CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-369

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13.A. PATENT INFORMATION

The Codeine/Chlorpheniramine Extended Release Suspension application represents a modification for the two listed OTC monograph drugs in terms of a new dosage form, dosing regimen, and extended drug-release pattern, for which investigations such as bioavailability or bioequivalence studies are essential to its approval. This 505(b)(2) NDA application relies on the Agency's previous finding of safety and efficacy by the FDA's Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilatory and Antiasthmatic Products. The Panel found codeine and chlorpheniramine, alone and in combination, to be safe and effective at recommended doses as per the following OTC monographs:

- Final Monograph for OTC Antitussive Drug Products, 52 FR 30055, Aug. 12, 1987
- Final Monograph for OTC Antihistamine Drug Products, 57 FR 58374, Dec. 9, 1992
- Tentative Final Monograph for Combination Products,53 FR 30561, Aug. 12, 1988

The following patents claim the drug or a method of using the drug that is the subject of this New Drug Application:

- U.S. Patent No. 5,980,882. Tentative expiration: 04/16/2017
  - Type of patent: drug product
  - Owner: Celltech Pharmaceuticals, Inc.
  - The undersigned declares that Patent No. 5,980,882 covers the formulation, composition, and/or method of use of codeine/chlorpheniramine extended-release suspension. This product is the subject of this application for which approval is being sought.

- U.S. Patent No. 4,762,709. Tentative expiration: 08/09/2005.
  - Type Of Patent: drug product
  - Owner: Celltech Pharmaceuticals, Inc.
  - The undersigned declares that Patent No. 4,762,709 covers the formulation, composition, and/or method of use of codeine/chlorpheniramine extended-release suspension. This product is the subject of this application for which approval is being sought.

To the best of our knowledge, there is no listed drug that is pharmaceutically equivalent to the drug product for which this application is submitted.

Gail Norris, Esq.
Vice President & General Counsel

14. PATENT CERTIFICATION

Celltech certifies that, in its opinion and to the best of its knowledge, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs. This 505(b)(2) NDA application relies on the Agency's previous finding of safety and efficacy by the FDA's Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilatory and Antiasthmatic Products.

Gail Norris, Esq.
Vice President & General Counsel

13.B. MARKET EXCLUSIVITY STATEMENT

Celltech certifies that the investigations included in this application do not meet the definition of "new clinical investigations" per 21 CFR 314.108(a). Thus, pursuant to 21 CFR 314.50(j), Celltech hereby states that the drug product subject of this application is not entitled to three (3) years of market exclusivity from the date of approval of this application. Investigations were sponsored by Celltech under IND 54,892.

EXCLUSIVITY SUMMARY FOR NDA # 21-369 SUPPL # N/A

Trade Name Codeprex
Generic name codeine polistirex/chlorpheniramine polistirex

Applicant Name Celltech Pharmaceuticals HFD # 570

Approval Date If Known 6/22/04

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /✓/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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 /___/ 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 /_✓__/

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 /_✓__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /___/ NO /_✓__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /___/ NO /___/

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

NDA# _____ _____

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). ***more in orange book.***

NDA# _19-111__ _Tussionex (chlorpheniramine polistirex and hydrocodone polistirex)

NDA# _19-746__ _Efidac 24 (chlorpheniramine maleate)

NDA# _18-397__ _Chlor-Trimeton (chlorpheniramine maleate and pseudoephedrine sulfate)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ NO /__✓_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /___/ 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 8:

_____

(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 /___/

(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 /___/

If yes, explain:

(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 /___/

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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

Investigation #2 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:

_____ _____

_____ _____

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 /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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 /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(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 /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(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 /___/

If yes, explain: _____

_____

_____

Christine Yu, R.Ph. Date
Regulatory Project Manager

_____

Badrul A. Chowdhury, M.D., Ph.D. Date
Division Director

Concurrence: S Barnes/25 June 2004
Form OGD-011347 Revised 05/10/2004

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

/s/

Badrul Chowdhury
6/25/04 04:03:45 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA # : 21-369 **Supplement Type (e.g. SE5):** Original **Supplement Number:**

Stamp Date: 13 April 2001 **PDUFA Date:** 22 June 2004 **HFD-**570

Trade and generic names/dosage form: Codeprex (codeine polistirex and chlorpheniramine polistirex) ER suspension

Applicant: Celltech Pharmaceuticals, Inc. **Therapeutic Class:** 4S

Indication(s) previously approved: None

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

Number of indications for this application(s): 1

Indication #1: temporary relief of cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis

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

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____**Partial Waiver** ✓ **Deferred** ✓ **Completed**
NOTE: More than one may apply.
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ion 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.**_____ **yr.** Birth **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** <6 years **Tanner Stage**_____

Reason(s) for deferral:

- ☑ **Products in this class for this indication have been 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): **June 22, 2007**

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

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.** ≥6 years **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** Adult **Tanner Stage**_____

Comments:
This application relies on the Agency's previous findings of safety and efficacy of the active drugs, including pediatric populations ages 6 and above, as described in the appropriate monographs. The relevant monographs for the constituent drugs are:

- Final Monograph for Antitussive Drug Products, for codeine as a narcotic antitussive [21 CFR 341.74]
- Final Monograph for OTC Antihistamine Drug Products, for chlorpheniramine maleate as an antihistamine [21 CFR 341.72]
- Final Monograph for Combination Cough, Cold and Bronchodilator Drug Products, for the combination of codeine and chlorpheniramine maleate [21 CFR 341.40]

Bioequivalence studies conducted to support this NDA did not include any pediatric patients. "Completion" of pediatric studies rely on the monographs. This product is indicated for children 6 years of age and older.

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}

Christine Yu, R.Ph.
Regulatory Project Manager

Concurrence: S Barnes/21 June 2004

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

/s/

Christine Yu
6/21/04 05:00:46 PM

CELLTECH

DEBARMENT CERTIFICATION STATEMENT

Celltech Americas, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Michael Tidd, M.D.
Vice President, Medical Affairs

19. FINANCIAL DISCLOSURE

In accordance with 21 CFR § 54.4, attached is a completed Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators. This certification is made for all Investigators and those Subinvestigators involved in the treatment or evaluation of research subjects in the pivotal studies designated COD-02001 and COD-02002. These studies meet the definition of a "covered clinical study" set forth in 21 CFR §54.2(e).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mr. Ian R. Garland	Chief Operating Officer
FIRM/ORGANIZATION: Celltech Pharmaceuticals, Inc.	
SIGNATURE: Ian R Garland.	DATE: 3-28-01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS (301) 443-2454 EF

Cod-02001: Food-Effect Bioavailability Study of an Extended-Release Suspension of Codeine 40 mg/Chlorpheniramine Maleate 8 mg

Principal Investigator	Sub-Investigators
Aziz L. Laurent, M.D.	Thomas L. Hunt, M.D., Ph.D. [redacted] Randall Phillips

Cod-02002: Steady State Bioavailability Study of an Extended-Release Suspension of Codeine 40 mg/Chlorpheniramine Maleate 8 mg Relative to an Immediate-Release Solution of Codeine 20 mg/Chlorpheniramine Maleate 4 mg

Principal Investigator	Sub-Investigators
Thomas L. Hunt, M.D., Ph.D.	Aziz L. Laurent, M.D. [redacted] Randall Phillips

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-369	Efficacy Supplement Type N/A	Supplement Number	
Drug: Codeprex (codeine polistirex/chlorphenirmaine polistirex) Extended-Release Suspension		Applicant: Celltech Pharmaceuticals	
RPM: Christine Yu		HFD-570	Phone # 301-827-1051
Application Type: ( ) 505(b)(1) (√) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(√) Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC) (Controlled Substances)	Schedule III
❖ User Fee Goal Dates	June 22, 2004
❖ Special programs (indicate all that apply)	(√) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee **Half-fee (see e-mail from Beverly Friedman, Telecon May 3, 2001)**	(√) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (√) No
• This application is on the AIP	( ) Yes (√) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ 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.	(√) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(√) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I (√) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	June 21, 2004

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	October 24, 2001
❖ Actions	
• Proposed action	(√) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE February 13, 2002
• Status of advertising (approvals only)	(√) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only) ***in DFS cc***	(√) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(√) 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)	Minor edit in AP letter
• Most recent applicant-proposed labeling	June 14, 2004
• Original applicant-proposed labeling	December 19, 2003
• 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 1/22/02 & 4/28/04 CSS 1/7/02 & 5/6/04 DDMAC 5/11/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Tussionex ER suspension, Dimetane-DC
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	June 14, 2004
• Reviews	Included with reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Fax dated June 1, 2004
• Documentation of discussions and/or agreements relating to post-marketing commitments	None other
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	√
❖ Memoranda and Telecons	√
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	September 21, 1998
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	N/A
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	1/31/02 and 6/21/04
❖ Clinical review(s) *(indicate date for each review)*	2/1/02 and 6/7/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	None submitted
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	6/21/04
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Filing review June 6, 2001 1/29/02 and 6/17/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Filing review, May 31, 2001 1/7/02 and 5/6/04
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	November 28, 2001
❖ CMC review(s) *(indicate date for each review)*	1/21/02 and 6/16/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	January 21, 2002
• 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)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 1/16/02 & 4/28/04 (√) Acceptable ( ) Withhold recommendation
❖ Methods validation	(√) Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	1/7/02, 4/9/04, 5/21/04, 6/9/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

17 page(s) of revised draft labeling has been redacted from this portion of the review.

CELLTECH

Facsimile

To:	Christine Yu
Company:	Division of Pulmonary and Allergy Drug Products
Fax number:	301-827-1271
From:	Mary Evelyn Towne
Date:	June 04, 2004
Subject:	NDA 21-369 for Codeprex: CMC agreement and Pharmacology Post Marketing study commitment.
Total number of pages:	8 including cover

Chris,

Please find attached Celltech's response (cover letter only) to the June 1, 2004 facsimile. Simultaneously, a hard copy has been sent via Federal Express.

I will give you a call on Monday, June 7 to confirm receipt of our June 4 response.

Thank-you.

Sincerely,

Mary Evelyn

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31766 Rochester, NY 14603-1766
Tel: 585-274-5840 Fax: 585-272-3952 E-Mail:

CELLTECH

June 4, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Fishers Document Room 8B-45
Office of Drug Evaluation II
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-369
Codeprex™ (codeine polistirex and chlorpheniramine polistirex)
Extended Release Suspension

CELLTECH'S RESPONSE TO THE JUNE 1, 2004 FACSIMILE

Dear Sir/Madam:

Reference is made to pending NDA 21-369 for Codeprex, the resubmission dated December 19, 2003, the FDA facsimile dated June 1, 2004 that identifies proposals for a pharmacology Post-marketing study commitment and CMC agreements, telephone contacts with Christine Yu, Dr. LaFrance and the undersigned on June 2, 2004 and a telephone contact with Dr. Shah and Dr. LaFrance on June 3, 2004.

As noted in the June 1, 2004 facsimile, a response by close of business Friday, June 4, 2004 is necessary for finalization of FDA reviews for action to the application.

The purpose of this communication is to provide Celltech's agreement to ***all*** proposals identified in the June 1 facsimile. Celltech appreciates the Agency's review of additional stability data in reference to item # 8 to consider 18 months expiration dating. As instructed by Christine Yu, the response is provided below point by point. The FDA proposals reflected in the facsimile are listed below in bold followed by Celltech's response.

Pharmacology/Toxicology Post Marketing Study Commitment

In vivo metabolism of codeine to [redacted] was demonstrated in the guinea pig; however, this species was not used in toxicology studies with codeine. Carcinogenicity studies with codeine were conducted using the Fischer 344/N rat and B6C3F1 mouse. We note that in vitro metabolism of codeine to [redacted] was demonstrated with a rat liver preparation; however, in vitro metabolism does not always correlate with in vivo metabolism.

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: 585-274-5840 Fax: 585-272-3952 E-Mail: mary.towne@celltechgroup.com

Your commitment to conduct the Post-marketing study as outlined below also incorporates your agreement to limit levels of ——— (your current LOQ) in the drug product until its qualification results are submitted and evaluated by the Division.

1. **Provide a Post-marketing study commitment to conduct and provide reports of preclinical studies for either option 1 or 2 as described below, within 6 months of approval. The commitment should include proposed dates for the submission of the protocol, study start, and final report submission.**

   a. [redacted]

   b. **Conduct two in vitro genetic toxicity tests (ICH Q3A) to assess the genotoxic potential of ———**

      - **If genotoxicity tests are negative, a new specification for ——— could be qualified by a 28-day toxicology study in the most appropriate species.**
      - **If ——— is genotoxic, levels of ——— in the drug product should be ——— . This may require the development of a more sensitive method for ———within this same time frame. Alternatively, additional testing could be performed in consultation with the Division to permit a higher level.**

Celltech commits to conduct and provide reports of preclinical studies for option b. "Conduct two in vitro genetic toxicity tests (ICH Q3A) to assess the genotoxic potential of ——— within 6 months of approval. The proposed dates for the submission of the protocols, study start dates and final reports submission are as follows:

- Submission of genetic toxicity protocols: June 4, 2004 (Included in this submission)
- Study start dates: ASAP pending FDA feedback on proposed protocols
- Final reports submission: No later than 6 months from the date of approval of the application

Provided in Tab 1 are the following draft protocols for FDA review and comment: 1) ——— ——— and 2) ———

CMC issues to be addressed by close of business Friday, June 4, 2004:

2. **Provide an agreement to qualify ——— as specified above in comment 1. In the interim, provide an agreement to limit levels of ——————— (your current LOQ) in the drug product. Submit a prior approval supplement to finalize ——— acceptance specification(s) based on results of the qualification study(ies).**

Provided in Tab 3 is revised stability specification and test method procedure SL-826-04 that supercedes SL-826-03 provided in the December 19, 2003 resubmission. SL-826-04 incorporates the limit level of ———————

Provided in Tab 4 is a revised post approval stability protocol P03260.3 that supercedes P03260.2 provided in the December 19, 2003 resubmission. P03260.3 incorporates the limit level of ——— ———

3. **Submit revised acceptance criteria proposed for *total impurities* in PEG treated codeine polistirex and coated codeine polistirex to be reflective of the data provided, e.g., ——— pages 4-442, 4-452 to 4-456, and 4-555, respectively).**

Provided in Tab 5 is revised intermediate procedure IN-1285-05 that supercedes IN-1285-04 provided in the December 19, 2003 resubmission. IN-1285-05 incorporates the revised acceptance criterion for *total impurities* in PEG treated codeine polistirex to ———

Provided in Tab 6 is revised intermediate procedure IN-1266-07 that supercedes IN-1266-06 provided in the December 19, 2003 resubmission. IN-1266-07 incorporates the revised acceptance criterion for *total impurities* in coated codeine polistirex to ———.

4. **Submit revised acceptance criterion proposed for *total impurities* in codeine phosphate to be reflective of the data (Volume 2, pp 4-68), e.g., ———.**

Provided in Tab 7 is revised raw material procedure RM-1232-06 that supercedes RM-1232-05. RM-1232-06 incorporates the revised acceptance criterion for *total impurities* in codeine phosphate to ——— The specification is reported to 2 decimal places in accordance with ICH guidance Q3A. Please note that RM-1232-06 also incorporates a revision implemented in version 05 to revise the calculation used in the related substances to correct for the % purity of the reference standard. Version 05 was implemented subsequent to the December 19, 2003 resubmission.

5. **Submit revised acceptance criterion proposed for *total impurities* in chlorpheniramine maleate to be reflective of the data (Volume 2, pp 4-123), e.g.,** ———

Provided in Tab 8 is revised procedure RM-1131C-02 that supercedes RM-1131C-01 provided in the December 19, 2003 resubmission. RM-1131C-02 incorporates the revised acceptance criterion for *total impurities* in chlorpheniramine maleate to ——— The specification is reported to 2 decimal places in accordance with ICH guidance Q3A.

6. **Submit revised proposed acceptance criterion for *total related impurities* in the drug product to be reflective of the data, e.g., ——— , especially when it is found below limit of quantitation (LOQ) of the method at ——— RH, and the contributing impurities such as *total unspecified impurities* remain below LOD and ——— remain below LOQ at ——— , RH.**

Provided in Tab 2 is revised finished product specification and test method procedure FP-826-04 that supercedes FP-826-03 provided in the December 19, 2003 resubmission. FP-826-04 incorporates the revised proposed acceptance criterion for *total related impurities* in the drug product to be reflective of the data, e.g., ———

Provided in Tab 3 is revised stability specification and test method procedure SL-826-04 that supercedes SL-826-03 provided in the December 19, 2003 resubmission. SL-826-04 incorporates the revised proposed acceptance criterion for *total related impurities* in the drug product to be reflective of the data, e.g., ———

Provided in Tab 4 is a revised post approval stability protocol P03260.3 that supercedes P03260.2 provided in the December 19, 2003 resubmission. P03260.3 incorporates the revised proposed acceptance criterion for *total related impurities* in the drug product to be reflective of the data, e.g., ———

7. **Submit an agreement to use the original dissolution method, ——— , for both codeine and chlorpheniramine release from the drug product. Submit revised acceptance criteria as follows for the release of codeine and chlorpheniramine to be reflective of the dissolution data provided for three stability lots and one bio-batch, stored at — months and —months respectively.**

   Update the method ——— accordingly and submit it for division's review prior to commercial production of the drug product.

