues relevant to clinical use. .

Based on the oral bioavailability of the total N-ac-cyst in rats, the oral dose of 1000 mg/Kg/day would be equivalent to 240 to 370 mg/Kg/day of an i.v. dose. The results of the 90-day i.v. toxicity study in dogs indicated that N-ac-cyst at i.v. doses of 200 and 400 mg/Kg/day produced transient clinical signs of toxicity including prolapse of the nictitating membranes, lacrimation, salivation, erythema of the ears, occasional restlessness, nervousness, and tremors. Ac-cyst was not teratogenic at oral doses of 500, 1000, and 2000 mg/g/day in rats and 250, 500, and 1000 mg/Kg/day in rabbits in the Segment II teratologic reproductive toxicity studies. N-ac-cyst was positive in the presence of metabolic activation in the *in vitro* mouse lymphoma cell forward mutation assay. The drug was not genotoxic in the Ames test *in vivo* mouse micronucleus test. From the preclinical standpoint, NDA 21-539 **is approvable**. Dr. Zhang recommends and the Pharmacology/Toxicology Supervisor, Dr. J. Choudary agrees that relevant findings of the preclinical studies should be included in the labeling. The sponsor should be asked to revise the labeling as recommended.

C. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (Dr. Tien-Mien Chen)

In support of their NDA, the sponsor submitted 14 literature articles describing the general PK of Ac-cyst. The reviewer notes that PK data in healthy volunteers/patients after i.v. administration of a similar regimen (the same loading dose but administered for 15 instead of [redacted] were available. However, no formal PK studies were conducted to support the proposed i.v. regimen. In order to extrapolate oral Mucomyst's safety/efficacy data to Acetadote i.v. use, simulations attempted to link the Ac-cyst plasma profiles after oral dosing of Mucomyst (with a reported oral bioavailability around 10%) and those after i.v. dosing of Acetadote were not successful.

As explained by Dr. S. Doddapaneni, Team Leader at the Division of Pharmaceutical Evaluation II, in the systemic circulation, Ac-cyst can be present in its intact as well as in various oxidized forms. Information quantifying the relative predominance of the various metabolic pathways is unavailable. When given orally, the entire dose of absorbed Ac-cyst passes through the liver, the site of action as well as metabolism. In contrast, when given intravenously only a fraction of the dose goes through the liver at any given time. Since, hepatic concentrations of Ac-cyst are

unknown, relying on systemic concentrations of total Ac-cyst (Ac-cyst and the various oxidized forms) as a way to bridge the oral and intravenous routes **is unrealistic.** For these reasons, the simulations conducted by the CPB reviewer to predict the systemic concentrations of total Ac-cyst to simulate the approved oral dosage regimen and proposed i.v. regimen (to extrapolate oral efficacy data to i.v. route) did not contribute further to link the data across the two routes of administration. Therefore, efficacy of the proposed intravenous dosage regimen should be supported by clinical trial(s) data. The Biopharm reviewer recommended labeling revisions (page 8 of Dr. Chen's review).

D. CLINICAL (Dr. R. Prizont)

In support of their submission, the sponsor submitted "primary" data on i.v. N-Ac-cyst from
a) five literature publications and
b) an interim analysis of on-going trial CM8801.

It is to be noted that **none of the patients enrolled in the Primary studies received the i.v. N-Ac-cyst dosing regimen in the proposed sponsor's label.** On page 17 of the MOR, details are given on each of these references, main study design, whether one site or multicenter, route of administration and dosage regimen, study population, summary of demographics, efficacy parameters evaluated and summary of efficacy results. From his analysis of these data Dr. Prizont concluded that one protocol of two of the historical US studies was the sole submitted documentation from historical publications, together with documentation from the interim analysis of CM8801 (at 20% of the planned patient enrollment).

These primary studies used open labeled designs, two were randomized, one use an active-active comparison design, and one the Keays study (1991) was placebo controlled.. These primary studies encompassed a total of 396 patients treated with various intravenous regimens of N-Ac-cyst, not necessarily the regimen proposed for labeling incorporation. In his review, Dr. Prizont notes that N-Ac-cyst was introduced more than 20y ago as an antidote to **prevent liver failure and high mortality due to liver complications from acetaminophen overdose.** The overall treatment, approved in 1983, includes initial gastric lavage, oral administration of activated charcoal, followed by 1330mg/Kg orally administered N-Ac-cyst **given over 72 hours.** A 1999 meta-analysis by Buckley et al. included 981 patients and revealed an unexpected low mortality after acetaminophen overdose, 0.2% , and a low morbidity of 3% (serum ALT > 1000 IU). Only 21% of these patients received N-Ac-cyst treatment.

After thoroughly and critically reviewing the information presented by the sponsor, Dr. Prizont concluded that only 3 of the 6 Primary studies were designed to show evidence of efficacy with the use of i.v. N-Ac-cyst as antidote to **prevent hepatic failure** from acetaminophen overdose. The MO Reviewer identified the Prescott Study (No. 5 in the Table listing the Clinical trials) as perhaps the best of the submitted studies for it included more than 25 patients in active-active comparison arms. This study revealed a 52% hepatic failure acetaminophen overdosed patients treated with N-Ac-cyst administered intravenously **after 10 h** from the overdose. In this study, hepatic failure was defined as mean serum ALT >3000 IU and serum bilirubin 3.4 mg/dl. This high proportion of hepatic failures was not different from the 58% seen in control patients treated with supportive treatments (serum ALT >2000, serum bilirubin 3.3 mg/dl). The other two

Primary studies had historical controls with orally administered N-Ac-cyst

Given the aforementioned lack of substantial evidence for effectiveness and low risk benefit ratio, Dr. Prizont recommends not to approve the proposed dosing regimen of Cumberland's i.v. formulation for the prevention of hepatic failure due to acetaminophen overdose. Although the MTL agrees with the MO in principle, the available data although imperfect, seem to offer certain opportunities within the approvability constraints (See below).

Based on the review of the submitted information, the MO concluded that i.v. has an acceptable margin of safety. Some revisions to the sponsor's proposed labeling are proposed. Other MO recommendations include addressing of [redacted] All these recommendations, as well as recommendations to address the CMC and microbiological deficiencies are reasonable and acceptable.

Regarding demonstration of efficacy, the MO recommends the following:

[redacted]

The MTL agrees that a study comparing the efficacy (and safety) of the proposed i.v. formulation to the already approved oral formulation is needed. But whether this is the only way leading to approvability needs to be carefully considered (See below).

The MO Reviewer proposes the following alternative:

[redacted]

F. STATISTICS (Dr. T. Permutt)

Dr. Permutt points out that the Keays study was a randomized, controlled experiment , but in a different clinical condition (fulminant hepatic failure) than then proposed indication. The "efficacy results" of the other studies from the literature appear to be fairly summarized, which is to say there were no results of the kind that would be taken as **substantial evidence of efficacy** according to the usual standards of review. He notes (once again) that all these studies used

different regimens than that recommended in the proposed labeling.

Dr. Permutt carried out a detailed review of the results of Study CM8801, a single randomized study conducted for the applicant by [redacted], at six hospitals in Australia. Five hundred patients were to be studied but the interim report includes data on only 96. The sponsor discussed with the Agency the submission of an application based on literature reports only, and the Agency had advised that at least an interim report of the CMAX study should also be included. The study compared two dosage regimens (loading dose of 150 mg /Kg given over 60 minutes vs the same loading dose given over 15 minutes). The **primary objective** was apparently to determine if the slower infusion would reduce the risk of adverse events, particularly anaphylactoid reactions. So, CMAX is primarily a safety trial. According to the report, "A secondary objective of the study was to assess the efficacy of the two treatments. The secondary endpoints used in the assessment of this objective were liver function tests (AST, ALT, INR)". Dr. Permutt notes that rather than a formal demonstration either of superior or of equivalent efficacy, the purpose seems to have been a general conclusion that the slower regimen, if it were safer, was not also notably less effective. The results of this study were also reviewed by the MO Reviewer. Only highlights from the Statistician's review are included in the current MTL secondary review.

Of the 96 patients discussed in the interim report, 61 were assigned to the slower infusion, but this imbalance would not affect interpretation of the results since, according to the statistician, it is of little consequence that different numbers of patients were randomized to the two treatments. There is no reason to think that the difference or similarity in outcomes between the two groups, which is what matters, should be systematically related to the size of the groups
A summary of the safety results in the interim report is given in the MO 's review. From the nonsignificant differences in all the safety comparisons, the sponsor concludes, "The overall safety profile of the 60-minute loading dose compared to the 15-minute loading dose appears preferable"

There are constraints when analyzing the efficacy data because two of the three planned liver function tests, AST and INR, are missing in a quarter to half of the patients. Only ALT was measured in nearly all patients randomized. As noted by Dr. Permutt, a two-sided p-value of 0.18 is reported for a rank-sum test on the ALT values. The rates for hepatotoxicity against the other categories combined were also found to be not statistically significant different, although the incidence of hepatotoxicity in the slower group (12%) was more than twice that in the faster group (5%). The interim report points out that all seven cases of hepatotoxicity occurred in patients who began therapy with Ac-cyst more than 8 hours after their overdose of acetaminophen. Thus, in the subgroup treated before 8 hours, **the rates were zero in both groups.** In his review, Dr. Permutt mentions that the sponsor's report argues that this may be the most relevant comparison. The MTL agrees with this assessment. Indeed, a number of literature reports show that once 8 hours has elapsed in patients with at risk blood paracetamol concentrations, sufficient NAPQI (a toxic metabolite of acetaminophen) has been produced to cause some hepatic injury. It is debatable whether a transaminase rise in patients who present later than 8h is useful in determining the relative efficacy of regimens being compared. The

sponsor concluded that the efficacy was not different between the two regimens and the proposed labeling recommends the slower regimen. Dr. Permutt further notes that reliable evidence of a difference between the regimens would be evidence of the effectiveness of Ac-cyst, which is necessary for approval but is not manifest elsewhere in the application. He also notes that the nonsignificant difference between the groups does not constitute such reliable evidence, but similar findings in a larger study, such Study CMAX continued to completion, might be a part of such evidence. It is pointed out that the fact that hepatotoxicity occurs in some of those patients not treated promptly (treated after 8 hours the overdosage has occurred) gives meaning to the observation that it has not occurred in those patients treated promptly (treated within 8h of the start of the overdosage), **regardless of the regimen.**

In conclusion, ignoring the regimen, 7 of 66 of late-treated patients suffered hepatotoxicity, compared to 0 of 29 early-treated patients. The MTL agrees with the conclusion that although this difference is not statistically significant, it seems more meaningful than other, nonsignificant results that are presented.

III. ADDITIONAL CONSIDERATIONS

In this section, an attempt is made at exploring the possibility that efficacy (and safety) may have been demonstrated under conditions other than those stipulated in the proposed labeling. A summary of the mode of administration of the test medication , with dose and dose regimen, is given in Table 1. The information summarized under the column REMARKS is , of course, based on the information presented in the publications, taken at face value since there is no other way for, except for the CMAX study, no source documents are available.

Table 1

NDA 21-539 : PRIMARY STUDIES: summary of mode of administration Dose/ Dose regimen

Study	Loading Dose	Maintenance Dose Initial	Follow-Up	Remarks
1.Keays (1991)	150 mg/Kg over 15 min	50 mg/Kg over 4h	100 mg/Kg over 16h	This randomized, single center study in fulminant hepatic failure patients showed significantly better survival among Ac-cyst-treated pts. (12/25=48%) compared to those given Placebo(5/25=20%); p=0.37. Also reported was a lower incidence of cerebral edema and cardiovascular dysfunction in the Ac-cyst compared to the control group.
2. Perry (1998)	140 mg/Kg over 60 min	12 doses of 70 mg/Kg every 4h		In pediatric pts. (mean age 15.6y) with acetaminophen overdose, a 52-h i.v. N-Ac-cyst infusion was as effective as a 72-h oral dosing regimen in the treatment of Acetaminophen overdosage. The parameters of evaluation included AST, ALT, PT, and serum bilirubin
3.Smilkstein (1991)	140 mg/Kg over 60 min	12 doses of 70 mg/Kg every 4h		In young adults and children presenting with acetaminophen overdose and stratified based on serum acetaminophen blood concentrations, a 48h i.v. N-Ac-cyst treatment was considered as efficacious as other N-Ac-cyst regimens when started with 10 hours of acetaminophen overdose.
4.Oh	150 mg/Kg	50 mg/Kg	100 mg/Kg	Complete protection against liver failure was seen in all 11 patients with paracetamol poisoning who were treated with

(1980)	over 15 min	over 4h	over 16h	i.v: Ac-cyst 4 hors after ingestion of the poison . Treatment 15 hours after ingestion was ineffective.
5.Prescott (1981)	**150 mg/Kg over 15 min**	**50 mg/Kg over 4h**	**100 mg/Kg over 16h**	In this active-active comparison study in adults with acetaminophen overdosage, i.v. administration of N-Ac-cyst was considered the safest and most effective treatment for paracetamol poisoning. This was especially true if the antidote was administered within 10 h after ingestion.
6.CMAX Study CM8801	**150 mg/Kg over 60 min or 150 mg/Kg over 15 min**	**50 mg/Kg over 4h**	**100 mg/Kg over 16h**	Results of this study were summarized in detail in Section II of the current review.
Proposed Label	**150 mg/Kg over**	**50 mg/Kg over 4h**	**100 mg/Kg over 16h**	

From this information, the conclusion is reached that there is some evidence of efficacy under experimental conditions different from those necessary for the proposed labeling .
The variables include 15 rather than 60 minutes administration of the loading dose, different patient populations, such as patients with fulminant hepatic failure rather than those with acetaminophen overdosage, adults vs children, different maintenance regimens in studies 2 and 3, single site vs multicenter studies, different parameters for efficacy evaluation (liver function tests vs frequency of liver damage, etc. Although some efficacy is supported in these studies, the conclusion is also reached that these data **do not represent substantial evidence of efficacy**. These data could be supportive but not pivotal, and **a definitive trial is needed for approval.**

IV. REGULATORY RECOMMENDATIONS

For NDA 21-539 to be approvable, in addition to addressing the CMC deficiencies, a definitive study convincingly demonstrating that the proposed regimen is safe and effective is needed.

Details of the definitive study design with regards to power, duration and parameters of

evaluation to be used in this definitive trial (s) can be discussed with the FDA statistician, in close interaction with the sponsor.

Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader (GI Drugs)
HFD-180

cc:
Archival NDA 21-539
HFD-180/Div. Files
HFD-/RJustice/JKorvick/SDoddapaneni/TPermutt/RPrizont/JChoudary/HGallo-Torres

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/s/

Hugo Gallo Torres
12/19/02 07:44:23 PM
MEDICAL OFFICER

Robert Justice
12/20/02 06:20:33 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: December 16, 2002

APPLICATION NUMBER: NDA 21-539; ACETADOTE® (acetylcysteine injection)

BETWEEN:

Attendee	Title	Company
A.J. Kazimi	CEO	Cumberland Pharmaceuticals, Inc.
Amy Rock, Ph.D.	Regulatory Affairs	Cumberland Pharmaceuticals, Inc.
Leo Pavliv, Pharm. D.	Director of Development	Cumberland Pharmaceuticals, Inc.
[redacted]		
[redacted]		

Phone: (615) 255-0068

AND

The Division of GI and Coagulation Drug Product Attendee	Title
Liang Zhou, Ph.D.	Chemistry, Manufacturing, and Controls (CMC)Team Leader
Ali Al-Hakim, Ph.D.	Review Chemist
Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager

Phone: (301) 827-7310

SUBJECT: CMC Information Request Letter Dated December 10, 2002

Background

NDA 21-539 for ACETADOTE® was submitted June 27, 2002 as a 505(b)(2) application for the IV treatment of moderate to severe [redacted]. A letter from the Division dated December 10, 2002 included comments and information requests regarding the CMC section of the application.