APPEARS THIS WAY
ON ORIGINAL

Time	*Chlorpheniramine Release* Rate Range (% Released)	*Codeine Release Rate Range* (% Released)
1 hr		
3 hr		
6 hr		
12 hr		

Provided in Tab 2 is revised finished product specification and test method procedure FP-826-04 that supercedes FP-826-03 provided in the December 19, 2003 resubmission. FP-826-04 incorporates the use of the original dissolution method, ——— for both codeine and chlorpheniramine release from the drug product and the revised acceptance criteria for the release of codeine and chlorpheniramine.

Provided in Tab 3 is revised stability specification and test method procedure SL-826-04 that supercedes SL-826-03 provided in the December 19, 2003 resubmission. SL-826-04 incorporates the use of the original dissolution method, ——— for both codeine and chlorpheniramine release from the drug product and the revised acceptance criteria for the release of codeine and chlorpheniramine.

Provided in Tab 4 is a revised post approval stability protocol P03260.3 that supercedes P03260.2 provided in the December 19, 2003 resubmission. P03260.3 incorporates the revised acceptance criteria for the release of codeine and chlorpheniramine.

8. **Acknowledge that the application <u>cannot</u> be approved with expiration dating period ——— at this time because of the pre-clinical concern with potential genotoxicity of ——— In order to extend the expiration dating period beyond —— months, submit a prior approval supplement.**

Based on agreement reached during a telephone contact of June 2, 2004 between Christine Yu and the undersigned, additional stability data will be submitted via Federal Express and facsimile for FDA review no later than EOB Monday, June 7, 2004 ——— The stability data will show, most notably, the ——— Presentation of the data will be a time cumulative format with all 4 lots (3 primary stability lots and 1 clinical lot) as shown on page 4-1913 of the resubmission.

Celltech acknowledges item #8 regarding no more than ___month expiration dating at this time. However, with the Agency's agreement upon review of the data noted above, the application ___ Celltech acknowledges that a prior approval supplement is needed to ___ The supplement is to contain the results of the genotoxicity studies and real time stability data.

CMC Agreements:

9. [redacted]

10. [redacted]

11 [redacted]

12. [redacted]

[redacted]

13. [redacted]

[redacted]

14. [redacted]

[redacted]

Please contact the undersigned at (585) 274-5840 or Norman D. LaFrance, MD, FACP, FACNP, Senior Vice President, Medical and Regulatory Affairs at (585) 274-5326 with any questions or comments regarding this complete response.

Sincerely,

/S/

Mary Evelyn Towne
Manager, Regulatory Affairs

CC: Christine Yu, Sr. Management Regulatory Officer,
Division of Pulmonary and Allergy Drug Products - desk copy and facsimile (cover letter only)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 1, 2004

To: Mary Evelyn Towne, Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph. /S/ Regulatory Project Manager
Company: Celltech Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: NDA 21-369 for Codeprex
CMC Agreement and Pharmacology Post-marketing study Commitment

Total no. of pages including cover: 2

Comments: ***** *Respond by COB June 4, 2004* *****

Document to be mailed: ☐ YES √ NO

We refer to your NDA 21-369 for Codeprex and to your submission dated December 19, 2003. Please consider the following proposals for a pharmacology Post-marketing study commitment and CMC agreements.

Pharmacology/Toxicology Post Marketing study Commitment

In vivo metabolism of codeine to ——— was demonstrated in the guinea pig; however, this species was not used in toxicology studies with codeine. Carcinogenicity studies with codeine were conducted using the Fischer 344/N rat and B6C3F1 mouse. We note that in vitro metabolism of codeine to ——— was demonstrated with a rat liver preparation; however, in vitro metabolism does not always correlate with in vivo metabolism.

Your commitment to conduct the Post-marketing study as outlined below also incorporates your agreement to limit levels of ——— (your current LOQ) in the drug product until its qualification results are submitted and evaluated by the Division.

1. Provide a Post-marketing study commitment to conduct and provide reports of preclinical studies for either option 1 or 2 as described below, within 6 months of approval. The commitment should include proposed dates for the submission of the protocol, study start, and final report submission.

   a. [redacted]

   b. Conduct two in vitro genetic toxicity tests (ICH Q3A) to assess the genotoxic potential of ———.

      - If genotoxicity tests are negative, a new specification for ——— could be qualified by a 28-day toxicology study in the most appropriate species.
      - If ——— is genotoxic, levels of ——— in the drug product should be ——— This may require the development of a more sensitive method for ——— within this same time frame. Alternatively, additional testing could be performed in consultation with the Division to permit a higher level.

CMC issues to be addressed by close of business Friday, June 4, 2004:

2. Provide an agreement to qualify ——— as specified above in comment 1. In the interim, provide an agreement to limit levels of ——— your current LOQ) in the drug product. Submit a prior approval supplement to finalize ——— acceptance specification(s) based on results of the qualification study(ies).

3. Submit revised acceptance criteria proposed for *total impurities* in PEG treated codeine polistirex and coated codeine polistirex to be reflective of the data provided, e.g., NMT ——— pages 4-442, 4-452 to 4-456, and 4-555, respectively).

4. Submit revised acceptance criterion proposed for *total impurities* in codeine phosphate to be reflective of the data (Volume 2, pp 4-68), e.g. ———

5. Submit revised acceptance criterion proposed for *total impurities* in chlorpheniramine maleate to be reflective of the data (volume 2, pp 4-123), e.g., ———

6. Submit revised proposed acceptance criterion for *total related impurities* in the drug product to be reflective of the data, e.g., ——— especially when it is found below limit of quantitation (LOQ) of the method at ———, and the contributing impurities such as *total unspecified impurities* remain below LOD and ——— remain below LOQ at ———

7. Submit an agreement to use the original dissolution method, ———, for both codeine and chlorpheniramine release from the drug product. Submit revised acceptance criteria as follows for the release of codeine and chlorpheniramine to be reflective of the dissolution data provided for three stability lots and one bio-batch, stored at — months and — months respectively.

   Update the method ——— accordingly and submit it for division's review prior to commercial production of the drug product.

Time	***Chlorpheniramine Release*** Rate Range (% Released)	***Codeine Release Rate Range*** (% Released)
	Method ———	**Method** ———
1 hr		
3 hr		
6 hr		
12 hr		

8. Acknowledge that the application cannot be approved with expiration dating period ——— at this time because of the pre-clinical concern with potential genotoxicity of ———

CMC Agreements:

9. 

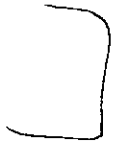
10. 

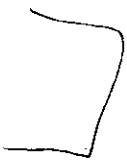
11. 

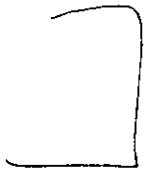
12. 

13. 

14. 







Your timely response by COB Friday, June 4, 2004, is necessary for us to finalize our reviews for action on your application.

If you have any questions or need clarification regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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

/s/

Christine Yu
6/1/04 06:25:30 PM
CSO

8 page(s) of revised draft labeling has been redacted from this portion of the review.

MEMORANDUM

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

Date: May 6, 2004

To: Badrul Chowdhury, M.D., Director
Division of Pulmonary Drug Products (HFD-570)

Through: Deborah Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

/S/

From: Lin-Whei Chuang, Pharmacologist
Controlled Substance Staff (HFD-009)

/S/ v

Subject: CSS Consultation on NDA #21-369 [505(B)(2) NDA Submission]
Drugs: Codeprex Extended-Release Suspension (codeine and chlorpheniramine maleate)
Indication: For relief of symptoms of the common cold, allergies, or following exposure to airborne irritants

Sponsor: Celltech Pharmaceuticals, Inc.

1. Background

The Division of Pulmonary Drug Products consulted with the Controlled Substance Staff (CSS) to review the drug abuse related sections of the revised proposed labeling for Codeprex, a new product that is an extended-release (ER) liquid suspension containing codeine (40 mg/10 mL) and chlorpheniramine maleate (8 mg/10 mL). CSS recommended on December 20, 2001 that Codeprex ER Suspension, formerly known as ——— be a prescription drug listed in Schedule III of the CSA [per 21 CFR 1308(e)(2)]. The current submission is the response to the Approvable letter received by the sponsor on February 13, 2002.

In the memorandum dated December 20, 2001, CSS recommended that the labeling include a) descriptions of neonatal withdrawal symptoms, b) a statement that the product is a controlled narcotic in Schedule III of the CSA, and c) warnings of development of dependence and tolerance after administration for an extended time period.

Recommendations

The sponsor has satisfactorily addressed the above three issues by including the appropriate statements in the Drug Abuse and Dependence sections of the draft labeling for Codeprex. In addition, the label no longer states [redacted]

The sponsor has adequately addressed the CSS comments from the December 20, 2001 consult. The CSS has two additional labeling recommendations:

1. CSS recommends the combination of the contents of two different sections under 'Abuse' and 'Dependence' into one section titled 'Abuse and Dependence' as shown below:

   Abuse and Dependence:

   Codeine must be administered under close supervision to patients with a history of drug abuse or dependence. Codeine can produce drug dependence and therefore has the potential for abuse.

   Dependence and tolerance may develop upon repeated administration. [redacted] An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period, [redacted]

   Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth [redacted]

2. CSS recommends that the section of 'Pediatric Use' be revised as follows:

Safety and effectiveness of Codeprex in patients under 6 years of age have not been established. Codeprex is not recommended for use in patients under 6 years of age. Patients under 2 years of age may be more susceptible to the respiratory depression effects of codeine, including respiratory arrest, coma, and death (see WARNINGS). Additionally, antihistamines may cause excitability in pediatric patients.

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

/s/

Lin Whei L. Chuang
5/6/04 01:32:23 PM
BIOPHARMACEUTICS

Michael Klein
5/6/04 02:13:24 PM
CHEMIST

SSeq#B
4/20/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): Controlled Substance Staff Corinne Moody, HFD-009			FROM: Christine Yu, R.Ph. Regulatory Project Manager, HFD-570	
DATE April 20, 2004	IND NO.	NDA NO. 21-369	TYPE OF DOCUMENT Complete Response	DATE OF DOCUMENT December 19, 2003
NAME OF DRUG Codeprex ER Suspension (codeine/chlorpheniramine)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG 3	DESIRED COMPLETION DATE May 24, 2004

NAME OF FIRM: Celltech Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform CSS labeling review of the revised proposed labeling. Wrap-up meeting for this application is scheduled May 25, 2004. Please contact me if you have any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

I :opy: proposed PI and immediate container label
A. ned: electronic PI

DH

15 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Marketing, Advertising and Communications, HFD-42, PKLN Room 17b-17

FROM:
Christine Yu, R.Ph.
Division of Pulmonary & Allergy Drug Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5 March 2004		21-369	NDA resubmission	19 December 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeprex Pennkinetic ER suspension (codeine 40 mg/ chlorpheniramine 8 mg per 10 ml dose)	Standard	3S	7 May 2004

NAME OF FIRM: Celltech Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform DDMAC review of NDA 21-369, especially with respect to whether 'pennkinetic' raises any concerns. Original NDA was submitted 13 April 2001; approvable action taken 13 Feb 2002. Complete response was received 22 December 2003. The draft PI is attached. A copy of the proposed immediate container label is provided as paper copy. Please contact me if you have any questions at 827-1051.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☑ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

13 page(s) of revised draft labeling has been redacted from this portion of the review.

CONSULTATION RESPONSE

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

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 01-0182-1
February 12, 2004	March 12, 2004	

TO: Badrul Chowdhury, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Christine Yu, R.Ph.
Project Manager
HFD-570

PRODUCT NAME:	**NDA SPONSOR:** Cell Tech Pharmaceuticals, Inc.
Codeprex™ Pennkinetic® (Codeine Polistirex and Chlorpheniramine Polistirex) Extended-Release Suspension **NDA#:** 21-369	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Codeprex™ Pennkinetic®. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III. of this review to minimize potential errors with the use of this product.

3. We recommend consulting the CDER Labeling and Nomenclature Committee for the proper designation of the established name.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

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 (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 30, 2004

NDA# 21-369

NAME OF DRUG: Codeprex™ Pennkinetic® (Codeine Polistirex and Chlorpheniramine Polistirex) Extended-Release Suspension

NDA HOLDER: Cell Tech Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for re-assessment of the proprietary name, "Codeprex™ Pennkinetic®", regarding potential name confusion with other proprietary or established drug names. Container labels and package insert labeling were provided for review and comment.

The name, Codeprex™ had previously been found acceptable by DMETS in a review dated, January 18, 2001 (ODS Consult# 01-0182), for this product. The term Pennkinetic® is the sponsor's trademark for the extended-release suspension dosage form.

PRODUCT INFORMATION

Codeprex™ Pennkinetic® is the proposed proprietary name for codeine/chlorpheniramine polistirex extended-release suspension. Codeprex™ Pennkinetic® is indicated for the temporary relief of mild to [redacted] cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever or other upper respiratory allergies. Codeine is an opiate antitussive, and chlorpheniramine is an antihistamine. Each teaspoonful (5 mL) of Codeprex™ Pennkinetic® contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients. The active ingredients are complexes of sodium polystyrene sulfonate to impart extended-release characteristics to the drug product. The suspension provides up to 12 hours of relief per dose and is for oral use only. The recommended dosage in adults and adolescents 12 years of age and older is two teaspoonfuls every 12 hours, not to exceed four teaspoonfuls in 24 hours. Children ages 6 to under 12 are to be given one teaspoonful every 12 hours, not to exceed two teaspoonfuls in 24 hours. Codeprex™ Pennkinetic® is a Schedule III controlled drug substance. Codeprex™ Pennkinetic® will be supplied as a pink to purple-pink colored, cherry-cream flavored suspension in 480 mL bottles.

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 Codeprex™ 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 was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Codeprex™ Pennkinetic®. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation 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.

Since the last review of Codeprex™, dated January 18, 2001, the Expert Panel identified two proprietary names that were thought to have the potential for confusion with Codeprex™ Pennkinetic®. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

[redacted]	[redacted]	[redacted]	[redacted]
Codrix	Acetaminophen and Codeine Phosphate Tablets USP, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg	Take one tablet every 4 hours as needed for pain.	SA
Ciprodex	Ciprofloxacin and Dexamethasone Otic Suspension, 0.3%/0.1%	Instill four drops in affected ear(s) two times a day for seven days	LA

**Frequently used, not all-inclusive.
***L/A (look-alike), S/A (sound-alike)

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, 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 & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified Celebrex, to have significant phonetic or orthographic similarities to Codeprex™. This product is listed in Table 2 (see below), along with the dosage forms available and usual dosage.

Table 2: Potential Sound-Alike/Look-Alike Names Identified by POCA

Celebrex	Celecoxib Capsules, 100 mg, 200 mg, and 400 mg	100 mg to 200 mg twice daily.	SA/LA

**Frequently used, not all-inclusive.
***L/A (look-alike), S/A (sound-alike)

C. SAFETY EVALUATOR RISK ASSESSMENT

In re-reviewing the proprietary name Codeprex™ Pennkinetic®, the primary concerns related to look-alike and sound-alike confusion with Ciprodex, Codrix, and Celebrex as having significant phonetic or orthographic similarity.

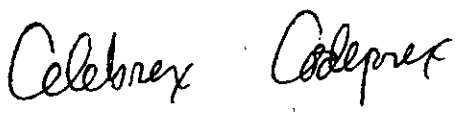
1. Sound-alike and or look-alike concerns

a. Codrix may sound similar to Codeprex™ when spoken. Codrix is a proprietary name for Acetaminophen and Codeine Phosphate Tablets USP, indicated for relief of pain. Sound-alike similarities may be attributed to the shared letters, "Cod", "r", and "x". However, the difference in syllables for the names and the distinctive "p" in Codeprex™ may serve to distinguish the names phonetically. In addition to sound-alike similarities, Codrix and Codeprex™ have similarities which may contribute to product confusion in the marketplace; both are controlled substances containing codeine. These products also have differences which make them distinct from each other. Product differences between Codrix and Codeprex™ include indications of use (for relief of pain vs. relief of mild to moderate cough and cold/allergy symptoms), dosage form (tablet vs. oral suspension), strengths (500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg vs. 20 mg/4 mg per teaspoonful), and dosing regimen (one tablet every 4 hours as needed for pain vs. two teaspoonfuls every 12 hours), respectively. DMETS believes that the potential for confusion is minimal given these differences and due to a lack of convincing sound-alike similarities.

b. Ciprodex looks similar to Codeprex™ when written. Ciprodex is the proprietary name for ciprofloxacin and dexamethsone otic suspension. Ciprodex is indicated for the treatment of superficial bacterial infections of the external auditory canal. Codeprex™ and Ciprodex may look similar when scripted. Both names begin and end with the same letters "C" and "ex". The letters that make up both names are almost identical (see writing sample below). However, when scripting these names, the upstroke "d" and downstroke "p" letters appear in opposite areas of each name. In Codeprex™, the letter "d" appears first followed by the "p" whereas in Ciprodex the order is reversed. The differences in the location of the up- and downstroke may also help to differentiate these two names.

In addition to the look or sound alike similarities, Codeprex™ and Ciprodex have potentially overlapping dosing intervals (every 12 hours vs. twice a day). Additionally, both products will be available in a single strength; thus the strength may be omitted when prescribers write prescriptions. However, there are other differences between the two products that may help to distinguish them. Because Codeprex™ is a liquid formulation, available in a stock bottle (473 mL), it is possible that it may be stored away from Ciprodex, with other liquid formulation stock bottles. Although separate storage of large liquids does not occur in all pharmacies, this practice could impede confusion between Ciprodex and Codeprex in those pharmacies where the products are spatially separated. The routes of administration are also different (oral vs. otic). Codeprex™ prescriptions are also expected to indicate a dispensing quantity (e.g., 120 mL, 240 mL, or 4 oz.) which will differ from the sizes available for Ciprodex (5 mL or 7.5 mL dropper bottles). Ciprodex directions to instill drops into the ear canal may also be distinctive. DMETS believes that the potential for confusion is minimal given these product differences.

c. Celebrex was identified as having sound-alike and look-alike similarities to Codeprex™. Celebrex is the proprietary name for celecoxib, a selective COX-2 inhibitor indicated for relief of pain in arthritis and management of acute pain. Celebrex and Ciprodex may look similar when scripted. Look-alike similarities may be attributed to corresponding placement of shared letters, "C", "e", and "rex". The letters "el" in Celebrex may also look like "od" in Codeprex™, especially if they are crowded together (see writing sample below). However, the "b" is orthographically distinct from the "p" in Codeprex™ because of the upstroke rather than downstroke.



In addition to the look or sound alike similarities, Codeprex™ and Celebrex have potentially overlapping dosing intervals (every 12 hours vs. twice a day). However, there are other differences between the two products that may help to distinguish them. Product differences between Celebrex and Codeprex™ include indications of

use (for relief of pain vs. relief of mild to moderate cough and cold/allergy symptoms), dosage form (capsule vs. oral suspension), and strengths (100 mg, 200 mg, and 400 mg vs. 20 mg/4 mg per teaspoonful), respectively. Because Codeprex™ is a liquid formulation, available in a stock bottle (473 mL), it is possible that it may be stored away from Ciprodex, with other liquid formulation stock bottles. Although separate storage of large liquids does not occur in all pharmacies, this practice could impede confusion between Ciprodex and Codeprex in those pharmacies where the products are spatially separated. Ciprodex directions to instill drops into the ear canal and quantities expressed in volumes (ounces or milliliters) may also be distinctive. DMETS believes that the potential for confusion is minimal given these product differences.

2. Safety Concerns regarding trademarked dosage form, Pennkinetic®

DMETS searched the Adverse Event Reporting System (AERS) in order to determine whether there were any medication errors as a result of Pennkinetic® dosage form (Extended-release Suspension) or the Pennkinetic name. The AERS was searched for products using the search term, "PENN%" and using the MedDRA preferred terms, MEDICATION ERROR, TREATMENT NONCOMPLIANCE, PHARMACEUTICAL PRODUCT COMPLAINT, ACCIDENTAL OVERDOSE, and OVERDOSE. This search strategy did not yield any results. Since Tussionex employs the same "Pennkinetic" trademarked dosage form, AERS was searched again using the search term, "TUSSIONEX%". None of the reports returned by this search were from medication errors resulting from this special dosage form (Extended-release Suspension) or the Pennkinetic® name. DMETS could find no evidence to raise safety concerns regarding trademarked dosage form, Pennkinetic®.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label and package insert labeling of Codeprex™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (473 mL)

To increase the prominence of the product strength and the "Each teaspoonful" statement on the principal display panel, we encourage an increase in font size and revision to the following format.

Each teaspoonful (5 mL) contains codeine polistirex and
chlorpheniramine polistirex equivalent to:
Codeine.....20 mg
Chlorpheniramine maleate.....4 mg

B. PACKAGE INSERT LABELING

No comments.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Codeprex™. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III. of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. We recommend consulting the CDER Labeling and Nomenclature Committee for the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Charles Hoppes
4/27/04 01:22:16 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
4/27/04 01:26:43 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/28/04 07:23:12 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
4/28/04 07:55:22 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DMETS

FROM: Christine Yu, R.Ph.
Regulatory Project Manager, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12 February 2004		21-369	Complete Response	December 19, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeprex Pennkinetic (codeine/chorpheniramine polistirex) ER suspension	Standard	4S	April 20, 2004

NAME OF FIRM: Celltech Pharmaceuticals, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform labeling and updated trade name review for the drug product. An approvable letter was issued 2/13/02. DMETS first review is dated 1/22/02 and is attached below. The approvable letter is also attached.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Attached Hard copy only: proposed labeling in color

Memorandum of Telephone Facsimile Correspondence

Date: January 9, 2004

To: Mary Evelyn Towne
Manager, Regulatory Affairs

Fax: 585-272-3952

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: NDA 21-369 for Codeprex
Minutes of December 10, 2003 teleconference

Reference is made to the meeting/teleconference held between representatives of your company and this Division on December 10, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

TELECONFERENCE MINUTES

DATE:	December 10, 2003
TIME:	10:30 - 11:30 AM
APPLICATION:	NDA 21-369
DRUG NAME:	Codeprex (codeine/chlorpheniramine) Extended-release suspension
INDICATION:	Temporary relief of [redacted] cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy watery eyes due to hay fever, other respiratory allergies, or allergic rhinitis.
IMTS#:	11561

Celltech Pharmaceuticals, Inc.
Simon Hatch, M.D., Director, Clinical Development
Norman LaFrance, M.D., Sr. VP, Medical & Regulatory Affairs
John Marini, M.S., Director, Process Technology
Mark Plis, B.S., Director, Analytical & Microbiological Services
Donna Radzik, Ph.D., Sr. VP, Technical Operations & Development
Peter Bach, Toxicologist
Mary Evelyn Towne, B.S., Manager, Regulatory Affairs

FDA, Division of Pulmonary & Allergy Drug Products (unless otherwise noted)
Vibhakar Shah, Ph.D., CMC Reviewer
Craig Bertha, Ph.D., CMC Team Leader (Acting)
Shinja Kim, Ph.D.Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer
Emmanuel Fadiran, Ph.D., CPB Team Leader
Charles Lee, M.D., Medical Officer
Lydia Gilbert-McClain, M.D., Medical Team Leader
Badrul Chowdhury, M.D., Ph.D., Director
Christine Yu, R.Ph., Regulatory Project Manager

Following a June 12, 2003, meeting to discuss with the Division their plans for responding to the February 13, 2002, approvable letter, Celltech submitted a request for teleconference dated September 25, 2003. The briefing package was submitted with the meeting request and contained 6 questions for discussion.

Minutes
After introductions but before the Division addressed the questions from the briefing package, Celltech confirmed that they received the facsimile correspondence sent by the Division regarding submission dated August 18, 2003.

Celltech's questions in Italics font are followed by the Division's response and discussion in normal font.

1. *Does the Division concur with the proposed release rate specifications of the drug intermediate, coated codeine polistirex, of:*

1 hour [redacted]
3 hour
8 hour

The Division stated that this is a review issue and will be evaluated once complete response with appropriate supportive data is submitted. Celltech should also provide rationale for the two different dissolution methods being proposed for codeine release from coated codeine polistirex and the drug product respectively in their response.

2. *Does the Division find the enclosed described plan for the preparation of finished product, i.e., direct input of lot(s) of coated codeine polistirex acceptable?*

The described plan is acceptable to the Division.

3. *Does the enclosed information satisfy the Division request for explanation for the need for as well as the differences between the dissolution method for chlorpheniramine release and the new proposed dissolution method for codeine release?*

Although this too is a review issue, the Division referenced Table 2 (TAB 2) of the briefing package and requested that Celltech submit a side-by-side comparison of codeine and chlorpheniramine release rate data from the drug product lots (containing [redacted] coating for the coated codeine polistirex prepared using the previous and the proposed modified manufacturing. process) using both dissolution methods (originally proposed and newly proposed) in order to evaluate the discriminating capability of these two methods. If applicable, the release rate data provided in the original submission for the drug product lot(s) containing [redacted] coated codeine polistirex may be used.

Additionally, the Division stated that since IVIVC (in vitro in vivo correlation) will not be used, Celltech needs to show that in vitro release profiles of both codeine and chlorpheniramine by the proposed dissolution methods is reflective of and comparable to their respective in-vivo release profiles.

4. *Does the Division find the planned testing on all incoming bottle lots described in this package acceptable and agree that non-volatile residue testing is not applicable to a [redacted] bottle used for a oral liquid dosage form?*

The Division noted that USP standards are minimum acceptance criteria. In absence of requested information, "identification by IR" does not assure changes, if any, in the composition of the [redacted] bottle. As a result, our earlier response as provided in June 12 2003 meeting to this concern [(Item 11 (a)] needs to be addressed.

Celltech stated that they will address this concern in their response.

5. *Does the Division concur that the CMC documentation as described in the enclosed plan will be sufficient for inclusion in the resubmission for FDA review and allow for a subsequent June 2004 product approval?*

   The Division reminded Celltech that comments from the February 13, 2002, letter, the June 12, 2003, meeting minutes, and this teleconference should be addressed in the response.

6. *Does the Division agree with the enclosed proposed labeling revisions in the Clinical Pharmacology and Adverse Reactions sections?*

   From a CPB perspective the Division stated that Celltech has provided the requested data and reasonable labeling revisions, but the data will be reviewed when a complete response to the approvable letter is submitted.

   From a clinical perspective, the Division noted that proposed labeling must be supported by data from the submission. Final labeling will be negotiated after the complete response has been reviewed.

The Division stated that the questions posed in the briefing package were issues that would be reviewed when a complete response is submitted.

Celltech noted their intention to provide a complete response by December 2003. They summarized the action items noted above, and the teleconference concluded at this time.

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

/s/

Christine Yu
1/9/04 02:44:33 PM

1/5/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-369

Celltech Pharmaceuticals, Inc.
755 Jefferson Road
Rochester, NY 14623

Attention: Mary Evelyn Towne
Manager, Regulatory Affairs

Dear Ms. Towne:

We acknowledge receipt on December 22, 2003, your December 19, 2003, resubmission to your new drug application for Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended Release suspension.

We consider this a complete, Class 2 response to our February 13, 2003, action letter. Therefore, the user fee goal date is June 22, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We are deferring submission of your pediatric studies until July 31, 2007.

If you have any question, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
1/5/04 04:45:06 PM

DL

9 page(s) of revised draft labeling has been redacted from this portion of the review.

DFS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: December 9, 2003

/S/

To: Mary Evelyn Towne, Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph. Sr. Regulatory Management Officer
Company: Celltech Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: NDA 21-369 for Codeprex
Submission dated August 18, 2003- Pharmacology comment

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

We have reviewed the proposed modifications of the toxicology study to qualify [redacted] (provided in an amendment dated August 18, 2003) and have the following comments.

It is acceptable to conduct the 28-day toxicology study in rats with the isolated impurity, [redacted] at the proposed oral doses in the absence of toxicokinetic measurements.

The proposed study using [redacted] It is unclear if the dose of [redacted] would provide a sufficient safety margin. Further, this study might be confounded by the effects of codeine.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu, R.Ph., Regulatory Project Manager, at 301-827-1051.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2003

To: Mary Evelyn Towne, Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph /S/ Regulatory Project Manager
Company: Celltech Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: NDA 21-369 for Codeprex
Regarding June 12, 2003 meeting minutes (Submission dated August 11, 2003)

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

We reference your submission dated August 11, 2003, in which you requested clarification/further comments about information discussed at the June 12, 2003, meeting for Codeprex (codeine/chlorpheniramine extended-release suspension).

1. Page 3 of meeting minutes, under question 8.3

   "The Division noted that the profile should not be artificial but should represent the actual quality of the drug product. They also requested that Celltech include the data generated from — rpm."

   Based on Celltech's background information and response provided in the August 11th submission, the Division recommends that Celltech submit NDA data showing optimization of dissolution method as a function of medium (pH) and paddle speed.

2. Page 6 of meeting minutes, under question 8.1

   "...the electronic version of the stability data will be provided in SAS data sets."

   Data must be reviewed from the archival copy. Per Guidance for Industry, "Providing regulatory submissions in electronic format- General considerations,"

   > Regulations in 21 CFR Part 11 *require* all datasets provided in electronic format to provide an accurate and complete copy of the data suitable for inspection, review, and copying. Currently, we are able to accept and archive datasets in SAS System XPORT transport format (Version 5 SAS transport file).

3. Page 9 of meeting minutes, Item 1(c)/1(d) and 2(c)/2(d)

   "...Revise the proposed acceptance criterion, NMT ———— for all applicable specified impurities..."

   Per ICH Q3A "Impurities in New Drug Substances":

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

4. Page 10 of meeting minutes, Item 8(f)(4)

   "...impurity (degradant) related to codeine in the drug product needs to be identified and qualified at or greater than —w/w, and, an impurity (degradant) related to chlorpheniramine in the drug product needs to be identified at or greater than — and qualified at or greater than —w/w."

Per ICH Q3B "Impurities in New Drug Products," Attachment 1, Thresholds for qualification of degradation products in new drug products:

For Total daily intake(TDI) 10 - 100 mg, threshold is 0.5% or 200 micrograms, ***which ever is lower***. Therefore:

	Total daily intake	Amount if at 0.5% level	Qualification Threshold
Codeine	80 mg	400 mcg	0.25% (200 mcg)
Chlorpheniramine	16 mg	80 mcg	0.5%

If you have any questions regarding this facsimile correspondence, please contact Ms. Christine Yu, R.Ph., Regulatory Management Officer, at 301-827-1051.

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/

Christine Yu
9/17/03 05:22:16 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: July 11, 2003

To: Mary Evelyn Towne
Manager, Regulatory Affairs

Fax: 585-272-3952

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: NDA 21-369 for Codeprex
Minutes of June 12, 2003 meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on June 12, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

MEETING MINUTES

DATE:	June 12, 2003
TIME:	3:30 - 4:30 PM
LOCATION:	Parklawn Conference K
APPLICATION:	NDA 21-369
DRUG NAME:	Codeprex (codeine polistirex and chlorpheniramine polistirex) ER suspension
INDICATION:	Temporary relief of [redacted] cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy watery eyes due to hay fever, other respiratory allergies, or allergic rhinitis.
IMTS#:	10498
SPONSOR:	Celltech Pharmaceuticals, Inc.
Represented by:	Simon Hatch, M.D., Director, Clinical Developmen Norman LaFrance, M.D., Sr. VP, Medical & Regulatory Affairs John Marini, M.S., Director, Process Technology Mark Plis, B.S., Director, Analytical & Microbiological Services Donna Radzik, Ph.D., Sr. VP, Technical Operations & Development Mary Evelyn Towne, B.S., Manager, Regulatory Affairs
FDA attendees:	Division of Pulmonary & Allergy Drug Products, HFD-570 Vibhakar Shah, Ph.D., CMC Reviewer Guirag Poochikian, Ph.D., CMC Team Leader Shinja Kim, Ph.D.Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer Emmanuel Fadiran, Ph.D., CPB Team Leader Charles Lee, M.D., Medical Officer Lydia Gilbert-McClain, M.D., Medical Team Leader (Acting) Marianne Mann, M.D., Deputy Director Badrul Chowdhury, M.D., Ph.D., Director Christine Yu, R.Ph., Regulatory Management Officer

Celltech submitted a request for a meeting and their briefing package on April 25, 2003, to discuss with the Division their plans for responding to the February 13, 2002, approvable letter.

Agenda (order based on the questions included in the briefing package)

Regulatory
Clinical Pharmacology & Biopharmacuetics (CPB)
Clinical & Labeling
Chemistry, Manufacturing & Controls (CMC)

Guidances for Industry referenced during the meeting

Guidances represents the Food and Drug Administration's (FDA's) current thinking on a topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Minutes Format
Appendix- Transparency presented by Celltech during the meeting

Minutes
The following slides presented by the Division include Celltech's questions (in normal font) then the Division's responses noted in Italics.