Today's Call

The call began with a discussion of the December 10, 2002 CMC information request letter. Items from the letter are bolded below, followed by the discussion in regular type.

1. **Regarding the drug substance information provided in the NDA:**

    a. **Clarify which [redacted] route is used for the proposed commercial manufacturing process.**
    b. **Clarify the use of [redacted] as a reagent/solvent in the manufacturing process.**
    c. **Regarding the drug substance specifications:**

        i- **include specified, unspecified, and unidentified impurities based on your test data;**
        ii- **tighten specifications for residual solvents based on your test data; establish a specification and acceptance criteria for heavy metals based on test data.**

Cumberland stated that [redacted] routes are used depending on the availability of starting materials. The Division responded that drug master file [redacted] only describes information about [redacted] method. Information about [redacted] methods should be submitted.

2. **Regarding the drug product manufacturing process:**

    a. **The trade name for the drug product in this application is ACETADOTE®, not [redacted]. Remove any reference to [redacted] throughout the entire NDA, specifically in batch records, the stability protocol, etc.**
    b. **Regarding the reference standard:**

        i. **Provide manufacturing information regarding the preparation of the working reference standard. The drug product injectable reference standard can not be compared to the USP reference standard. Propose specifications (acceptance criteria, tests, methods with code number, etc.) which are suitable to the drug product reference standard.**
        ii. **Provide information related to the storage and testing of the reference standard.**
        iii. **Provide information related to the storage and testing of the reference standard.**

    c. **Provide scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this drug product.**

Regarding item 2(a), Cumberland stated that they would delete all references to [redacted] throughout the NDA. Regarding item 2(b)(i), the Division explained that the USP reference standard does not contain all of the tests needed for an injectable drug product. Cumberland

should develop an appropriate reference standard that includes all necessary tests and consult the "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products" dated February 1987. Regarding item 2(c), the Division explained that data should be provided to support any justification for the inclusion of Edetate, since a non-trivial amount is included in the formulation.

3. **Regarding the drug product specifications:**

   a. **Include specifications for the related drug substances (e.g., acceptance criteria, test methods, etc). Refer to the ICH Guidances for Industry entitled , "Q3B Impurities in New Drug Products" and "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances".**
   b. **Change the name of the ——— test to "Volume in Container" because it is different from the actual ——— test described in the ICH Q6A guidance.**
   c. **Include the ——— test and ——— in the tests and specifications for the drug product.**
   d. **Tighten the specifications for the bacterial endotoxin limit based on test data.**
   e. **Establish microbial limit acceptance criteria.**

4. **Regarding the container closure system, provide:**

   a. **Manufacturing information and components/composition or provide a letter of authorization referencing the appropriate Drug Master File(s);**
   b. **Computability information (extractables, integrity, etc.) for the drug product solution;**
   c. **CMC information (manufacturing and testing) especially if the —— cap comes in contact with the drug product solution;**
   d. **A description and drawings of the various components of the container/closure system including vials, stoppers and —— cap;**
   e. **Actual samples of the container closure system to facilitate our review.**

5. **Regarding the drug product stability:**

   a. **The proposed stability protocol is unacceptable.**
   b. **We recommend modifying the proposed stability protocol to include the following:**

      i- **adequate specifications (see item 3 above);**
      ii- **appropriate test time points (e.g., 0, 3, 6, 9, 12, 18, and 24 months);**
      iii- **perform stability studies on both vial sizes.**

   c. **Submit an updated stability protocol and corresponding data for batches # 990907 and # 200125 in tabular format to facilitate our review of your request regarding expiry dating.**

Cumberland stated that they were preparing a response to items #3 and #4. Regarding item #5, Cumberland stated that they are modifying the stability protocol and preparing a response.

6. **Regarding methods validation:**

   Submit three copies of the methods validation package prepared according to the guideline entitled, "Submitting Samples and Analytical Tests for Methods Validation" and refer to 21 CFR 314.50 (e).

7- **Regarding the [redacted] solution used for intravenous infusion:**

   Provide compatibility studies between the drug product solution and the [redacted] solution including test data that are generated at different time points showing that the drug product solution remains within the proposed specifications throughout the 21 hours infusion period. Perform testing using infusion conditions (i.e. storage, temperature, light, etc.).

Cumberland stated that they were preparing a response to item #6 and that they would submit data in response to item #7 in January, 2003.

[redacted]

The call was then concluded.

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/s/

Brian Strongin
12/30/02 03:16:09 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

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 June 27, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACETADOTE® (acetylcysteine injection).

We also refer to your submission dated October 17, 2002.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the drug substance information provided in the NDA:

   a. Clarify which [redacted] route is used for the proposed commercial manufacturing process.
   b. Clarify the use of [redacted] as a reagent/solvent in the manufacturing process.
   c. Regarding the drug substance specifications:

      i- include specified, unspecified, and unidentified impurities based on your test data;
      ii- tighten specifications for residual solvents based on your test data;
      iii- establish a specification and acceptance criteria for heavy metals based on test data.

2. Regarding the drug product manufacturing process:

   a. The trade name for the drug product in this application is ACETADOTE®, not [redacted] Remove any reference to [redacted] throughout the entire NDA, specifically in batch records, the stability protocol, etc.
   b. Regarding the reference standard:

      i. Provide manufacturing information regarding the preparation of the working reference standard. The drug product injectable reference standard can not be compared to the USP reference standard. Propose specifications (acceptance criteria,

tests, methods with code number, etc.) which are suitable to the drug product reference standard.

ii. Provide information related to the storage and testing of the reference standard.

c. Provide scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this drug product.

3. Regarding the drug product specifications:

a. Include specifications for the related drug substances (e.g., acceptance criteria, test methods, etc). Refer to the ICH Guidances for Industry entitled , "Q3B Impurities in New Drug Products" and "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances".
b. Change the name of [redacted] test to "Volume in Container" because it is different from the actual [redacted] test described in the ICH Q6A guidance.
c. Include the [redacted] test and [redacted] in the tests and specifications for the drug product.
d. Tighten the specifications for the bacterial endotoxin limit based on test data.
e. Establish microbial limit acceptance criteria.

4. Regarding the container closure system, provide:

a. Manufacturing information and components/composition or provide a letter of authorization referencing the appropriate Drug Master File(s);
b. Computability information (extractables, integrity, etc.) for the drug product solution;
c. CMC information (manufacturing and testing) especially if the [redacted] cap comes in contact with the drug product solution;
d. A description and drawings of the various components of the container/closure system including vials, stoppers and [redacted] cap;
e. Actual samples of the container closure system to facilitate our review.

5. Regarding the drug product stability:

a. The proposed stability protocol is unacceptable.
b. We recommend modifying the proposed stability protocol to include the following:

i- adequate specifications (see item 3 above);
ii- appropriate test time points (e.g., 0, 3, 6, 9, 12, 18, and 24 months);
iii- perform stability studies on both vial sizes.

c. Submit an updated stability protocol and corresponding data for batches # 990907 and # 200125 in tabular format to facilitate our review of your request regarding expiry dating.