8.1 Regulatory:

Does the Division concur the classification of the resubmission is a class 2 with an expected FDA goal date of 6 months from time of receipt for the review?

We concur.

Clinical Pharmacology & Biopharmacuetics

8.1 Regulatory:

Does the Division concur that the updated sections identified in Tab 2 will be sufficient for inclusion in the resubmission for the FDA's complete review and subsequent approval for the original NDA 21-369?

Does the Division concur with the formatting and organization of the resubmission as identified in Tab 2?

The CPB section is acceptable.

8.3 Biopharmaceutics:

Does the Division concur that the studies conducted as outlined in this information package serve as an adequate basis for the drug product approval?

- *Drug product approval is a review issue but we concur that appropriate studies have been conducted/proposed.*
- *Please provide dissolution data using the new method (——— on bio- and/or stability batches, which were utilized to show stability for codeine in the original NDA submission.*

The Division asked why two different dissolution methods were being used on the stability batches and stated that using the same method for both codeine and chlorpheniramine would be more efficient.

Celltech responded that the original release method produced the 0 - 12 hour profile that was too flat, but they will be providing comparative data for codeine on the original and the new method.

The Division noted that the profile should not be artificial but should represent the actual quality of the drug product. They also requested that Celltech include the data generated from — rpm.

APPEARS THIS WAY
ON ORIGINAL

Clinical and Labeling

8.1 Regulatory
Question 2

Does the Division concur that the updated sections identified in Tab 2 will be sufficient for inclusion in the resubmission for the FDA's complete review & subsequent approval for the original NDA 21-369?

The reviews of the published literature on safety for codeine and chlorpheniramine and the ISS should address safety in the following subgroups: gender, pediatric patients, elderly patients, and by race. The proposed contents of the clinical data section are otherwise acceptable and will allow review of the submission. Approval is a decision that will be based on review of the content of the submission.

8.1 Regulatory
Question 3

Does the Division concur with the formatting and organization of the resubmission as identified in Tab 2?

The proposed formatting and organization of the clinical sections of the proposed NDA index are acceptable.

8.4 Labeling
Question 1

Is the trade name "Codeprex" still acceptable to the Division or will it be subject to a re-review 90 days prior to the NDA action letter?

The proposed trade name will be re-reviewed prior to action on the NDA to rule out any objections based upon approvals of other proprietary names from the last trade name review performed by the Office of Drug Safety.

8.4 Labeling
Question 2

If FDA published the Final Rule on Content and Format of Prescription labeling, what effect, if any, will this have on the Codeprex draft labeling under review?

It is unlikely that publication of the Final Rule would have an effect on the draft labeling under review.

Chemistry, Manufacturing and Controls

8.1 Regulatory:

Does the Division concur that the updated sections identified in Tab 2 will be sufficient for inclusion in the resubmission for the FDA's complete review and subsequent approval for the original NDA 21-369?

Does the Division concur with the formatting and organization of the resubmission as identified in Tab 2?

The TOC index provided for CMC section appears to be adequate, however, we would like to confirm that

- *the electronic version of the stability data will be provided in SAS data sets.*
- *the paper submission will also include the stability data in a format that was indicated in a telecon dated June 07, 2001.*
- *any cross-referenced item/topic/data set in the submission will include volume/page number.*

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Celltech confirmed that the NDA resubmission will provide the CMC information in the format requested above.

8.2 CMC
Question 1

Does the Division concur that the data and information identified in this information package to be included in the complete response will serve as adequate information for each specified issue for the approval of Codeprex ER Suspension packaged in the amber [redacted] bottle/ [redacted] cap utilizing the [redacted] Leaflet which is described in the original NDA?

APPEARS THIS WAY
ON ORIGINAL

8.2 CMC
Question 1

Response

- *Approvability of the NDA submission is a **review issue** and it will depend on the **adequacy** of the complete response to Agency's action letter.*

- *The data and information identified in April 25, 2003 briefing package, **appear** to constitute a complete response to the Agency's February 13, 2002 AE Letter. However, note that the final decision regarding the **completeness** and **adequacy** of your response will be made once it is submitted and reviewed by the Agency.*

Celltech stated that they understood and agreed with the Agency's response.

8.2 CMC
Question 2

Does the Division agree to the filing of the resubmission with ~ months stability data with the commitment to amendment the resubmission with an updated stability report to include the —month stability data?

- *We recommend at a minimum —months stability data on 3 lots of the drug product at the time of submission.*
- *Since this resubmission will have —months for review under PDUFA goals, the expiration dating period of the drug product will be determined by the stability data available at the time of the resubmission.*

CMC
Question from fax dated June 9, 2003

Celltech considers the ——— supplied by ——— approved for use based on the information provided in the NDA submission and requests FDA concurrence for their interpretation in that regard.

Label(s), being an integral part of the ——— is approved when the NDA is approved. On resubmission of the NDA, current status of all drug master files (DMFs) pertaining to ——— will be re-evaluated and an appropriate action will be taken, if needed.

Additional CMC comments

The items in the following section of the minutes were not presented during the meeting but were points for discussion.

The Division reiterated that adequacy of the information provided in the briefing package in response to Agency's comments of February 13, 2002, letter is a review issue once submitted. Nonetheless, based on **cursory** review of the information submitted, the Division has the following **preliminary comments** for the items/issues identified below (pages 3-20 of the briefing package). The Division also noted that **these comments are not all inclusive**. Celltech should address these comments/concerns in the resubmission of the NDA.

Item 1(c)/1(d): Review issue

- Revise the proposed acceptance criterion, [redacted] for all applicable specified impurities related to codeine phosphate (page 4).
- The proposed acceptance criterion, [redacted], for total impurities related to codeine phosphate is a review issue (page 4).
- We concur with your decision to qualify [redacted] at proposed level, [redacted]. However, note that the stability data should be the basis for its proposed acceptance criterion, not the level at which it is qualified (page 4).

Item 2(c)/2(d): Review issue

- Revise the proposed acceptance criterion, [redacted], for all applicable specified impurities related to chlorpheniramine maleate (page 5).
- The proposed acceptance criterion, [redacted], for total impurities related to chlorpheniramine maleate is a review issue (page 5).

In response to the first bullets under Item 1 and 2, Celltech stated that they will work with their suppliers to provide the second significant figure for the acceptance criterion.

Item 4(b): Review issue

- The proposed acceptance criterion, [redacted] for total impurities in PEG treated codeine polistirex is a review issue (page 6).

Item 4(c): Review issue

- To ensure lot to lot consistency, define, specify and validate the manufacturing losses during the coating process of PEG-3350 treated codeine polistirex.
- To ensure lot to lot consistency, specify and validate codeine assay and [redacted] codeine release rate for coated codeine polistirex.

Celltech responded that, although the process is validated, some losses are not recoverable and that they have proposed specifications based on useable material. They may accept the Agency's recommendations or provide justification.

Item 4(e)/4(f): Review issue

Item 4 (a)/4(h): Review issue

The proposed acceptance criteria for codeine release rate from coated codeine polistirex are too wide and indiscriminative between time points and as a result do not provide adequate assurance for batch to batch consistency and quality of this drug intermediate.

Item 4(g): Review issue (pages 9-10)

- Provide complete PSD profile of coated codeine polistirex that is representative of a batch (beginning to end).
- Propose PSD acceptance criteria that are reflective of a typical PSD profile of a batch.

Item 8(e): Review issue

- Explain the differences observed in PSD results by two different sample preparations between coated codeine polistirex and the drug product suspension (page 56).
- Is the particle size of —— critical for the redispersability (physical stability) of the suspension? How is it controlled and what methods have been used (e.g., microscopy, laser diffraction or combination methods)
- Despite the claimed interference from —— the PSD results obtained from the neat suspension are significantly different than the placebo and —— itself. What does this indicate? Can it be quantitatively equated to the redispersability of the suspension?
- Unless we understand the scientific basis of the differences observed in PSD of the suspension by two sample preparations, we can not concur with your sample pretreatment approach for the PSD determination of the suspension.

The Division stated that one approach may not be adequate by itself to explain the differences observed in the PSD, provide data to support the approach chosen.

Item 8(f)(4): Review issue

- Your proposal to qualify impurities related to either of chlorpheniramine or codeine above ——percent is **not acceptable**. (Refer to ICH Guidance for Industry Q3A "Impurities in New Drug Substances" and Q3B "Impurities in New Drug Products.")
- Qualification level of an impurity is based on the maximum daily dose of its respective parent active(s). As a result, an impurity (degradant) related to codeine in the drug product needs to be identified and qualified at or greater than ——, and, an impurity (degradant) related to chlorpheniramine in the drug product needs to be identified at or greater than ——and qualified at or greater than ——

Item 11(a): Review issue

- In order to assure consistency in composition of the resin of the — bottle and the consistent quality of incoming — bottles, it is essential to establish non-volatile residue profile and establish appropriate acceptance criteria with supportive data. Identification of resin by IR and

thermal analysis may not be adequate to ensure consistency in composition of the resin and any other additives/ingredients that may have been used during the fabrication of the bottle.

Item 11(b): Review issue

- As part of the NDA submission, appropriate specification documentation with an unique identifier for all the acceptance criteria that are performed on each of the incoming packaging materials is required (criteria for rejecting incoming shipments).

Item 13/14/15: Review issues

Clinical Pharmacology & Biopharmaceutics (CPB) may have additional comments regarding these issues.

- Explain the concept of — batches of coated codeine polistirex (CCDPSTX) having
- What impact is expected on the bioavailability of codeine from the — of CCDPSTX batches having Vs. — of CCDPSTX batches having
- CCDPSTX batches having
- Define and specify the desired target codeine release for Codeprex ER suspension in the master batch record (i.e., — .
- Given that the release mechanism for codeine and chlorpheniramine are similar, explain the need for separate dissolution methods.
- Explain the differences between the dissolution method for chlorpheniramine release and newly proposed dissolution method for codeine release.

Celltech presented overhead titled, "Coated codeine polistirex process flow" (see attachment).

The Division expressed concern about what appears to be inadequate control of the coating process that may result in dose dumping. Celltech should address in the response why, if the coating process was validated,

Celltech stated that there are inherent variabilities in the process, but they will have tight controls over the coating process so that the final drug product will be equivalent to the biobatch.

The meeting concluded this time.

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

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

/s/

Christine Yu
7/11/03 01:51:26 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2003

/S/

To: Mary Evelyn Towne, Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Celltech Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: NDA 21-369 for Codeprex
Submission dated June 16, 2003

P/T fax impurity
see P/T amendment dated 6/23/03

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

You have reported the presence of an impurity, [redacted] in the codeine phosphate drug substance, and have proposed to qualify this impurity with a 28-day toxicology study in rats.

We have reviewed the proposed qualification scheme for [redacted] provided in an amendment dated June 16, 2003, and have the following comment.

If you plan histological evaluation of tissues from only control and [redacted] dose treatment groups, you will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- for any macroscopic findings in the [redacted] dose groups for a given tissue, you will need to look at that tissue for all of the dose groups;
- for an increase in the incidence of a finding in the [redacted] dose group for a tissue, even if not statistically significant, you will also need to look at the next [redacted] dose group;
- for an excessive decrease in body weight or survival in the examined dose group, you should examine [redacted] dose groups.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu, R.Ph., Regulatory Management Officer, at 301-827-1051.

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/

Christine Yu
7/10/03 01:50:55 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: March 17, 2003

To: Mary Evelyn Town
Manager, Regulatory Affairs

Fax: 585-272-3952

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: NDA 21-369 Codeprex
Minutes of July 15, 2002, ~~teleconference~~ meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on July 15, 2002. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

MEETING MINUTES

DATE:	July 15, 2002
TIME:	3:00 - 4:00 PM
LOCATION:	Parklawn CR "C"
APPLICATION:	NDA 21-369
DRUG NAME:	Codeprex (codeine/chorpheniramine) extended-release suspension
IMTS#:	8678
SPONSOR:	Celltech Pharmaceuticals, Inc.
Represented by:	Norma Cappetti, Director, Regulatory Affairs [redacted], Pharmacokinetic Consultant Paul Hafey, Director, Product Development Simon Hatch, M.D., Director, Clinical Development Donna Radzik, Ph.D., Sr. VP, Technical Operations & Dvm [redacted], Pharmaceutical Consultant Mary Evelyn Towne, Manager, Regulatory Affairs
FDA PARTICIPANTS:	Division of Pulmonary & Allergy Drug Products, unless noted otherwise Young Moon Choi, Ph.D., CPB reviewer Emmanuel Fadiran, Ph.D., CPB Team Leader Henry Malinowski, Ph.D., Director, DPE II Vibhakar Shah, Ph.D., CMC reviewer Guirag Poochikian, Ph.D., CMC Team Leader Charles Lee, M.D., Medical Officer Mary Purucker, M.D., Medical Team Leader Badrul Chowdhury, M.D., Ph.D., Medical Team Leader Marianne Mann, M.D., Deputy Director Robert Meyer, M.D., Director Christine Yu, R.Ph., Regulatory Project Manager

Background

NDA 21-369 for Codeprex was received April 13, 2001. On February 13, 2002, the Division sent a Approvable letter with extensive Chemistry, Manufacturing, and Controls (CMC) and Clinical Pharmacology & Biopharmaceutics (CPB) comments. Following a request from Celltech on February 21, 2002, the Division sent a facsimile clarification dated March 13, 2002. Furthermore, a teleconference was held on April 3, 2002.

With apparent disagreement with the Division about conclusions drawn from the data, Celltech consulted [redacted] who agreed with Celltech's conclusion. Celltech requested a face-to-face meeting to resolve differences between the company and the Agency with respect to dissolution specifications for the drug product.

Agenda

10 minutes- Celltech presentation
10 minutes- Division presentation
40 minutes- Discussion

Attachments
Celltech's presentation

Minutes
Celltech presented their conclusions about the data, see Attachment provided at the end of the meeting minutes.

The Division presented the following CMC comments and concerns.

1. CPB will address the issue of in vitro-in vivo correlation (IVIVC) for *codeine* and *chlorpheniramine* release.
2. Release rates of *codeine* and *chlorpheniramine* decrease with storage time and temperature for all nine lots at all dissolution time points (especially at 1h, 3h, 6h, and 12h) from their corresponding initial release values.
3. No IVIVC data are provided for all these lots beyond their initial release value (time = 0 month) to demonstrate that the percent decreases observed in release rates of *codeine* and *chlorpheniramine* are bioequivalent with storage time and temperature
4. From lot to lot quality control viewpoint, the dissolution data submitted both for *codeine* and *chlorpheniramine* do not provide adequate assurance for their consistent release rates (and thereby their bio-availability) through the shelf-life of the drug product as well as the identification of the drug product lots of different qualities at release.
5. Dissolution specifications cannot be set until the inconsistencies observed in release rates of *codeine* and *chlorpheniramine* with storage (time and temperature) and the corresponding IVIVC for these two components are satisfactorily addressed with adequate data.

The Agency noted that Celltech has chosen not to conduct clinical trials to demonstrate clinical efficacy and safety but to demonstrate bioequivalence to an approved reference product. The reference product in this case is immediate-release (IR), whereas the product for which Celltech is seeking approval is modified-release. The Agency proceeded to address Celltech's one question from the briefing package.

Celltech's specific question

Since the Agency considered a decreased fluctuation index, higher C_{min} values, and equivalent AUC_{ss} values as the relevant parameters for the determination of bio-and therapeutic equivalence, why does the Agency insist on the relevance of C_{max} in the IVIVC?

Please note that the extended release formulation should not exceed the C_{max} of the immediate release formulation.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

The Agency's response

To utilize the ——approach to setup the dissolution specification:

The three formulations —— should be equivalent to each other with respect to AUC, Cmax, and Cmin (if applicable) to ensure that these three formulations are bioequivalent to biobatch formulation —— not to the IR solution.

It is inappropriate to compare only AUC with IR solution after single dose, since there is no way to compare the Cmin, especially for the — coating formulation of chlorpheniramine, which has substantially lower dissolution rate, as well as substantially lower plasma concentration at — hours after administration than other two formulations.

The Agency stated that IVIVC with codeine was not established. On the other hand, IVIVC for chlorpheniramine was established but not validated. Therefore, the IVIVC cannot be used to set dissolution specifications. Futhermore, ——cannot be used to set dissolution specifications since

the three formulations are not bioequivalent to each other. Thus, the Agency proposed the following dissolution specifications based on the mean dissolution data from the biobatches.

Chlorpheniramine

Time (hr)	Biobatch (LotCL00047A)	Sponsor's proposal	Agency's recommendation
1			
3			
6			
12			
24			

Codeine

Time (hr)	Biobatch (LotCL00047A) Average (range); n=12	Sponsor's proposal	Agency's recommendation
1			
3			
6			
12			
24			

APPEARS THIS WAY
ON ORIGINAL

Celltech questioned the relevance of Cmax in an application where the Cmax of the IR reference product, in comparison to a MR product, would be expected to be higher.

The Agency responded that Cmax comparison between the IR reference and the MR product is used in assessing safety and efficacy. However Cmax, as well as AUC and Cmin, of the new MR product is relevant in determining bioequivalency (BE) between the 3 formulations [redacted] coating) and the clinical batch [redacted] coating).

The Agency continued by stating that the observed batch to batch differences were due to the manufacturing process not being under control. Celltech should refine the manufacturing process so that batch to batch consistency is achieved and develop a new formulation with target coating level that does not show decrease in release rate over time. If Celltech desires to use [redacted] to set dissolution specifications, then the 3 formulations should show bioequivalence to the biobatch with respect to Cmax, and AUC and similar Cmin.

In response to Celltech's question about why an "approvable (AE)" action was taken for this application instead of a "not approvable (NA)," the Agency responded that under the Food and Drug Administration Modernization Act of 1997 (FDAMA), CDER has moved to taking AE actions, unless the applications has major issues (usually safety) that are not surmountable.

The Agency concluded the meeting by stating that for applications seeking approval based on BE, the requirements for 21 CFR 320.1 must be met. The CMC and CPB issues as specified above must be addressed before this NDA can be approved. The Agency must have data that provides assurance that there is batch-batch consistency and that the consumer would receive the same in vivo effect over the shelf life of the product.

The meeting adjourned at this time.

APPEARS THIS WAY
ON ORIGINAL

Attachment D

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

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

/s/

Christine Yu
3/17/03 05:50:30 PM

Memorandum of Telephone Facsimile Correspondence

Date: March 14, 2003

To: Mary Evelyn Town
Manager, Regulatory Affairs

Fax: 585-272-3952

From: Christine Yu, R.Ph.
Regulatory Project Manager /S/

Subject: NDA 21-369
Minutes of April 3, 2002, teleconference

Reference is made to the meeting/teleconference held between representatives of your company and this Division on April 3, 2002. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

MEMORANDUM OF TELECONFERENCE

DATE:	April 3, 2002
APPLICATION:	NDA 21-369
DRUG NAME:	Codeprex (codeine/chorpheniramine) extended-release suspension
IMTS#:	8674
SPONSOR:	Celltech Pharmaceuticals
Represented by:	Norma Cappetti, Director, Regulatory Affairs [redacted] Pharmacokinetic Consultant Paul Hafey, Director, Product Development John Marini, Director, Process Development Andrew Morgan, Director, Regulatory Affairs Mary Evelyn Towne, Manager, Regulatory Affairs Joe Magee, Senior Principal Investigator
FDA PARTICIPANTS:	Division of Pulmonary & Allergy Drug Products, HFD-570 Young Moon Choi, Ph.D., CPB reviewer Emmanuel Fadiran, Ph.D., CPB TL Vibhakar Shah, Ph.D., CMC reviewer Guirag Poochikian, Ph.D., CMC Team Leader Christine Yu, R.Ph., Regulatory Project Manager

Background

NDA 21-369 for Codeprex was received April 13, 2001. On February 13, 2002, the Division sent a Approvable letter with extensive Chemistry, Manufacturing, and Controls (CMC) and Clinical Pharmacology & Biopharmaceutics (CPB) comments. Following a request from Celltech on February 21, 2002, the Division sent a facsimile clarification dated March 13, 2002, which included the following.

> You state that a Level A *in vitro- in vivo* correlation (IVIVC) was established for chlorpheniramine, but this was not appropriately validated and therefore, cannot be used for setting dissolution specification at this time. We recommend that the
>
> [redacted]
>
> The [redacted] study (Study 1109-99) has been completely reviewed. The dissolution specification for codeine cannot be widened based on the results due to nonequivalence of the tested formulations.

We note that there were substantial reductions of release rate for both bio- and stability batches for codeine and chlorpheniramine upon storage. If the level A IVIVC correlation for chlorpheniramine is validated, then it may be used to predict *in vivo* performance of a product with reduced release rate, but you did not submit codeine data of a batch with significantly reduced release rate so that *in vivo* performance may be predicted. Therefore, in order to obtain a longer shelf-life, provide data to show that *in vivo* performance would be same for a batch with significantly reduced release profile, especially for codeine for the newly requested/proposed shelf-life. If a new formulation is developed to improve stability, comparative bioavailability/ bioequivalence studies may be needed depending on the level of the formulation change.

Celltech requested this teleconference for further clarification from the Division regarding the dissolution specifications for the final drug product.

Teleconference

The Division stated that the data submitted by Celltech showed high variability in dissolution with storage of the drug product Based on dissolution data alone, the expiration dating will be [redacted] Also because bio-equivalency (BE) was not established between the formulations ([redacted] was not an acceptable method for determining the dissolution specifications.

Celltech asked for clarification of why the in vitro-in vivo correlation (IVIVC) was not acceptable. They stated that they believed that they had achieved Level A correlation for codeine and validated with the external formulation to set specifications. They believed that they had confirmed the Division's agreement for their plans for IVIVC in a teleconference with the Division on October 18, 1999.

The Division clarified that in determining BE between two *modified release* formulations both the Cmax and the AUC of the proposed product and the reference product must be comparable. On the other hand, if an immediate -release (IR) formulation is the reference product for a modified release (MR) formulation, as in this NDA, the safety and efficacy studies may reference the IR formulation, *but* determination of dissolution specifications for the MR product is contingent on a validated IVIVC.

The Division explained that in order to establish IVIVC, 3 formulations (different dissolution profiles, [redacted] should be used. Based on the dissolution profiles of the three formulations, the serum levels would be predicted for the external validation formulation. If the in vivo levels of the validation formulation match those predicted from the dissolution profiles, then IVIVC is established. The Division stated that the serum levels predicted for the external validation formulation for Codeprex did not match the in vivo levels achieved. Therefore, IVIVC was not established.

The Division stated that they will check previous communications and proceeded to summarize the discussion with the following.

- Bio-equivalence of the three different formulations ———— was not demonstrated. Therefore, ——— cannot be used to set dissolution specifications.

  Dissolution data was relied on to determine expiration dating. However, the data submitted showed high variability in dissolution with the product at release and over storage. Thus, allowable expiration is ———— (Generally, if BE is achieved with the product at release, then the product should also be bio-equivalent after storage, refer to comment 8g in Approvable letter dated February 13, 2002.)

- IVIVC was not validated.

The Division stated that since neither BE was demonstrated or IVIVC established, an alternative recommendation was faxed on March 13, 2002.

The teleconference concluded at this time.

Post-teleconference Notes
After reviewing the October 18, 1999, teleconference minutes as well as other previous communications, the Division did not find any statement that contradicted what was said by the Division during this teleconference.

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

/s/

Christine Yu
3/14/03 02:33:06 PM
CSO

MEMORANDUM

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

DATE: February 5, 2003

TO: File

THROUGH : Emmanuel Fadiran, Ph.D.
Clinical Pharmacology & Biopharmaceutics, Team Leader

Charles Lee, M.D.
Medical Officer

James Gebert, Ph.D.
Biometrics Reviewer

FROM: Christine Yu, R.Ph.
Regulatory Project Manager

SUBJECT: IND 54,892, Codeprex (codeine/chlorpheniramine) extended release suspension, related NDA 21-369 (AE letter dated February 13, 2002)

Communications with Celltech regarding submission dated January 8, 2003- new protocols for pivotal pharmacokinetic studies

On January 30, 2003, the Division faxed to Celltech the following clinical pharmacology & biopharmaceutics (CPB) and clinical comments regarding studies CD-00800 and CD-00900 that were to begin January 26 and 31, 2003.

1. For study CD-00900, we recommend that you conduct a single dose comparative bioavailability study that compares the codeine/chlorpheniramine extended-release suspension with the immediate release solution of codeine /chlorpheniramine. One way of achieving this would be to : Alternatively, a separate single dose study may be conducted.

2. The study protocols do not contain information about how the safety endpoints will be reported. If data from these studies will be submitted to support the NDA, descriptive analyses of adverse events, vital signs, physical examinations, and electrocardiograms (ECGs) should be provided.

On Monday, February 3, 2003, Celltech requested clarifications of the comments in the fax. In two separate impromptu telecons, we provided the following clarifications. Celltech participants were Mary Evelyn Towne, Manager, Regulatory Affairs, and Dr. Simon Hatch, Director of Clinical Development.

Regarding Comment 1 (with C. Yu and Dr. Emmanuel Fadiran, CPB Team Leader)
Celltech stated that in a immediate-release (IR) comparator arm is included the multiple-dose (MD) steady-state study (CD-00900).

Dr. Fadiran clarified that because the drug product has been reformulated (manufacturing process changes), Celltech should have a IR comparator arm in the single-dose (SD) study. He referred Celltech to the July 2002 Draft Guidance for Industry, entitled, "Bioavailability and Bioequivalence studies for orally administered drug products-General considerations." Dr. Fadiran stated that if a IR comparator arm in a SD study is not included (or, alternatively, a stand-alone SD study), this will be a review issue when the study results are submitted to the NDA.

Regarding Comment 2 (with C. Yu and Dr. Charles Lee, Medical Officer)
Celltech was not sure if the Division was asking for more safety information. Dr. Hatch stated that they plan to submit a safety analysis for each study but were not planning to submit a revised Integrated Safety Summary (ISS).

Dr. Lee agreed that a safety analysis should be provided for each study. The safety parameters that Celltech plans to monitor are acceptable.

I added that a safety update is required to be submitted with the NDA resubmission as per CFR 314.50(d)(5)(vi). Regarding submission of a updated ISS, Dr. Lee stated that with the resubmission of the NDA, an updated ISS assessing safety across the new studies conducted should be submitted. The ISS update should capture additional safety information from the time of the original NDA submission to the time of the resubmission.

Celltech then contacted me on Tuesday, February 4th to inform the Division that Celltech would like to ——————————
Celltech's statisticians have indicated that the statistical impact ——————————
—————— They would like the Division to look at their statistical plan for managing
—————— and provide concurrence/comments in a timely fashion so that, if
——————————

After discussion with Drs. Fadiran and Gebert (Biometrics reviewer), I responded to Celltech on Wednesday February 5th that, although it is Celltech's decision to make, ——————
——————————
—————— If this study report is submitted, the statistical analysis of bio-equivalence would be consulted to Mr. Donald Schuirmann of the Quantitative Methods Research (QMR) in the Office of Pharmacoepidemiology & Statistical Science. Although Celltech would like the Division to provide feedback by February 7th on their statistical proposal in managing the ——

[redacted] this would not be possible since most consults outside the Division take at least 60 days.

Dr. Hatch stated that Celltech will take these considerations under advisement in determining whether Celltech [redacted] conduct a separate SD study that includes a IR comparator. He added that Celltech would not [redacted], approval of the NDA.

Ms. Towne stated that she will keep me informed about Celltech's decision.

To bring closure to these conversations, Ms. Towne informed me later that day (February 5th), that Celltech has decided to perform a SD comparative bioavailability study that compares the Codeprex ER suspension with the IR solution of codeine /chlorpheniramine. They will not be adding the [redacted]

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

/s/

Christine Yu
2/6/03 06:23:47 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2003

To: Mary Evelyn Towne Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph. /S/ Regulatory Project Manager
Company: Celltech Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: IND 54,892 codeine/chlorpheniramine ER suspension
Clinical Pharmacology & Biopharmaceutics and clinical comments

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

We refer to your submission to IND 54,892 dated January 8, 2003 (submission 020). We note your statement that studies CD-00800 and CD-00900 will be initiated January 26 and 31, 2003, respectively, and have the following clinical pharmacology/biopharmaceutics and clinical comments. Additional comments from CMC and pharmacology/toxicology will be forwarded upon review completion.

1. For study CD-00900, we recommend that you conduct a single dose comparative bioavailability study that compares the codeine/chlorpheniramine extended-release suspension with the immediate release solution of codeine /chlorpheniramine. One way of achieving this would be [redacted] Alternatively, a separate single dose study may be conducted.

2. The study protocols do not contain information about how the safety endpoints will be reported. If data from these studies will be submitted to support the NDA, descriptive analyses of adverse events, vital signs, physical examinations, and electrocardiograms (ECGs) should be provided.

[redacted]

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

/s/

Christine Yu
1/30/03 06:41:21 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 13, 2002

To: Mary Evelyn Town Manager, Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Celltech Pharmaceuticals	Division of Pulmonary & Allergy Drug Products
Fax number: 585-272-3952	**Fax number:** 301-827-1271
Phone number: 585-274-5840	**Phone number:** 301-827-1051

Subject: NDA 21-369 Response to Correspondence dated February 21, 2002.

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES √ NO

We have the following responses to your correspondence dated February 21, 2002, requesting clarification and references for comments in the approvable letter from the Division dated February 13, 2002.

1. Clarification of comment 8(g)1:

   You state that a Level A *in vitro- in vivo* correlation (IVIVC) was established for chlopheniramine, but this was not appropriately validated and therefore, cannot be used for setting dissolution specification at this time. We recommend that the ——— study data be used for external validation of the IVIVC. If the IVIVC is validated with this analysis,

   [ ]

   The ——— has been completely reviewed. The dissolution specification for codeine cannot be widened based on the results due to nonequivalence of the tested formulations.

   We note that there were substantial reductions of release rate for both bio- and stability batches for codeine and chlorpheniramine upon storage. If the level A IVIVC correlation for chlorpheniramine is validated, then it may be used to predict *in vivo* performance of a product with reduced release rate, but you did not submit codeine data of a batch with significantly reduced release rate so that *in vivo* performance may be predicted. Therefore, in order to obtain a longer shelf-life, provide data to show that *in vivo* performance would be same for a batch with significantly reduced release profile, especially for codeine for the newly requested/proposed shelf-life. If a new formulation is developed to improve stability, comparative bioavailability/ bioequivalence studies may be needed depending on the level of the formulation change.

2. References for pharmacology/toxicology labeling comments:

   Preclinical statements in labeling refer primarily to results published by the National Toxicology Program (NTP) or reported in other codeine and chlorpheniramine product labels. References are detailed below for the respective subsections.

   a. Carcinogenesis, Mutagenesis, Impairment of Fertility subsection

      Codeine
      Carcinogenicity – NTP
      Mutagenicity – NTP

Chlorpheniramine
Carcinogenicity – NTP
Mutagenicity – NTP
Fertility – Ornade® Spansule® Capsules, NDA 12-152

b. Pregnancy subsection

Codeine
Arzneimittelforschung 26: 551-554, 1976 (Article in German)
Cited in other product labels.

Chlorpheniramine
Ornade® Spansule® Capsules, NDA 12-152
Arzneimittelforschung 18: 188-194, 1968

c. Overdosage subsection

Chlorpheniramine - NTP

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

/s/

Christine Yu
3/13/02 05:07:08 PM
CSO

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

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 8/14/01	**DUE DATE:** 1/18/01	**ODS CONSULT:** 01-0182

TO:

Robert J. Meyer, M.D.
Director, Division of Pulmonary Drug Products
HFD-570

THROUGH:

Christine Yu
Project Manager
HFD-570

PRODUCT NAME:	**NDA SPONSOR:**
Codeprex (codeine/chlorpheniramine extended-release suspension) 20 mg/4 mg per 5 mL **NDA #:** 21-369	Celltech Pharmaceuticals, Inc.

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Pulmonary Drug Products (HFD-570), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Codeprex" 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 "Codeprex". This name 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 names from the signature date of this document. 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.

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-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 18, 2001

NDA NUMBER: 21-369

NAME OF DRUG: Codeprex
(codeine/chlorpheniramine extended-release suspension)
20 mg/4 mg per 5 mL

NDA HOLDER: Celltech Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary Drug Products (HFD-570), for assessment of the tradename "Codeprex", regarding potential name confusion with other proprietary/generic drug names. The sponsor had previously submitted the tradename — for review, but the Division indicated that the name was not acceptable due to concerns that the name was promotional in nature and that the — may be confusing.

PRODUCT INFORMATION

Codeprex is the proposed proprietary name for codeine/chlorpheniramine extended release suspension. Codeprex is indicated for the temporary relief of — cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever or other upper respiratory allergies. Codeine is an opiate antitussive, and chlorpheniramine is an antihistamine. Each teaspoonful (5 mL) of Codeprex contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients. The suspension provides up to 12 hours of relief per dose and is for oral use only. The recommended dosage in adults and adolescents 12 years of age and older is two teaspoonfuls every 12 hours, not to exceed four teaspoonfuls in 24 hours. Children ages 6 to under 12 are to be given one teaspoonful every 12 hours, not to exceed two teaspoonfuls in 24 hours. Codeprex is a Schedule III controlled drug substance. Codeprex will be supplied as a pink to purple-pink colored, cherry-cream flavored suspension in 480 mL bottles.