6. Regarding methods validation:

   Submit three copies of the methods validation package prepared according to the guideline entitled, "Submitting Samples and Analytical Tests for Methods Validation" and refer to 21 CFR 314.50 (e).

7- Regarding the [redacted] solution used for intravenous infusion:

   Provide compatibility studies between the drug product solution and the [redacted] solution including test data that are generated at different time points showing that the drug product solution remains within the proposed specifications throughout the 21 hours infusion period. Perform testing using infusion conditions (i.e. storage, temperature, light, etc.).

[redacted]

If you have any questions, call Brian Strongin, R.Ph., M.B.A. at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team leader for the
Division of Gastrointestinal and
Coagulation Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

Liang Zhou

12/10/02 04:45:40 PM

APPEARS THIS WAY
ON ORIGINAL

CUMBERLAND PHARMACEUTICALS

DUPLICATE

NDA 21-539

RECEIVED
DEC 0 3 2002
FDR/CDER

2 December 2002

Robert Justice M.D., Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Food and Drug Administration
Parklawn Building, Room 6B-45
5600 Fishers Lane
Rockville, MD 20857

BL
ORIG AMENDMENT

RE: NDA 21-539
ACETADOTE® (Acetylcysteine Injection)
Amendment

Dear Dr. Justice:

In conformance with 21 CFR §314.50, and the Guidance for Industry entitled "Applications Covered by Section 505(b)(2)", dated October 1999, Cumberland Pharmaceuticals Inc. submitted a New Drug Application (NDA 21-539) for Acetylcysteine, for the treatment of acetaminophen overdosage on July 1, 2002. The Agency filed this application on August 30, 2002.

Reference is made to the telephone contacts between Mr. Brian Strongin, Regulatory Project Manager and Dr. Amy Rock of Cumberland Pharmaceuticals, Inc. on 26 and 27 November 2002.

As discussed with Mr. Strongin, this submission consists of a revised FDA Form 356h, and revised draft labeling.

Please direct any inquiries to Amy Rock, Ph.D, Cumberland Pharmaceuticals Regulatory Affairs, at (615) 255-0068.

Sincerely,

A. J. Kazimi
Chief Executive Officer

APPEARS THIS WAY
ON ORIGINAL

Encls.

CUMBERLAND PHARMACEUTICALS INC.
209 10th Avenue South, Suite 332 • Nashville, Tennessee 37203 • Telephone: (615) 255-0068 • Facsimile: (615) 255-0094
www.cumberlandpharma.com

4 page(s) of draft labeling has been removed from this portion of the review.

MEMORANDUM OF TELECON

DATE: November 26, 2002

APPLICATION NUMBER: NDA 21-539; ACETADOTE® (acetylcysteine injection)

BETWEEN:

Name:	Amy Rock, Ph.D.
Title:	Regulatory Affairs, Cumberland Pharmaceuticals, Inc.
Phone:	(615) 255-0068

AND

Name:	Brian Strongin, R.Ph., M.B.A.
Title:	Regulatory Health Project Manager, The Division of GI and Coagulation Drug Products, HFD-180
Phone:	(301) 827-7310

SUBJECT: Claimed User Fee Exclusion

Background

NDA 21-539 for ACETADOTE® was submitted June 27, 2002 as a 505(b)(2) application for the IV treatment of [redacted] acetaminophen overdose. Despite this proposed indication, Cumberland included instructions for [redacted] intravenous administration in the Dosage and Administration section of the proposed package insert.

On the User Fee Cover Sheet included in Volume 1.1 of NDA 21-539, Cumberland claimed User Fee Exclusions both as a non-fee paying 505(b)(2) application and as an application that qualifies for the orphan exception under section 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act. In an October 19, 2001 letter from the FDA, Office of Orphan Products Development, Cumberland was granted orphan drug designation for acetylcysteine for the intravenous treatment [redacted]. Today's call concerns these claimed user fee exclusions.

(NOTE: NDA 13-601 for Mucomyst (acetylcysteine 20%) and Mucomyst-10 (acetylcysteine solution 10%) was approved January 31, 1985 for oral use as an antidote for acetaminophen overdosage. An intravenous formulation is not approved in the U.S.)

Today's Call

I explained that NDA 21-539 did not qualify for an orphan drug user fee exception. The following is stated in the Instructions for Completing User Fee Cover Sheet Form FDA 3397 on the back of the form: .

> Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated."

NDA 21-539 received orphan designation only for the IV treatment of moderate to severe acetaminophen overdosage.
— the application does not qualify for an orphan drug user fee exclusion.

This application also does not qualify as a non-fee paying 505(b)(2) application. The following is stated in the Instructions for Completing User Fee Cover Sheet Form FDA 3397 on the back of the form:

> Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

NDA 21-539 does not qualify as a non-fee paying 505(b)(2) application because the IV dosing information is, "... a new indication for a use" (an indication not included in the labeling of NDA 13-601 for Mucomyst).

Cumberland was offered the following options:

1. Pay a user fee.
2. Withdraw t — the application and submit a separate 505(b)(2) application for — You may reference NDA 21-539 where appropriate.
3. —

Ms. Rock stated that she would consider these options and call the Agency back with its decision.

The call was then concluded.

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/s/

Brian Strongin
12/18/02 03:49:39 PM
CSO

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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 June 27, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACETADOTE® (acetylcysteine injection).

We are reviewing the clinical, clinical pharmacology and biopharmaceutics, and sterilization validation sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

1. Provide a tabular summary of clinical efficacy data (and text if available) including; dates of randomization; discontinuations; dates of efficacy endpoint measurements; data on subsets of patients according to gender, sex, race, and age; and patient narratives in WORD 97.
2. Provide prospective protocols of placebo-controlled trials or other relevant pivotal trials.
3. Provide patient informed consent forms or forms signed by investigators or institutional IRBs certifying that patients were enrolled according to the latest amended Declaration of Helsinki.
4. Provide an assessment of the safety and effectiveness of ACETADOTE® in pediatric patients as required under 21 CFR 314.55.
5. Provide a revised Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" including a list of relevant clinical investigators as required under item #2.
6. Provide a copy of the proposed unannotated labeling on diskette in WORD 97.

Clinical Pharmacology and Biopharmaceutics

An article(s) published in Arzneimittel forschung 1989; 39:382-6 is listed as authored by DeCaro L. et al (Volume 1.6, page 35, Clinical Pharmacology and Biopharmaceutics section) and by Holdiness, MR (annotated labeling reference, Volume 1.3, page 22). Please clarify whether these are the same or different articles. If they are different articles, provide the location (volume and page number) of the article by Holdiness, MR or submit the article for review.

Sterilization Validation

Provide a complete sterilization validation package. Include an introductory narrative with an overview of the product and process. Refer to the guidance entitled, "Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" available of the CDER website. Provide relevant information supporting the processes used to render the product sterile and the product specification.

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
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/

Julieann DuBeau
9/24/02 04:29:28 PM

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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 07/15/02	DUE DATE: 09/15/02	ODS CONSULT #: 02-0153

TO:

Robert Justice, M.D.
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH:

Brian Strongin
Project Manager
HFD-180

PRODUCT NAME:	**NDA SPONSOR:**
Acetadote (Acetylcysteine Injection)	Cumberland Pharmaceuticals, Inc.
NDA: 21-539	

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name "Acetadote" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name "Acetadote." In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 9, 2002

NDA: 21-539

NAME OF DRUG (S): **Acetadote**
Acetylcysteine Injection

NDA HOLDER: Cumberland Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult is written in response to a July 15, 2002 request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180) for an assessment of the proposed proprietary name, "Acetadote." The container labels, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Acetadote contains the active ingredient, acetylcysteine, and is indicated for the intravenous treatment of [redacted]. However, Acetadote may be administered [redacted] intravenously [redacted]. The following dosing regimen is recommended for IV administration:

- Loading Dose: 150 mg/kg in 200 mL of 5% dextrose, infuse intravenously over [redacted]
- Maintenance Dose: 50 mg/kg in 500 mL of 5% dextrose, infuse intravenously over 4 hours, followed by 100 mg/kg in 1,000 mL 5% of dextrose, infuse intravenously over 16 hours.

[redacted]

APPEARS THIS WAY
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II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Acetadote" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies, outpatient and inpatient, and one verbal prescription studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Acetadote. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. The expert panel consists of members of DMETS Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two names that were thought to have the potential for confusion with Acetadote. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage. Additionally, there was a discussion involving a medical word that is thought to have look-alike and sound-alike potential with the proposed name Acetadote: "Antidote."

2. DDMAC has no objection to the proposed proprietary name Acetadote with regards to promotional claims.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html

[5] Data provided by Thomson and Thomson' SAEGIS™ Online Service, available at www.thomson-thomson.com.

Table 1 (Acetadote)

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Acetadote	Acetylcysteine Injection: [redacted]	Loading Dose: 150 mg/kg in 200 mL of 5% dextrose, infuse IV over [redacted] Maintenance Dose: 50 mg/kg in 500 mL of 5% dextrose, infuse IV over 4 hours, followed by 100 mg/kg in 1,000 mL 5% of dextrose, infuse IV over 16 hours. [redacted]	
Acetasol HC	Otic Solution: 1% hydrocortisone, 2% acetic acid, 3% propylene glycol diacetate, 0.015% sodium acetate and 0.02% benzethonium chloride	Insert saturated wick; keep moist 24 hours. Remove wick and instill 5 drops 3 or 4 times daily.	LA/SA*
Acetasol	Otic Solution: 2% acetic acid with 3% propylene glycol diacetate, 0.02% benzethonium chloride, 0.015% sodium acetate		
Metadate ER	Methylphenidate HCL Extended-Release Tablets, USP; 10 mg and 20 mg	5 mg to 30 mg BID.	LA/SA*
Metadate CD	Methylphenidate HCL Extended-Release Capsules, USP; 20 mg	20 mg to 60 mg QD, before breakfast.	

*SA = Sound-alike
*LA = Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

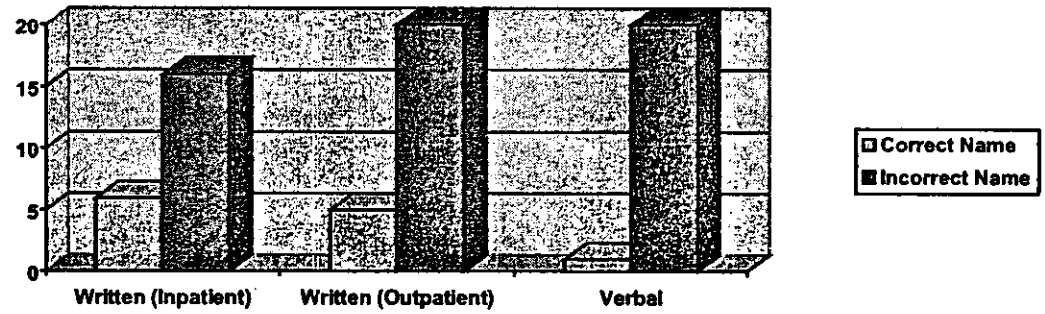
Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Acetadote with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. Inpatient and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Acetadote (see page 5). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Acetadote

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: Acetadote 80 mL x 1	Verbal Rx: Please dispense 80 mL of Acetadote. Drink all at one time. No refill
Inpatient Rx: DC Acetadote	

2. Results for Acetadote

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	32	22 (69%)	6 (27%)	16 (73%)
Written Outpatient	39	25 (64%)	5 (20%)	20 (80%)
Verbal	34	21 (62%)	2 (10%)	19 (90%)
Total	105	68 (65%)	13 (19%)	55 (81%)



Among the verbal prescription study participants for **Acetadote** 19 of 21 (90%) participants interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Acetadote." The incorrect responses were *Acetadete (10), Acetadate (6), Acctadete (1), Acetate (1),* and *Acitadate (1).*

Among the written prescription study participants for **Acetadote**, 36 of 47 (77 %) participants interpreted the name incorrectly. The majority of the incorrect name interpretations were misspelled variations of "Acetadote." The incorrect responses were *Acetadate (19), Asitadote (1), Afedidote (1), Azadote (1), Afeditil (1), Acetidote (2), Asedadote (1), Acididote (1), Afetadote (1), Afedidote (2), Acedodote (1), Asetadote (1), Afededote (1), Acitadote (1), Acetadyl (1),* and *Asidote (1).*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Acetadote", the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Acetadote were Acetasol and Metadate. Additionally, there was a discussion involving a medical word that is thought to have look-alike and sound-alike potential with the proposed name Acetadote: "Antidote."

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Acetadote and Acetasol or Metadate. The misinterpretations also did not overlap with any other currently approved drug names. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name Acetadote. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Metadate CD and Metadate ER contain the active ingredient methylphenidate, and are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy. The name Metadate may look and sound alike to Acetadote as they share the similar letter combinations "etadate" and "etadote." However, there are distinguishing factors between Metadate CD/ER and Acetadote, which may decrease the potential risk of medication errors. First, Metadate CD/ER and Acetadote do not share an overlapping dosage form. Metadate CD is available as 20 mg extended-release capsules and Metadate ER is available as 5 mg and 10 mg extended release tablets. Acetadote will be available as 20% (200 mg/mL) solution for ——— intravenous administration. Furthermore, Acetadote must be diluted in dextrose 5%, ——— prior to administration. Second, the dosing regimen is different. For Metadate CD and Metadate ER, a dose of 10 mg to 60 mg daily is recommended. For Acetadote, a loading dose of 150 mg/kg diluted in dextrose 5%, ——— followed by maintenance doses, is recommended. Third, Acetadote is an antidote used for acetaminophen poisoning; therefore, it is exclusively used in the emergency settings. Metadate CD and ER are mainly used in the outpatient settings. Lastly, although Metadate ER/CD can look and sound similar to Acetadote, the modifiers "CD" and "ER" clearly distinguishes one name from the other.

Acetasol HC contains the following ingredients: 1% hydrocortisone, 2% acetic acid, 3% propylene glycol diacetate, 0.015% sodium acetate, and 0.02% benzethonium chloride. Acetasol contains all the ingredients contained in Acetasol HC except hydrocortisone. Acetasol products are indicated for the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation. The names Acetasol and Acetadote sound and look similar as they share the same beginning "Aceta." However, the risk of confusion between Acetasol and Acetadote is minimal for several reasons. First, although both Acetasol and Acetadote are available as solutions, they do not share an overlapping route of administration. Acetasol is available as an otic solution, which is administered to the ears. Acetadote will be available as a solution for ——— intravenous administration. Second, the dosing regimen is different. A wick of cotton saturated with Acetasol is applied into the ears for 24 hours and after the removal of the wick, 5 drops of Acetasol is administered three to four times daily. For Acetadote, a loading dose of 150 mg/kg diluted in dextrose 5% ———, followed by maintenance doses, is recommended. Third, Acetadote is an antidote used for acetaminophen poisoning; therefore, it is exclusively used in the emergency settings. This strict use of Acetadote will further decrease the risk of name confusion with Acetasol. Additonally, it is unlikely that Acetasol would be routinely stocked in the inpatient settings. Lastly, the endings "sol" and "dote" are different enough to distinguish one name from the other.