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 that sound alike or look alike to "Codeprex" 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 trademark electronic search system[4] (TESS) was conducted. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. 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 (inpatient and outpatient) and one verbal prescription study, 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 "Codeprex". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising 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.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Codeprex. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard 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, 2000, 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 & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Celebrex	Celecoxib 100 mg, 200 mg capsules	Osteoarthritis: 200 mg per day Rheumatoid Arthritis: 100 to 200 mg twice a day	S/A, L/A
Cognex	Tacrine hydrochloride 10 mg, 20 mg, 30 mg, 40 mg capsules	10 mg four times a day (40 mg/day) increased after 4 weeks to 20 mg four times a day (80 mg/day)	S/A
Adipex-P	Phentermine hydrochloride 37.5 mg tablets, capsules	37.5 mg daily, given before breakfast or 1-2 hr after breakfast	S/A
Catapres (Catapres-TTS)	Clonidine hydrochloride, 0.1 mg, 0.2 mg, 0.3 mg tablets and transdermal system	Tablet: 0.1 mg twice daily Transdermal: 0.1 mg (Catapres-TTS-1) applied once every 7 days	S/A
Cortiplex (not marketed)	Corticosteroid preparation	Not marketed in U.S.	S/A
CorePlex (OTC)	Multi-nutrient supplement, capsules	One capsule three times a day	S/A
Coreplex (OTC)	Hawthorn herbal supplement, 500 mL bottle	Dosage not specified.	S/A
Codegest Expectorant (C-V) (not marketed)	Guaifenesin 100 mg, PPA 12.5 mg, codeine phosphate 10 mg per 5 mL	Not marketed in U.S.	S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved 112 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Codeprex with other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of marketed and unapproved drug products and a prescription for Codeprex (see below). These prescriptions were scanned into a computer and were then 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 interpretation 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.

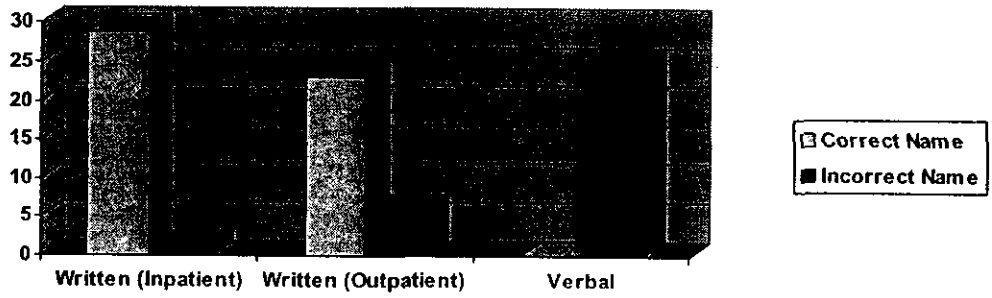
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: Codeprex As directed #1 Refills: 0	Codeprex Use as directed. Dispense one with no refills
Inpatient RX: Codeprex 2 tsp q12h prn cough	

2. Results:

The results are summarized in Table I.

Table I

Study	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	39	30 (77%)	29 (97%)	1 (3%)
[illegible]	38	29 (76%)	23 (79%)	6 (21%)
[illegible]	35	25 (71%)	0 (0%)	25 (100%)
[illegible]	112	84 (75%)	52 (62%)	32 (38%)



Among the verbal outpatient Codeprex prescriptions, none of the respondents interpreted the name correctly. Many of the incorrect name interpretations were phonetic variations of "Codeprex". Fifteen respondents interpreted the verbal order to be either Cordiprex or Cortiprex. Other interpretations included: Cortiplex, Cortoprex, Cardaprex, Cortaprex, Cortipres, and Cordapres.

When examining the interpretations from the written inpatient and outpatient prescriptions, 52 of 59 (88%) of the respondents interpreted the name correctly. Incorrect responses included the following phonetic variations: Codiplex, Codeprex, Codiprik, and Codprex.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Codeprex", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Codeprex were *Celebrex, Cognex, and Adipex*. Similarly, through independent review, several other marketed and unmarketed drug names (Catapres, Cortiplex, CorePlex, Coreplex, Codegest) were also determined to have potential for confusion with the proposed name Codeprex.

Celebrex, celecoxib hydrochloride, is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities via inhibition of cyclooxygenase-2 (COX-2). Celebrex is indicated for relief of the signs and symptoms of rheumatoid and osteoarthritis. The recommended oral dose for osteoarthritis is 200 mg per day administered as a single dose or as 100 mg twice per day. For relief of the signs and symptoms of rheumatoid arthritis, the recommended oral dose is 100 to 200 mg twice per day. Celebrex is available as 100 mg and 200 mg capsules. Although Celebrex can sound alike and look alike to Codeprex, there are differences between the two that help to limit the risk for confusion. Celebrex is available as capsules, and Codeprex is available as an oral syrup. Celebrex is available in two different

strengths and therefore must be prescribed with an accompanying strength. However, Codeprex is a combination product that is only available in one strength (20 mg/4 mg per 5 mL) and does not require a strength to be written. Both Celebrex and Codeprex belong to different pharmacologic classes and have completely different indications for use. In addition, a prescription for Codeprex would require the use of the word "teaspoon/tablespoon" or "mL/cc" in order to provide dosing instructions or total amount dispensed, thus adding another checkpoint for errors. Thus, due to the differences in dosage form, strength, dosing instructions, indication, and pharmacologic class, the risk of a product mix-up between Celebrex and Codeprex is minimal.

Cognex, tacrine hydrochloride, is a reversible cholinesterase inhibitor indicated for the treatment of mild to moderate dementia of the Alzheimer's type. The initial dose of Cognex is 40 mg/day (10 mg four times a day) for a minimum of four weeks. Cognex is supplied as capsules containing 10, 20, 30, and 40 mg of tacrine. The name Cognex sounds similar to Codeprex. However, Cognex is available as a capsule formulation while Codeprex will be available as an oral liquid. The two drugs have different dosage forms, strengths, and indications. Additionally, Cognex is usually dosed four times a day for a minimum of four weeks, while Codeprex is to be prescribed as twice day for a much shorter duration of time. The risk of a product mix-up due to name confusion between Cognex and Codeprex appears to be minimal.

Adipex-P, phentermine hydrochloride, is indicated as a short-term adjunct in the management of obesity. The usual adult dose is one capsule or tablet daily, administered before breakfast or 1-2 hours after breakfast. Adipex-P is available in tablets and capsules containing 37.5 mg phentermine hydrochloride. Although Adipex and Codeprex sound similar, the two drugs have many factors that help to distinguish one from the other. Both drugs belong to different pharmacologic classes and are available in different dosage forms Cognex is prescribed as a once a day dose while Codeprex is given twice daily. As stated earlier, because Codeprex is an oral liquid, the directions for use or the total amount dispensed will need to include a liquid measurement therefore adding another error checkpoint. The risk of confusion between these two products is low.

Catapres, clonidine hydrochloride, is indicated in the treatment of hypertension. The product is available as oral tablets in three dosage strengths: 0.1 mg, 0.2 mg and 0.3 mg. The initial dose is 0.1 mg twice daily, with therapeutic does ranging from 0.2 mg to 0.6 mg per day in divided doses. Catapres is also available as a transdermal system, which is known as Catapres-TTS, that provides continuous systemic delivery of clonidine for 7 days. Catapres-TTS is available in the following strengths: 0.1 mg, 0.2 mg, and 0.3 mg. To initiate therapy, Catapres-TTS dosage should be titrated according to individual therapeutic requirements, starting with Catapres-TTS-1. The patches are supplied as four pouched systems and four adhesive overlays per carton. Catapres and Codeprex sound alike when pronounced and each have three syllables. There are many differences between the two drugs that may help to minimize confusion and potential error. Catapres and Codeprex have different dosage forms, strengths, pharmacologic classes, and indications for use. The usual daily dosing also differs between Catapres and Codeprex. Catapres patches are dispensed in four pack cartons and each patch is worn on the skin for seven days. Catapres oral tablets are often dosed twice daily, as is Codeprex liquid, but the need to differentiate between the various strengths of the tablets (and patches) will help to minimize confusion between the two drug names.

One respondent from the voice studies interpreted the name to be Cortiplex. According to Saegis[1], Cortiplex is an Italian launched corticosteroid drug product whose last year of recorded sales was 1995. Cortiplex is not marketed in the U.S. and therefore the risk of a medication error is low.

CorePlex and Coreplex are both over-the-counter products available in the U.S. market. Both names are the spelled the same way except that one has a capital "P" in the middle. CorePlex is a multi-nutrient supplement including vitamins, minerals, and phytochemicals. CorePlex is available in a capsule formulation that is taken three times a day. Coreplex, on the other hand, is an herbal product containing various aqueous extracts of hawthorn, passion flower, and hibiscus. Coreplex is a liquid extract thought to aid in the functioning of the cardiovascular system. CorePlex (Coreplex) and Codeprex sound similar to one another, but there are differences between the products that help to minimize the risk of error. Codeprex is a prescription medication while both the CorePlex (Coreplex) products are available over-the-counter. CorePlex is available as a capsule given three times a day, and Codeprex is a liquid preparation taken twice a day. Coreplex is also a liquid preparation, but due to the difference in indication, pharmacologic class, non-prescription status it is unlikely that the products would be confused with one another.

Codegest is an oral liquid expectorant containing guaifenesin, phenylpropanolamine, and codeine. Codegest is a Schedule V controlled substance. Codegest and Codeprex sound alike when pronounced aloud. Codegest contains the ingredient phenylpropanolamine (PPA) which has been implicated as a cause of hemorrhagic strokes, especially in young women. Codegest was recalled from the market, along with all products containing PPA, in November 2000. Thus, confusion between Codegest and Codeprex is not likely at this time.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels and insert labeling of Codeprex, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has reviewed the current container labels and insert labeling and has identified several areas of possible improvement, which might minimize potential user error. The container label and draft insert labeling provided and reviewed included the earlier proposed tradename ———

A. CONTAINER LABEL

1. We recommend that the word "DOSAGE" be changed to ' ————————

2. It is important that the practitioner be able to readily distinguish between the different combinations of potencies of this product. In addition, the quantitative amount of each active ingredient should be placed in direct conjunction with the most prominent display of the proprietary name. We recommend the expression of strength appear on the principal display panel in either of the following manners:

Codeprex

(codeine/chlorpheniramine extended-release suspension)

Each teaspoonful (5 mL) contains:
Codeine.....20 mg
Chlorpheniramine maleate .....4 mg

OR

Codeprex

(codeine/chlorpheniramine extended-release suspension)
20 mg/4 mg per 5 mL

B. INSERT LABELING

No comments.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name Codeprex.

This is considered a tentative decision and 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 names from this date forward.

DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3231.

_____

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
1/18/02 01:25:01 PM
CSO

Carol Holquist
1/18/02 03:11:50 PM
PHARMACIST

Jerry Phillips
1/22/02 08:08:10 AM
DIRECTOR

SB for RJM 8/14/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):	FROM:
DRA, HFD-400	Christine Yu, R.Ph. DPADP, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 13, 2001		21-369	Original NDA	April 13, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeine/chlorphenirmaine Extended Release suspension	Standard	Type 4	October 31. 2001

NAME OF FIRM: Celltech Pharmaceuticals. Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform trade name (proprietary name) review for "Codeprex."

SIGNATURE OF	METHOD OF DELIVERY (Check one)
/S/	☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Attached: Draft package insert (with a previously proposed name)
Enclosed: bottle label (with a previously proposed name), copy of correspondence from Celltech.

15 B03

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

MEMORANDUM OF TELECONFERENCE

DATE: June 7, 2001

APPLICATION: NDA 21-369 Codeine/chlorpheniramine extended release suspension

BETWEEN: Celltech Pharmaceuticals, Inc. (unless indicated)

Name: Sharon Dirksen, Manager, Clinical Development
Andrew Morgan, Director, Regulatory Affairs
[redacted] Director, Pharmacokinetics & Biopharmaceutics and Product Development Management, [redacted]
Mary Evelyn Towne, Manager, Regulatory Affairs

AND Division of Pulmonary & Allergy Drug Products (DPADP)

Name: Young Moon Choi, Clinical Pharmacology & Biopharmaceutics Reviewer
Vibhakar Shah, Chemistry Reviewer
Christine Yu, Regulatory Project Manager

Paper NDA 21-369 was submitted and received April 13, 2001. This teleconference was initiated by the Division to provide clarifications and comments and to request additional information.

1. On May 31, 2001, the Division informed Celltech that the pharmacokinetic information files listed in Appendix 4, Volume 23 of the submission could not be located. Celltech contacted [redacted], the contract research organization (CRO), who then requested clarification on whether the Division needed paper archival copies for both the program and data files for the information requested.

   The Division clarified that for the files listed in Appendix 4, Volume 23, only the data files need to be submitted in paper archival copy. The program files do not need to be submitted in paper.

2. Chemistry, Manufacturing & Controls (CMC)

   a) Stability data

      Dr. Shah stated that data provided for release rate/dissolution for codeine and chlorpheniramine represent an average value at each time point rather than individual values for the samples tested, e.g., n=12, n=16, and requested the following information.

      - Provide individual values for time release of codeine and chlorpheniramine for all lots of the drug product that are placed on stability.
      - Pool these values for each timepoint at specified storage conditions for each lot in a tabular format, and submit these data in paper archival copy and electronic reviewer copy to facilitate the review process. See attached sample faxed to Celltech on June 7, 2001.

b) Likewise, for all lots of the drug product placed on stability, pool data for each attribute at each timepoint and a storage condition in tabular format. Provide a paper archival copy and an electronic copy as a reviewer's aid.

c) To facilitate the review, provide narrative portions of the CMC section in electronic format. Include the following:

- All pharmaceutical science reports (with or without images).
- All acceptance specifications for drug substance, drug product intermediates and drug product (e.g., tabular format).
- Container closure information, as appropriate.

Celltech stated that they would provide this information within 3-4 weeks from the date of this teleconference.

3. Clinical Pharmacology and Biopharmaceutics

a) The submission contains dissolution data at 1, 3, 6, 12, and 24 hours. In a previous IND teleconference, the Division had requested data at 8 and 10 hours timepoints. If that data is available, Dr. Choi requested Celltech to submit it to the NDA.

Celltech stated that they need to check if that data is available.

b) In determining specifications, three different media selections are needed for method development. Dr. Choi stated that the data is not included in the submission.

Celltech replied that they will get back to the Division.

c) Dr. Choi stated that the method of development was in the IND submission but was not provided in the NDA; a reference made to the agreement made in the IND stage.

Celltech responded that the development report is contained in Volume 17 under specifications and analytical methods section.

4. The Division, after consideration of the name '—' concluded that the proposed trade name was not acceptable for the following two reasons.

- — portion of the name is not a recognized word in the English language and may cause confusion.
- The proposed name may be overly promotional.

The Division requested that Celltech submit several alternative proposals for the name of the product.

Attachment

Alternative Presentation Format for stability data

Attribute:										
Proposed Specification:										
Storage Condition:										
Time point	**Strength X**					**Strength Y**				
(month)	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**	**Lot #**
Batch size	**250 L**	**300 L**	**500L**	**500 L**	**500 L**	**250 L**	**300 L**	**500L**	**500 L**	**500 L**
0 (initial)										
1										
2										
3										
6										
9										
12										
18										
24										
36										
48										
60										
Expiry										

Footnote:

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

/s/

Christine Yu
7/13/01 01:53:37 PM
CSO

MEMORANDUM OF TELECON

DATE: May 3, 2001

APPLICATION: NDA 21-369 Codeine/chlorpheniramine extended-release suspension

SPONSOR: Celltech Pharmaceuticals, Inc.

BETWEEN: Andrew Morgan, Director, Regulatory Affairs

AND David Hilfiker, Regulatory Project Manager, DPADP, HFD-570
Christine Yu, Regulatory Project Manager, DPADP, HFD-570

NDA 21-369 was submitted April 13, 2001. This teleconference was intended to provide responses to Celltech regarding questions had been under discussion in the Division.

1. David Hilfiker informed Andrew Morgan that Christine Yu has been assigned to this NDA.
2. The Division has found the half-fee for the NDA acceptable.
3. In reference to Celltech's Waiver Request for Pediatric Studies, the Division plans to grant a deferral at approval of the NDA and request submission of post-marketing pediatric usage and safety information.