The expert panel also noted that the proposed proprietary name Acetadote sounds and looks similar to the medical word "antidote." According to the Stedman's Medical Dictionary (27th Edition), the word "antidote" is defined as follows: "An agent that neutralizes a poison or counteracts its effects." There are numerous antidotes such as Antivenin, atropine sulfate, acetylcysteine, and Flumazenil available in the U.S. market. Because there are numerous kinds of antidotes used in the clinical settings, a specific "antidote" is ordered for a "specific" type of poisoning. For instances, atropine sulfate is an antidote for organophosphate poisoning and the proposed product Acetadote (acetylcysteine) is an antidote for acetaminophen poisoning. Therefore, it is unlikely that the word "antidote" would be confused for the proposed product "Acetadote." Even if the proposed name Acetadote is confused as the medical word "antidote", the order would have to be clarified as to what kind of "antidote".

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

DMETS has reviewed the container labels, carton and insert labeling. We have identified several areas of improvement that will minimize potential user errors.

A. GENERAL COMMENT

The currently available acetylcysteine-containing products are used as an adjuvant therapy for abnormal, viscid, or inspissated mucus secretions in chronic bronchopulmonary disease and for acetaminophen poisoning. However, the proposed product Acetadote is only to be used as an antidote for [redacted] We recommend sufficient education regarding the appropriate use of this product upon the launch of this product.

B. CONTAINER LABEL [redacted]

1. We recommend expressing the primary and secondary strength as follows: [redacted] We also recommend increasing the prominence of the strength by increasing their font sizes.

2. In order to prevent medication errors due to the similarity in labeling among the [redacted] strengths [redacted] we recommend highlighting the "strengths" with the use of contrasting color, boxing, or some other means.

3. We recommend relocating the statement "FOR [redacted] INTRAVENOUSE USE" to the front of the label to increase its prominence, as is seen on the container label.

4. We recommend adding the statement, "Rx Only."

C. CARTON LABELING [redacted]

1. See comments under B1 and B2.

2. Please change the statement [redacted] to "Rx Only."

3. We believe the expression of strength in the "Each mL" statement is confusing. Revise to read: Each mL contains 200 mg acetylcysteine, 0.5 mg disodium edetate..."

D. INSERT LABELING

1. Through out the package insert, please change [redacted] to an acceptable abbreviation "IV" for "intravenous."

2. TITLE:

   The firm has proposed "For Intravenous Use" within the title. This should be revised to include [redacted] also.

3. DESCRIPTION:

   A. See comment in TITLE.

   B. The quantitative amounts of inactive ingredients should be included (e.g., 0.5 mg disodium edetate).

4. INDICATION AND USAGE

   The firm proposes that the product is indicated only for IV treatment [redacted]. However, the DOSAGE and ADMINSTRATION section supports [redacted]

IV. RECOMMENDATIONS

A. DMETS has no objection to the use of the primary proprietary name, Acetadote.

B. DMETS recommends implementation of the labels and labeling as outlined in section III of this review.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward. We would appreciate feedback of the final outcome of this consult.

We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarification, please contact Sammie Beam at 301-827-3242.

Hye-Joo Kim Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support

Concur:

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support

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/s/

Hye-Joo Kim
9/16/02 10:03:47 AM
PHARMACIST

Alina Mahmud
9/16/02 10:05:37 AM
PHARMACIST

Jerry Phillips
9/16/02 10:26:47 AM
DIRECTOR

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-539	Brand Name	Acetadote
OCPB Division (I, II, III)	II	Generic Name	Acetylcysteine
Medical Division	GI & Coagulation	Drug Class	Naturally occurring amino acid
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	[redacted]
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Sterile Solution
		Dosing Regimen	For IV: 150 mg/kg infused over [redacted] 50 mg/kg infused over 4 hrs, and then 100 mg/kg infused over 16 hrs.
Date of Submission	06/27/02	Route of Administration	IV
Estimated Due Date of OCPB Review	11/01/02	Sponsor	Cumberland
Medical Division Due Date	12/01/02	Priority Classification	P
PDUFA Due Date	01/01/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	[redacted]	[redacted]		
Mass balance:		1		Literature data
Isozyme characterization:		0		
Blood/plasma ratio:		0		
Plasma protein binding:		0		
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]		
Healthy Volunteers-	[redacted]	[redacted]		
single dose:		1		Literature Data
multiple dose:		0		
Patients-	[redacted]	[redacted]		
single dose:		1		Literature Data
multiple dose:		0		
Dose proportionality -	[redacted]	[redacted]		
fasting / non-fasting single dose:		0		
fasting / non-fasting multiple dose:		1		Literature Data (oral data)
Drug-drug interaction studies -	[redacted]	[redacted]		
In-vivo effects on primary drug:		0		
In-vivo effects of primary drug:		1		Literature Data
In-vitro:		0		
Subpopulation studies -	[redacted]	[redacted]		
ethnicity:		0		
gender:		0		
pediatrics:		1		Literature Data
geriatrics:		0		
renal impairment:		0		
hepatic impairment:		1		Literature Data
PD:	[redacted]	[redacted]		

Phase 2:		0		
Phase 3:		0		
PK/PD:	N/A			
Phase 1 and/or 2, proof of concept:		0		
Phase 3 clinical trial:		0		
Population Analyses -	N/A			
Data rich:		—	—	
Data sparse:		—	—	
II. Biopharmaceutics				
Absolute bioavailability:	X	2		Literature Data
Relative bioavailability -	N/A			
solution as reference:		0		
Alternate formulation as reference:		0		
Bioequivalence studies -	N/A			
Traditional design; single / multi dose:		0		
Replicate design; single / multi dose:		0		
Food-drug interaction studies:	N/A	0		
Dissolution:	N/A	0		
(IVIVC):		0		
Bio-wavier request based on BCS		0		
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:		0		
Chronopharmacokinetics		0		
Pediatric development plan		0		
Literature References		5		
Total Number of Studies		14		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ? No!	Needs to be sent	An article(s) published in Arzneimittel forschung 1989; 39:382-6 had different authors, by DeCaro L. et al (under PK section reference on page 35, Vol. 1.6) and by Holdiness MR. (under annotated Labeling reference on page 22, Vol. 1.3). Please provide clarification if this is the same or different article(s). If they are different, please provide the location of the article by Holiness MR. (page # and vol. #) or submit the article for review.
QBR questions (key issues to be considered)	Do the published articles support the labeling of this NDA?	
Other comments or information not included above		
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D. 08/07/02	
Secondary reviewer Signature and Date	Suresh Doddapaneni, Ph.D. 08/07/02	

CC: NDA 21-539, HFD-850 (Electronic Entry or Lee), HFD-180 (R. Prizont, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng)

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/s/

Tien-Mien Chen
8/8/02 04:36:38 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/16/02 07:41:22 AM
BIOPHARMACEUTICS

Office of Pharmaceutical Science
Microbiology Staff

PRODUCT QUALITY MICROBIOLOGY CRITERIA FOR NEW NDA SUBMISSIONS

45-DAY NDA FILING MEETING

NDA : **21-539**

1. On its face, is the microbiological section of the NDA organized in a manner to allow substantive review to begin?

~~YES~~ **NO**

2. Is the microbiological section indexed and paginated in a manner to allow substantive review to begin?

~~YES~~ **NO**

3. On its face, is the microbiological section presented legibly in English so that substantive review can begin?

YES ~~NO~~

4. Has the applicant submitted an overall description of the sterilization process for the subject drug product?

~~YES~~ **NO**

5. Has the applicant submitted descriptions of all ancillary sterilization processes used in the production of the final product?

~~YES~~ **NO**

6. Has the applicant submitted descriptions, protocols, and results of validation experiments concerning sterilization processes used in the manufacture of the drug product?

~~YES~~ **NO**

7. Has the applicant submitted all special studies requested during pre-submission meetings?

~~YES~~ ~~NO~~ **N/A**

8. From the standpoint of sterility assurance, has sufficient information been submitted to determine the microbiological safety of the product for its intended use? If the application is not fileable, describe why not below.

Volume 1.7 was provided for consultative review as a "Microbiology Section." The section begins by asserting the information conforms with the 1999 guidance on *Applications covered by Section 505(b)(2)*. Section IV of that guidance states, "The requirements for 505(b)(1) and 505(b)(2) applications are described at 21 CFR 314.50. Additional requirements for certain 505(b)(2) applications are described at 21 CFR 314.54." The Technical Section (d) of a 315.50 application should include information supporting the sterilization processes and their validation experiments to support the manufacturing and product specification for a sterile drug. The NDA submission (volume 1.7) includes SOPs for product testing and there is no discussion of the sterilization processes.

The Table of Contents for the CMC section was examined and indicated the presence of a blank batch record. All validation information listed was part of the analytical methods section. There is no discussion in this section of the sterilization processes.

The applicant should refer to the 1994 guidance *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (http://www.fda.gov/cder/guidance/cmc2.pdf). Relevant information should be provided supporting the processes used to render the product sterile, and the product specification.

Microbiology recommends **REFUSE TO FILE.**

David Hussong/Review Microbiologist

Peter Cooney/Supervisory Microbiologist

HFD-805

filename: 21-539 RTF.doc

APPEARS THIS WAY
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/s/

David Hussong
7/30/02 02:01:38 PM
MICROBIOLOGIST

Peter Cooney
7/30/02 04:03:43 PM
MICROBIOLOGIST

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:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ACETADOTE® (acetylcysteine injection)

Review Priority Classification: (P) Priority

Date of Application: June 27, 2002

Date of Receipt: July 1, 2002

Our Reference Number: NDA 21-539

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 30, 2002 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be January 1, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Brian Strongin
7/26/02 04:44:08 PM

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Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-539

Name of Drug: Acetadote (acetylcysteine injection)

Sponsor: Cumberland Pharmaceuticals, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination CMAX, HATS, and META analyses

Resubmission Letter Date: July 21, 2003 *[Original Submission Date: June 27, 2002]*

Resubmission Receipt date: July 24, 2003 *[Original Receipt Date: July 1, 2002]*

Filing Date: September 22, 2003

User-fee Goal Date: January 24, 2004

Proposed Indication: ———————————————————

Other Background Information: NDA 21-539 was submitted as a 505(b)(2) application. Safety and efficacy is supported by studies which Cumberland Pharmaceuticals did not conduct or have a right of reference. Cumberland did submit interim data from CMAX Study Number CM8801 in support of safety.

Mucomyst (acetylcysteine solution 20%) and Mycomyst-10 (acetylcysteine solution 10%) were approved January 31, 1985 (as an efficacy supplement to NDA 13-601) for oral use as an antidote for acetaminophen overdosage. An intravenous formulation of N-acetylcysteine is approved in Australia, Canada, South Africa, and Europe as an antidote for acetaminophen toxicity.

On December 30, 2002, the Agency issued a Not Approvable (NA) Letter resulting from clinical and chemistry, manufacturing, and control (CMC) deficiencies. In that letter, the Agency requested that the sponsor:

1. [redacted]

2.

3. [redacted]

4. [redacted]

In addition, the Agency requested the sponsor to provide a safety update that includes data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. The NA letter also included recommendations and additional information requests resulting from clinical and CMC reviews.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1.1, first unnumbered page
2. Form FDA 356h (original signature)	X		Volume 1.1, page 2 under "Form 356h" tab
a. Establishment information		X	Establishment information is included in the CMC section
b. Reference to DMF(s) & Other Applications	X		Appendix G
3. User Fee FDA Form 3397	X		N/A
4. Patent information & certification	X		See Original Submission
5. Debarment certification (Note: Must have a definitive statement)	X		See Original Submission
6. Field Copy Certification	X		See Original Submission
7. Financial Disclosure	X		See Original Submission
8. Comprehensive Index	X		Volume 1.1 under "Overall Table of Contents" tab.
9. Pagination	X		Number in lower right hand of page.

10. Summary Volume	X		Volume 1.2

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11. Review Volumes	X		Appropriate review volumes have been distributed to all reviewers.
12. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Submitted via WORD file. Placed on shared drive: *N:/Labeling in Progress/ Acetadote_NDA21-539_Labeling proposed 072103.doc*
b. annotated PI		X	Requested from sponsor
c. immediate container		X	Requested from sponsor
d. carton		X	Requested from sponsor
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	This information will be requested if necessary.
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)		X	N/A
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)		X	N/A

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		X	See Original Submission
2. Foreign Marketing History		X	See Original Submission
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 1.7,
b. Nonclinical Pharmacology/Toxicology		X	N/A
c. Human Pharmacokinetic & Bioavailability		X	N/A
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis	X		Vols. 1, and 4 through 6 Also submitted via EDR
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		See Safety Update, Vol. 6
5. Summary of Safety	X		See safety update, Vol. 6
6. Summary of Efficacy		X	N/A

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators		X	N/A
2. Controlled Clinical Studies			
a. Table of all studies		X	N/A
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)		X	
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)		X	
4. Integrated Summary of Safety (ISS)		X	
5. Drug Abuse & Overdosage Information		X	N/A
6. Integrated Summary of Benefits & Risks of the Drug		X	
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X		Vol. 1 under "Overall Response" tab

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	A pediatric assessment or the location of this information in the application will be requested from Cumberland Pharmaceuticals.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			APPEARS THIS WAY ON ORIGINAL
a. Proposed unannotated labeling in MS WORD		X	This information will be requested from Cumberland Pharmaceuticals.
b. Stability data in SAS data set format (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
c. Efficacy data in SAS data set format (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)		X	N/A

Y=Yes (Present), N=No (Absent)

[a]AGUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS≅ (FEBRUARY 1987).

[b]AGUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS≅ (FEBRUARY 1987).

[c]AGUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS≅ (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

CONCLUSIONS

1. NDA 21-539 is filable from an administrative perspective.
2. Cumberland Pharmaceuticals will be requested to provide a paper copy of the proposed labeling.

Paul E. Levine, Jr. R.Ph., J.D.
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-539

Name of Drug: Acetadote (acetylcysteine injection)

Sponsor: Cumberland Pharmaceuticals, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Paper

Submission Date: June 27, 2002

Receipt Date: July 1, 2002

Filing Date: August 30, 2002

User-fee Goal Date: January 1, 2003

Proposed Indication _____

Other Background Information: NDA 21-539 was submitted as a 505(b)(2) application. Safety and efficacy is supported by studies which Cumberland Pharmaceuticals did not conduct or have a right of reference. Cumberland did submit interim data from CMAX Study Number CM8801 in support of safety.