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

/s/

Christine Yu
7/5/01 03:28:20 PM
CSO

SSB for RJM 7/11/01

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: June 12, 2001

TO: C.T. Viswanathan, Ph.D.
Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Christine Yu, Regulatory Project Manager, HFD-570

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-369
~~~~~~~~~~~~~~~~~~~~ (codeine/chlorpheniramine)

Study/Site Identification:

The following study pivotal to approval has been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
COD-02002		

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **November 28, 2001**. We intend to issue an action letter on this application by **January 30, 2002**.

Should you require any additional information, please contact Ms. Christine Yu at 301-827-1051.
~~~~~~~~~~~~~~~~~~~~

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

/s/

Christine Yu
7/11/01 11:08:53 AM

250 for NDM 6/14/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Controlled Substance Staff Attn: Corinne Moody HFD-009	FROM: Christine Yu Project Manager, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 11, 2001		21-369	Original NDA	April 13, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(codeine/chlorpheniramine)	Standard	Type 4	Division goal date 1/30/2002

NAME OF FIRM: Celltech Pharmaceutical, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform CSS labeling review. We request that the labeling consult be completed no later than December28, 2001. We intend to issue an action letter on this application by January 30, 2002.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
/S/	☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

0003
attn: Label
Package Circular (hard copy & disk)

Electronic Mail Message

Date:	5/31/01 1:40:32 PM	
From:	Michael Klein	(KLEINM)
To:	Christine Yu	(YUC)
Cc:	Corinne Moody	(MOODY)
Cc:	Deborah Leiderman	(LEIDERMAND)
Cc:	Silvia Calderon	(CALDERONS)
Cc:	Dannette Locklear	(LOCKLEARD)
Subject:	NDA 21-369 Filing	

This memo responds to the consult from HFD-570, concerning filing of NDA # 21-369, for [redacted] (containing codeine and chlorpheniramine). We have no filing issues related to the submission, as it concerns the abuse potential and scheduling of [redacted] in the Controlled Substances Act (CSA). The product is already currently in Schedule III and this is so stated in the NDA.

The liquid formulation contains codeine (dose of 40 mg/10 mL) and chlorpheniramine maleate (dose of 8 mg/10 mL) in an extended-release suspension for oral administration twice daily.
The concentration of codeine in the proposed formulation is 4 mg/mL, which is greater than the 2.2 mg/mL limit allowing exemption of codeine from Rx requirements [21 CFR 329.20(a)(3)]. Therefore, this combination drug product is proposed as a Rx product categorized as a C-III controlled substance in accordance with 21 CFR 1308.13(e)(2).

Codeine preparations are listed in Schedule III as described below:

"Narcotic drugs (as base) in limited quantities as set forth below:

(1) No more than 1.8 grams codeine/100 mL or no more than 90 mg/dosage unit, with an equal or greater quantity of an isoquinoline alkaloid of opium.
(2) NMT 1.8 grams codeine/100 mL or NMT 90 mg/Dosage Unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts."

APPEARS THIS WAY
ON ORIGINAL

SB for KJM 5-11-01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): Controlled Substance Staff, HFD-009

FROM: Christine Yu
Project Manager, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 10, 2001		21-369	Original NDA	April 13, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Codeine / Chlorpheniramine	Standard	Type 4	UF deadline 2/13/2002

NAME OF FIRM: Celltech Pharmaceutical, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW)

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform CSS review of original NDA 21-369.
Filing meeting scheduled June 1, 2001.
Division Goal date: January 30, 2002.

SIGNATURE OF REQUESTER	/S/	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-369

Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY 14603-1766

Attention: R. Andrew Morgan, R.Ph.
Director, Regulatory Affairs

Dear Mr. Morgan:

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 Products: [redacted]
codeine/chlorpheniramine Extended-Release Suspension

Review Priority Classification: Standard (S)

Date of Application: April 13, 2001

Date of Receipt: April 13, 2001

Our Reference Number: NDA 21-369

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 12, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 13, 2002 and the secondary user fee goal date will be April 13, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Christine Yu
5/10/01 12:03:06 PM
Signing for Sandy Barnes, CPMS

14 page(s) of revised draft labeling has been redacted from this portion of the review.

4.A.3 DRUG PRODUCT

4.A.3.2 Composition

Label Claim: 8mg chlorpheniramine maleate per 10 mL
40 mg codeine base per 10 mL

Ingredients	Spec. No.	mg/10 mL
Dye, D&C Red #33 Certified		
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF		
Sucrose, NF		
Glycerin, USP		
Propylene Glycol, USP		
Methylparaben, NF		
Propylparaben, NF		
Xanthan Gum, NF		
Citric Acid (Anhydrous), USP		
Edetate Disodium, USP		
Flavor, Artificial Cherry Cream		
Polysorbate 80, NF		
Coated Codeine Polistirex		
Chlorpheniramine Maleate, USP		
Water, Purified, USP		

[1]Based on anhydrous basis
[2]Input quantities vary slightly based on assay of resin bound codeine. The total amount of coated codeine polistirex is equivalent to 40 mg of codeine base. The calculation is based on the following equation:

Coated Codeine Polistirex = (40 mg)(100) / (% Assay)

Residue on ignition ⟨281⟩—Heat 2 g in an open porcelain or platinum dish over a flame: it volatilizes without emitting an acrid odor and on ignition yields not more than 0.1% of residue.

Organic acids—To 20 g add 100 mL of a mixture of neutralized alcohol and water (1 in 2), agitate thoroughly, and heat to boiling. Add 1 mL of phenolphthalein TS, and titrate rapidly with 0.1 N sodium hydroxide VS, with vigorous agitation, to a sharp pink end-point in the alcohol-water layer: not more than 0.4 mL of 0.1 N sodium hydroxide is required.

Fixed oils, fats, and rosin—Digest 10 g with 50 mL of sodium hydroxide solution (1 in 5) at 100° for 30 minutes. Separate the water layer, and acidify it with 2 N sulfuric acid: no oily or solid matter separates.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

White Wax

» White Wax is the product of bleaching and purifying Yellow Wax that is obtained from the honeycomb of the bee [*Apis mellifera* Linné (Fam. Apidae)] and that meets the requirements of the *Saponification cloud test.*

Packaging and storage—Preserve in well-closed containers.

Melting range, *Class II* ⟨741⟩: between 62° and 65°.

Saponification cloud test—Place 3.00 g in a round-bottom, 100-mL boiling flask fitted with a ground-glass joint. Add 30 mL of a solution prepared by dissolving 40 g of potassium hydroxide in about 900 mL of aldehyde-free alcohol maintained at a temperature not exceeding 15°, and then when solution is complete, warming to room temperature and adding aldehyde-free alcohol to make 1000 mL. Reflux the mixture gently for 2 hours. At the end of this period, open the flask, insert a thermometer into the solution, and place the flask in a container of water at a temperature of 80°. Rotate the flask in the bath while both the bath and the solution cool: the solution shows no cloudiness or globule formation before the temperature reaches 65°.

Fats or fatty acids, Japan wax, rosin, and soap—Boil 1 g for 30 minutes with 35 mL of 3.5 N sodium hydroxide contained in a 100-mL beaker, maintaining the volume by the occasional addition of water, and allow the mixture to cool at room temperature for about 2 hours: the wax separates, leaving the liquid clear, turbid, or translucent, but not opaque. Filter the cool mixture, and acidify the clear filtrate with hydrochloric acid: the liquid remains clear or shows not more than a slight amount of turbidity or precipitate.

Acid value ⟨401⟩—Warm about 3 g, accurately weighed, in a 200-mL flask with 25 mL of neutralized dehydrated alcohol until melted, shake the mixture, add 1 mL of phenolphthalein TS, and titrate the warm liquid with 0.5 N alcoholic potassium hydroxide VS to produce a permanent, faint pink color: the acid value so obtained is between 17 and 24.

Ester value ⟨401⟩—To the solution resulting from the determination of *Acid value* add 25.0 mL of 0.5 N alcoholic potassium hydroxide VS and 50 mL of aldehyde-free alcohol, reflux the mixture for 4 hours, and titrate the excess alkali with 0.5 N hydrochloric acid VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). The ester value so obtained is between 72 and 79.

Yellow Wax

» Yellow Wax is the purified wax from the honeycomb of the bee [*Apis mellifera* Linné (Fam. Apidae)].

NOTE—To meet the specifications of this monograph, the crude beeswax used to prepare Yellow Wax conforms to the *Saponification cloud test.*

Packaging and storage—Preserve in well-closed containers.

Other requirements—It meets the requirements for *Melting range, Saponification cloud test, Fats or fatty acids, Japan wax, rosin, and soap, Acid value,* and *Ester value* under *White Wax.*

White Ointment—*see Ointment, White USP*

White Petrolatum—*see Petrolatum, White USP*

Xanthan Gum

» Xanthan Gum is a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris*, then purified by recovery with Isopropyl Alcohol, dried, and milled. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt. It yields not less than 4.2 percent and not more than 5.0 percent of carbon dioxide, calculated on the dried basis, corresponding to not less than 91.0 percent and not more than 108.0 percent of Xanthan Gum.

Packaging and storage—Preserve in well-closed containers.

Identification—To 300 mL of water in a 400-mL beaker, previously heated to 80° and stirred rapidly by mechanical means, add, at the point of maximum agitation, a dry blend of 1.5 g of Xanthan Gum and 1.5 g of locust bean gum. Stir until the mixture dissolves, and then continue stirring for 30 minutes longer. Do not allow the temperature of the mixture to drop below 60° during the stirring. Discontinue stirring, and allow the mixture to cool at room temperature for not less than 2 hours: a firm, rubbery gel forms after the temperature drops below 40°, but no such gel forms in a control solution prepared in the same manner with 3.0 g of Xanthan Gum and without locust bean gum.

Viscosity ⟨911⟩—Place 250 mL of water in a 400-mL beaker, and add a dry blend of 3.0 g of Xanthan Gum and 3.0 g of potassium chloride slowly while stirring at 800 rpm, using a low-pitched propeller-type stirrer. Add an additional quantity of 44 mL of water, rinsing the walls of the beaker. Approximately 10 minutes after the addition of the dry blend of Xanthan Gum and the potassium chloride to the water, remove the beaker from the propeller-type stirrer, and vigorously stir the solution by hand to ensure that all the particles around the edge of the beaker are in solution. Return the beaker to the stirrer, and agitate at 800 rpm for a total mixing time of 2 hours. Then adjust the temperature to 24 ± 1°, and stir by hand in a vertical motion to eliminate any thixotropic effects or layering. [NOTE—Each hand mixing should be not more than 15 to 30 seconds, and the last hand mixing should occur immediately prior to measuring the viscosity.] Equip a suitable rotational viscosimeter with a spindle having a cylinder 1.27 cm in diameter and 0.16 cm high attached to a shaft 0.32 cm in diameter, the distance from the top of the cylinder to the lower tip of the shaft being 2.54 cm, and the immersion depth being 5.00 cm (No. 3 spindle). With the spindle rotating at 60 rpm, immediately observe and record the scale reading. Convert the scale readings to centipoises by multiplying the readings by the constant for the viscosimeter spindle and speed employed. The viscosity at 24° is not less than 600 centipoises.

Microbial limits ⟨61⟩—It meets the requirements of the tests for *Salmonella* species and *Escherichia coli.*

A. Chemistry, Manufacturing, and Controls Information

4.A.3 DRUG PRODUCT

4.A.3.1 Components

A complete list of the components in Codeine/Chlorpheniramine Extended-Release Suspension is shown below:

Component Name	Function
Codeine Phosphate, USP (as Coated Codeine Polistirex)	Active Ingredient
Chlorpheniramine Maleate, USP	Active Ingredient
[redacted] (Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF)	Suspending agent
Dye, D&C Red #33 Certified	Coloring agent
Sucrose, NF	Sweetener
Glycerin, USP	Solvent
Propylene Glycol, USP	Solvent
Methylparaben, NF	Preservative
Propylparaben, NF	Preservative
Xanthan Gum, NF	Suspending agent
Citric Acid (Anhydrous), USP	Buffering agent
Edetate Disodium, USP	Chelating agent
Flavor, Artificial Cherry Cream [redacted]	Flavoring agent
Polysorbate 80, NF	Surfactant
Purified Water, USP	Solvent

Loss on drying ⟨731⟩—Dry it at 105° for 2.5 hours: it loses not more than 15.0% of its weight.

Ash—Weigh accurately about 3 g in a tared crucible, and incinerate at about 650° until free from carbon. Cool the crucible and its contents in a desiccator, and weigh: the weight of the ash is between 6.5% and 16.0%, calculated on the dried basis.

Arsenic, *Method II* ⟨211⟩: 3 µg per g.

Lead ⟨251⟩—Prepare a *Test Preparation* as directed for organic compounds, and use 5 mL of *Diluted Standard Lead Solution* (5 µg of Pb) for the test: the limit is 5 µg per g.

Heavy metals, *Method II* ⟨231⟩—[NOTE—Use a platinum crucible for the ignition.] The limit is 0.003%.

Limit of isopropyl alcohol —

Internal standard solution—Dissolve about 500 mg of tertiary butyl alcohol in about 500 mL of water, and mix.

Standard stock solution—Dissolve a suitable quantity of isopropyl alcohol, accurately weighed, in water to obtain a solution having a known concentration of about 1 mg of isopropyl alcohol per mL.

Standard solution—Pipet 4 mL of the *Standard stock solution* and 4 mL of the *Internal standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Disperse 1 mL of a suitable antifoam emulsion in 200 mL of water contained in a 1000-mL, round-bottom distilling flask having a 24/40 standard taper ground joint. Add about 5 g of Xanthan Gum, accurately weighed, and shake for 1 hour on a wrist-action mechanical shaker. Connect the flask to a fractionating column, and distill about 100 mL, adjusting the heat so that foam does not enter the column. Add by pipet 4 mL of the *Internal standard solution*, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 3.2-mm × 1.8-m stainless steel column packed with 80- to 100-mesh surface silanized packing S3, or equivalent. The column temperature is maintained at 165°, the injection port and detector block temperatures are maintained at 200°, and helium is used as the carrier gas.

Procedure—Separately inject equal volumes (about 4 to 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and determine the peak responses of isopropyl alcohol and tertiary butyl alcohol in each chromatogram. [NOTE—The retention time of tertiary butyl alcohol is about 1.5 relative to that of isopropyl alcohol.] Calculate the weight, in mg, of isopropyl alcohol in the quantity of Xanthan Gum taken by the formula:

$$4C\,(R_U / R_S),$$

in which C is the concentration, in mg per mL, of isopropyl alcohol in the *Standard stock solution*; and R_U and R_S are the peak response ratios of isopropyl alcohol to tertiary butyl alcohol obtained from the *Test solution* and the *Standard solution*, respectively; not more than 0.075% is found.

Pyruvic acid —

Standard preparation—Transfer 45 mg of pyruvic acid, accurately weighed, to a 500-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a glass-stoppered, 50-mL flask, and proceed as directed under *Test preparation*, beginning with "Add 20.0 mL of 1 N hydrochloric acid".

Test preparation—Dissolve 600 mg of Xanthan Gum, accurately weighed, in water to make 100.0 mL, and transfer 10.0 mL of the solution to a glass-stoppered, 50-mL flask. Add 20.0 mL of 1 N hydrochloric acid, weigh the flask, and reflux for 3 hours, taking precautions to prevent loss of vapors. Cool, and add water to make up for any weight loss during refluxing. Transfer 2.0 mL of this solution to a 30-mL separator containing 1.0 mL of a solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid (1 in 200), mix, and allow to stand for 5 minutes. Extract the mixture with 5 mL of ethyl acetate, and discard the aqueous layer. Extract the hydrazone from the ethyl acetate with three 5-mL portions of sodium carbonate TS, collect the extracts in a 50-mL volumetric flask, dilute with sodium carbonate TS to volume, and mix.

Procedure—Determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 375 nm, with a suitable spectrophotometer, using sodium carbonate TS as the blank. The absorbance of the *Test preparation* is not less than that of the *Standard preparation*, corresponding to not less than 1.5% of pyruvic acid.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements. [NOTE—A G16 column has been shown to be an appropriate secondary column.]

Assay—Proceed with Xanthan Gum as directed for *Procedure* under *Alginates Assay*, using about 1.2 g of Xanthan Gum, accurately weighed.