Mucomyst (acetylcysteine solution 20%) and Mycomyst-10 (acetylcysteine solution 10%) were approved January 31, 1985 (as an efficacy supplement to NDA 13-601) for oral use as an antidote for acetaminophen overdosage. An intravenous formulation of N-acetylcysteine is approved in Australia, Canada, South Africa, and Europe as an antidote for acetaminophen toxicity.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1.1, first unnumbered page
2. Form FDA 356h (original signature)	X		Volume 1.1, unnumbered page behind the "Field Copy Certification" tab
a. Establishment information		X	Establishment information is included in the CMC section
b. Reference to DMF(s) & Other Applications		X	This information will be requested if necessary.
3. User Fee FDA Form 3397	X		Volume 1.1 behind the "User Fee" tab
4. Patent information & certification	X		Volume 1.1 behind the "Patent Information" tab
5. Debarment certification (Note: Must have a definitive statement)	X		Volume 1.1 behind the "Debarment Certification" tab
6. Field Copy Certification	X		Contained in the cover letter
7. Financial Disclosure	X		Volume 1.1 behind the "Financial Information" tab. A list of investigators must be attached to the Financial Disclosure form will be requested from Cumberland.
8. Comprehensive Index	X		Volume 1.1 behind the "Index" tab.
9. Pagination	X		Each volume is paginated separately.
10. Summary Volume	X		Volume 1.2

11. Review Volumes	X		Appropriate review volumes have been distributed to all reviewers.
12. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Volume 1.1, page 16
b. annotated PI	X		Volume 1.2, page 1
c. immediate container	X		Volume 1.1, unnumbered pages following the unannotated PI
d. carton	X		Volume 1.1, unnumbered pages following the unannotated PI
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	This information will be requested if necessary.
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		CMAX Study CM8801 Volume 1.21, page 1
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Volume 1.22 – 1.28

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 1.2, page 24
2. Foreign Marketing History	X		Volume 1.2, page 27
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 1.2, page 28
b. Nonclinical Pharmacology/Toxicology	X		Volume 1.2, page 36
c. Human Pharmacokinetic & Bioavailability	X		Volume 1.2, page 45
d. Microbiology	X		Volume 1.2, page 53 (sterility process information)
e. Clinical Data & Results of Statistical Analysis	X		Volume 1.2, page 55
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 1.2, page 77
5. Summary of Safety	X		(ISS) Volume 1.11, page 101
6. Summary of Efficacy	X		(ISE) Volume 1.11, page 5

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Volume 1.9, page 1
2. Controlled Clinical Studies			
a. Table of all studies	X		Volume 1.9, page 46
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		CMAX Study No. CM8801 Synopsis: Volume 1.9, page 49 Protocol: Volume 1.9, page 179 Related Publications: Volume 1.9, page 176; Volume 1.10, page 91 List of Investigators: Volume 1.9, page 60 Clinical/Stat Report: Volume 1.9, page 47
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Volume 1.11, page 5
4. Integrated Summary of Safety (ISS)	X		Volume 1.11, page 101
5. Drug Abuse & Overdosage Information		X	N/A
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 1.11, page 332
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		X	This information, or its location in the application will be requested.

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	A pediatric assessment or the location of this information in the application will be requested from Cumberland Pharmaceuticals.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD		X	This information will be requested from Cumberland Pharmaceuticals.
b. Stability data in SAS data set format (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
c. Efficacy data in SAS data set format (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	This information will be requested from Cumberland Pharmaceuticals if necessary.
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)		X	N/A

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

NDA 21-539 is filable from an administrative perspective.

The following information will be requested from Cumberland Pharmaceuticals:

1. An analysis of safety and efficacy data by race, gender, and age subgroups or the location of this information in the application
2. A pediatric assessment or the location of this information in the application
3. A copy of the proposed unannotated labeling on diskette in Word 97
4. A list of investigators to attach to the Financial Disclosure Form

The need for the following information will be requested at the filing meeting. All necessary information will be requested from the sponsor.

1. English translations of foreign labeling
2. Stability data in SAS data set format
3. Efficacy data in SAS data set format
4. Biopharmacological information and study summaries in MS WORD

Name
Regulatory Project Manager

cc:
Original NDA 21-539
HFD-180/RPM/B.Strongin
HFD-180/Reviewers
draft: BKS/July 24, 2002
final: BKS/July 24, 2002

ADMINISTRATIVE REVIEW

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/s/

Brian Strongin
7/26/02 08:19:36 AM
CSO

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Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 26, 2002

From: David Hoberman, HFD-715

Subject: Acetadote (acetylcysteine) Injection

To: File: (NDA#21-539)

The sponsor has submitted a very early (unplanned) interim analysis of a randomized trial comparing two IV infusion rates of Acetadote for the treatment of acetaminophen poisoning. The ultimate target sample size is 500 patients, but the number of patients with usable data in this interim analysis is only about 30. At the filing meeting on July, 26, 2002, it was decided to ignore this data for the purpose of filing and to tell the sponsor to submit results of the trial when it is finished. Thus, at this time, there is no purpose for a review for this NDA from Biometrics.

David Hoberman, Ph.D.
Mathematical Statistician

cc:
Arch NDA# 21-539
HFD-180
HFD-180/HGallo-Torres
HFD-715/DHoberman, TPermutt, ENevius, CAnello

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/s/

David Hoberman
7/26/02 01:29:17 PM
BIOMETRICS

Thomas Permutt
8/9/02 10:07:10 AM
BIOMETRICS
concur

S. Edward Nevius
8/17/02 02:50:06 PM
BIOMETRICS
Concur.

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21539/000
Stamp: 01-JUL-2002
Regulatory Due: 01-JAN-2003
Applicant: CUMBERLAND PHARMS
209 10TH AVE SOUTH STE 332
NASHVILLE, TN 37203
Priority: 3P
Org Code: 180

Action Goal: 31-DEC-2002
District Goal: 02-MAR-2003
Brand Name: ACETADOTE (ACETYLCYSTEINE) 10/30ML SOLUT
Estab. Name:
Generic Name: ACETYLCYSTEINE

Dosage Form: (SOLUTION)
Strength: 10ML AND 30ML

Application Comment: THIS APPLICATION MAY HAVE REFUSE TO FILE ISSUES. HOWEVER, IF ACCEPATED FOR FILING, THIS APPLICATION COULD BE GIVEN A DESIGNATION AS A PRIORTY (P) DRUG. (on 26-JUL-2002 by A. AL HAKIM (HFD-820) 301-827-7467)

FDA Contacts:
B. STRONGIN (HFD-180) 301-827-7310 , Project Manager
A. AL HAKIM (HFD-820) 301-827-7467 , Review Chemist
L. ZHOU (HFD-180) 301-827-7471 , Team Leader

Overall Recommendation: ACCEPTABLE on 30-JUL-2002 by S. ADAMS (HFD-324) 301-594-0095
ACCEPTABLE on 05-AUG-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:
AADA:
Responsibilities:

Profile: SVT
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-JUL-2002				ALHAKIMA
SUBMITTED TO DO	29-JUL-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	30-JUL-2002			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
BASED ON 5/01 AC EI					
OC RECOMMENDATION	30-JUL-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: [redacted]

DMF No: ——
AADA:
Responsibilities: ——————————

Profile: CSN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-AUG-2002				ALHAKIMA
OC RECOMMENDATION	05-AUG-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-539	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: ACETADOTE ® (acetylcysteine injection)	Applicant: Cumberland Pharmaceuticals, Inc.	
RPM: Brian Strongin, R.Ph., M.B.A.	HFD-180	Phone # 7-7473
Application Type: () 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	() Standard (X) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	January 1, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(N/A) Paid user Fee (User Fee exclusion received due to Orphan Designation. See 10/19/01 letter from Office of Orphan Products Development.)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	July 26, 2002

General Information	
❖ Actions	
• Proposed action	() AP ( ) TA () AE (X) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(N/A) Materials requested in AP letter (N/A) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X – Package Insert (December 2, 2002 submission)
• Original applicant-proposed labeling	X – Package Insert (June 27, 2002 submission)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS Trade Name Review – September 16, 2002 No labeling meetings or DDMAC labeling review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X [Mucomyst® (acetylcysteine)]
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X (December 2, 2002)
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	December 15, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**(INSERT DATES WHEN AVAILABLE)**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**(INSERT WHEN READY)**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	**X (INSERT DATE WHEN AVAILABLE)**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (8/16/02 and 12/6/02)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X (12/4/02)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (12/4/02)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**X ((INSERT DATE WHEN AVAILABLE)**
❖ Facilities inspection (provide EER report)	X (Acceptable 8/5/02)
❖ Methods validation	() Completed N/A () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (12/1/02)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

7/2/02

APPEARS THIS WAY
ON ORIGINAL