Xanthan Gum Solution

» Prepare Xanthan Gum Solution of the designated percentage strength as follows (see *Pharmacy Compounding* ⟨795⟩):

Xanthan Gum	
for 0.1% Solution	100 mg
for 1.0% Solution	1.0 g
Methylparaben	100 mg
Propylparaben	20 mg
Purified Water, a sufficient quantity to make	100 mL

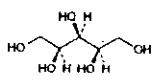
Dissolve an accurately weighed quantity of Propylparaben in Purified Water with heating to about 50° and stirring. Cool, and dilute quantitatively, and stepwise if necessary, with Purified Water to obtain 90 mL of solution containing 20 mg of Propylparaben. Heat to about 50°, and add the Methylparaben, with stirring, to dissolve. Cool, stir with a blender, slowly sift the Xanthan Gum into the vortex, and continue to blend for 2 minutes after the Xanthan Gum has been added. Add 10 mL of Purified Water, and blend for 5 minutes. Allow to stand for 1 hour for excess foam to subside, and remove most of the remaining foam by passing the solution through a strainer. Add Purified Water, if necessary, to make the final volume 100 mL, and stir. [NOTE—Depending on the volume needed and the equipment available, adjust the formula proportionately.]

Packaging and storage—Preserve in tight, light-resistant containers, and store at room temperature.

Labeling—Label it to state, as part of the official title, the percentage content of xanthan gum.

Beyond-use date—Six weeks after the day on which it was compounded.

Xylitol



$C_5H_{12}O_5$ 152.15

Xylitol.

Xylitol.

» Xylitol contains not less than 98.5 percent and not more than 101.0 percent of $C_5H_{12}O_5$, calculated on the anhydrous basis.

MEMORANDUM

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

Date: December 20, 2001

To: Robert Meyer, M.D. Director
Division of Pulmonary Drug Products (HFD-570)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)
Office of the Center Director (CDER)

From: Michael Klein, Ph.D.
Controlled Substance Staff (HFD-009)
Office of the Center Director (CDER)

Subject: CSS Consultation on NDA # 21-369 [505(B)(2) NDA Submission]
Drugs: ——— (of codeine and chlorpheniramine maleate)

Sponsor: Celltech Pharmaceuticals, Inc.

1. Background

The Division of Pulmonary Drug Products has consulted with the Controlled Substance Staff on the abuse potential and scheduling under the Controlled Substances Act (CSA) for ———, a new product which is an extended-release (ER) liquid suspension containing codeine and chlorpheniramine maleate. The Integrated Summary of Safety (ISS), draft labeling, study protocols, and abuse-related information has been provided. The Sponsor has proposed that ——— be a prescription drug listed in Schedule III of the CSA [per 21 CFR 1308.13(e)(2)].

2. Product

——— is indicated for the relief of symptoms of the common cold, allergies, or following exposure to airborne irritants, and offers twice daily dosing. The product is formulated to contain codeine (in a dose of 40 mg/10 mL) and chlorpheniramine maleate (in a dose of 8 mg/10 mL) in an extended-release suspension for oral administration twice daily. The ER product utilizes an ion exchange resin bound with active ingredients which are then coated with ethylcellulose. The pink to purple-pink colored, cherry-cream flavored suspension will be available in 480 mL bottles. The formulation and regimen provides a total dose equivalent to that approved for an immediate-release (IR) product

every 6 hours. An IR formulation of 40 mg codeine and 8 mg chlorpheniramine maleate per 10 mL to be administered every 6 hours served as reference product in clinical trials.

The submission is a 505(b)(2) NDA that relies on earlier FDA finding of safety and efficacy for the two active ingredients. Thus, safety and efficacy studies were not conducted to support NDA approval. The findings for codeine and chlorpheniramine are in accordance with the Final Monograph for OTC Antitussive Drug Products, 52 FR 30055 (8-1287) and the Final Monograph for OTC Antihistamine Drug Products (57 FR 58374, 12-9-92), respectively, and the Tentative Final Monograph for Combination Products, 53 FR 30561 (8-12-88).

3. **Integrated Summary of Safety (ISS)**

All three studies in the ISS enrolled healthy volunteers to characterize the bioavailability of the ER formulation of 40 mg codeine and 8 mg chlorpheniramine maleate. The object of the studies was primarily to characterize the pharmacokinetic parameters of the ER formulation, two of the studies used the IR suspension as a comparator rather than placebo. The remaining study evaluated the bioavailability of the ER formulation in fed and fasted state; as such, comparator drug was not needed. Because the three clinical studies enrolled healthy volunteers, the number of (treatment-emergent) adverse drug events was small. Overall, ADEs were those known to occur with administration of codeine and/or chlorpheniramine maleate. There were no deaths, serious or significant adverse events in any of the three studies.

The studies conducted in support of this application were not designed to generate data to assess abuse potential or withdrawal effects. Also, design of studies did not allow for an analysis of long-term effects of the formulations.

3. **Recommendations**

a. [redacted] meets the requirements of a C-III narcotic. In order to be listed in C-III, the preparation must contain codeine or its salts calculated as the free anhydrous base, in limited quantities as set forth below: no more than 1.8 grams codeine per 100 mL or no more than 90 mg per dosage unit, with either an equal or greater quantity of an isoquinoline alkaloid of opium or one or more active, non-narcotic ingredients in recognized therapeutic amounts. The concentration of codeine in the proposed formulation is 4 mg/mL (400 mg/100 mL), consistent with C-III products. [redacted] cannot be a C-V product which are required to contain no more than 200 mg codeine per 100 mL or per 100 grams.
b. Pharmacologic properties of codeine and chlorpheniramine containing preparations are summarized in the draft product labeling and originate from the literature since large efficacy trials were not conducted.
c. The draft labeling adequately describes many warnings typical of opioids that are of concern: hypersensitivity to codeine and cross-sensitivity to other opioids, production

of dose-related respiratory depression, excretion of drug and metabolites to breast milk, and drug interactions.

d. Also, use is not recommended in pediatric patients under 6 years old and caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture are included in the labeling.
e. The patient information section warns of drowsiness and impaired mental and/or physical abilities.
f. Patients are also warned that the suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.
g. As neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery, the abuse and dependence section of the label must adequately describe symptoms typical of opiate withdrawal which occur after birth.
h. The drug abuse and dependence section should state that ——— is a controlled narcotic in Schedule III of the Controlled Substances Act (CSA).
i. Abuse of ——— was not studied or compared with other opioids and as such, the probability of abuse should not be minimized. The portion of the label that states that codeine has less abuse potential than other substances needs to be revised. Though the ——— formulation will be listed in C-III, codeine substance is a C-II narcotic. In the section on dependence, the words "psychic and physical" should be deleted. The warning should state: "Dependence and tolerance may develop upon repeated administration. An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period." Information regarding the neonatal withdrawal should be included.

CC:
NDA #21-369
HFD-009/ LeidermanD/ MoodyC/ CalderonS/ MaustA/ BonsonK/LocklearD/ KleinM
HFD-570/ MeyerR/ YuC

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

/s/

Michael Klein
12/21/01 10:38:10 AM
CHEMIST

Original of DFS entry was faxed to Review Division on 12-20-01. CSS requested review of final draft labeling.

Deborah Leiderman
1/7/02 12:40:03 PM
MEDICAL OFFICER

MEETING MINUTES

Date:	September 21, 1998
Place:	Parklawn Building, Conference Room B
Meeting Type:	End-of-Phase 2
Sponsor:	Medeva Pharmaceuticals, Rochester, NY
Drug:	Codeine/chlorpheniramine polistirex Extended Release Suspension
IND #:	54,892
IMTS#:	3009

FDA Participants:	David Hilfiker	Project Manager
	Susan Johnson	Medical Officer
	Robert Meyer	Medical Team Leader
	Vibhakar Shah	CMC Reviewer
	Luqi Pei	Pharmacology/Toxicology Reviewer
	Joseph Sun	Pharmacology/Toxicology Team Leader
	Bradley Gillespie	Clinical Pharmacology/Biopharmaceutics Reviewer
	Ramana Uppoor	Clinical Pharmacology/Biopharmaceutics Team Leader
Medeva Participants:	Terrance Coyne	Medical, Scientific, and Legal Affairs
		Pharmacokinetic Consultant
	R. Andrew Morgan	Regulatory Affairs
	Mary Evelyn Towne	Regulatory Affairs
	Donna Radzik	Pharmaceutical Sciences
	Larry Miller	Pharmaceutical Sciences

The following agenda was followed:

Introductions	both	5 minutes
Overview	Medeva	10 minutes
CMC issues	FDA	50 minutes
Clinical Pharmacology issues	FDA	10 minutes
Clinical Pharmacology overview	Medeva	10 minutes
Preclinical issues	FDA	(none)
Clinical/regulatory issues	FDA	20 minutes

BACKGROUND:

A pre-meeting dossier was submitted by the sponsor on July 22, 1998. The meeting was requested in a June 26, 1998, submission.

OVERVIEW OF THE ISSUES:

After introductions, the sponsor presented an overview of the development plan and the current issues for discussion (see attachment 1).

CMC ISSUES:

Vibhakar Shah, CMC reviewer, addressed the questions posed in the pre-meeting background package. (For reference, these questions are written in italics with discussion following.)

6b. We would like to obtain the Agency's agreement/understanding of the active ingredients in this drug product and the methods for control of these materials.

1. The drug substances ("active ingredients") for codeine/chlorpheniramine polistirex ER suspension are codeine polistirex and chlorpheniramine polistirex.

2. FDA asked the sponsor to explain what causes t [redacted]. On page 34 of the pre-meeting dossier, the sponsor explains the necessity of treatment of the codeine polistirex resin with Polyethylene Glycol 3350 (PEG) [redacted] The sponsor explained that [redacted]

   FDA asked, is the codeine polistirex resin is stored for any length of time prior to the PEG treatment? The sponsor replied that PEG treatment [redacted]

3. FDA asked if the sponsor had detected the presence of any [redacted] in codeine polistirex/PEG-treated codeine polistirex. If that is so, the underlying concern is that free codeine would result in a "dumping" of codeine. FDA suggested that the

sponsor develop [redacted] and the sponsor agreed. FDA further suggested that the sponsor provide a complete release rate profile (release to [redacted] for codeine in in-process materials (e.g., PEG-treated codeine polistirex and coated codeine polistirex).

4. FDA reminded the sponsor that any impurity at levels ≥ 0.1% w/w in in-process materials/drug substance should be identified. The sponsor acknowledged this comment.

5. With reference to the *in situ* preparation of chlorpheniramine polistirex as per the flow diagram on page 53 of the pre-meeting dossier, FDA asked the sponsor to explain the rationale for [redacted] The sponsor clarified that only coated codeine polistirex [redacted] is to be used in the commercial manufacturing process. This flow diagram explains the synthesis of the clinical supplies used for pharmacokinetic studies during the developmental phase of the formulation.

6. During the manufacturing process. [redacted]

7. FDA asked if resin-bound chlorpheniramine could displace resin-bound codeine over a period of time in storage. The sponsor agreed [redacted] FDA stressed the importance that the data consistently show that [redacted] is present in the drug [redacted] from batch to batch. The sponsor questioned the necessity of a specification for [redacted] in the final product if these levels are controlled to in-process specifications throughout the process FDA replied that a

more information on the proposed test method and the Division can evaluate its utility.

2. FDA commented that the sponsor should consider measuring and reporting the particle size distribution rather than particle size. The sponsor stated that they had considered using a ——— However, due to the poor ——— properties of the viscous suspension, this method could not be utilized. The best approach for particle size determination for this product is via visual microscopy (page 57 of the pre-meeting dossier). The sponsor proposed to report ——— . FDA asked the sponsor to submit further information on the proposed method for evaluation.

3. FDA commented that the sponsor should develop an assay to quantify the amounts

4. FDA commented that the sponsor should fully characterize the release rate profile, at least until the dissolution is ———

5. For impurities and degradation products in the drug product, the Division referred the sponsor to current ICH guidelines regarding this issue. FDA asked the sponsor to include individual entry for each of the impurities/degradation products related to codeine and chlorpheniramine. A footnote may be added to indicate that a particular impurity is controlled at the raw material/drug substance level. FDA reminded the sponsor that any impurity/degradation product related to codeine or chlorpheniramine at ——— or greater should be identified. Additionally, specifications for total unspecified and total impurities for each API should also be established.

6.c.8.
We would like to obtain the Agency's guidance and agreement as to the format of the EA, possibly excluding certain items.

For guidance pertaining to the Environmental Assessment, FDA suggested that the sponsor refer to Federal Register Notes of July 29, 1997, and July 27, 1998. The sponsor acknowledged that they have these two documents.

6.c.7. & 6.c.9.c.
We would like to obtain the Agency's agreement on filing the NDA for codeine/chlorpheniramine extended-release suspension with ~ months of data in the ——— RH condition and ~ months of data in the ——— RH condition as described

in our stability protocol with data from the on-going studies to be submitted upon availability.

1. FDA prefers the submission of — months of stability data at long-term conditions (RH) and — months of stability data at accelerated conditions (RH). At the time of filing the NDA, all stability data should be generated for 3 separate batches.

2. FDA further reminded the sponsor that expiration dating for the drug product will be limited to the stability data submitted in the original NDA application and may not be extended beyond at the time of issuing an action.

(Additional CMC Comments for the sponsor)

1. With reference to codeine phosphate and chlorpheniramine maleate:

   a. FDA reminded the sponsor that any impurity/degradation product should be identified if ≥ 0.1% w/w.

   b. The sponsor should establish specifications for total unspecified and total impurities for both codeine and chlorpheniramine.

   c. The sponsor should establish specifications for residual solvents that are used in the manufacture of these two compounds rather than for the solvents that are listed in USP <467>.

   d. The proposed microbial limit must be supported with data.

   e. FDA emphasized that the proposed specifications (USP) for codeine phosphate and chlorpheniramine maleate should be supported with adequate data. Otherwise, the proposed specifications should be tightened to reflect the actual data.

   f. The sponsor should provide numerical values for the proposed specifications rather than "meets requirements."

2. FDA commented that appropriate CFR references should be provided in the NDA for the artificial cherry cream flavoring used in the suspension.

3. Regarding the [redacted] for the drug product, FDA asked that the sponsor submit appropriate authorized DMF references for all of the components of the [redacted] and provide the following:

a. [redacted]

b. [redacted]

c. [redacted]

4. FDA asked the sponsor to submit adequate responses to comments 21 and 22 of an April 10, 1998, FDA letter.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS ISSUES

Bradley Gillespie, Clinical Pharmacology & Biopharmaceutics Reviewer, presented his comments on 3 overheads (see attachment 2).

6.c.5.
We would like the Agency's agreement on the proposed dissolution method for the Quality Control of the final product.

FDA proposed that the sponsor submit a method development report in the near future, and then FDA could give the sponsor comments via teleconference so that a dissolution method can be established prior to beginning Phase 3 of development. Further, FDA referred the sponsor to dissolution methods developed for Tussionex and Delsym drug products.

7.g.
We would like to obtain the Agency's agreement/understanding as to the extended-release characteristics of chlorpheniramine polistirex equivalent to 8 mg chlorpheniramine maleate.

See attachment 2 for comments. The sponsor clarified that the pilot human pharmacokinetic data submitted in the pre-meeting background package are not intended to be pivotal data, and that pivotal pharmacokinetic assessments of the two active ingredients would be performed with human subjects. When the extended release product is compared to an

immediate release product in a bioequivalence study, comparisons should focus on area under the plasma concentration curve (AUC), fluctuation index, and trough concentrations.

7.g.
We would like the Agency's agreement on the proposed approach for the establishment of IVIVC for codeine/chlorpheniramine extended-release suspension.

See attachment 2 for comments.

(Additional Comments)

See attachment 2 for miscellaneous comments. The sponsor agreed to resubmit the protocols that were originally submitted in the pre-meeting background package, because the original copies were illegible.

PHARMACOLOGY & TOXICOLOGY COMMENTS

Luqi Pei, Pharmacology & Toxicology Reviewer, verbally conveyed one comment for the sponsor's future consideration.

The sponsor should consider the need to identify and/or qualify impurities in the drug substance, and identify and/or qualify impurities, extractables, and degradants in the drug products. With regard to the qualification of impurities and degradation products, the sponsor should refer to the ICH guidelines for additional information.

CLINICAL COMMENTS

Susan Johnson, Medical Officer, offered several clinical comments for the sponsor's consideration (see attachment 3).

1. For the basis of approval, the sponsor must establish that the drug product is either bioequivalent to an approved reference product or must demonstrate clinical efficacy and safety through well-controlled clinical trials. Also, FDA strongly encouraged that all pivotal studies be performed with the to-be-marketed formulation.

2. The marketing status of this product is in question. In general, any product which can potential be marketed as over-the-counter (OTC) must be reviewed for OTC status. The concentration of codeine in the sponsor's drug product (4 mg/mL) is greater than the upper limit for OTC codeine products (2.2 mg/mL) under the current

DEA regulations. However, the Division is unclear on whether the extended release characteristics of this drug product relate to the immediate release specifications. Since the sponsor wishes to market their product as a prescription drug product and would be unlikely to pursue development of the product further as an OTC, FDA agreed to promptly explore this issue further.

3. The sponsor's proposed cold indication for this drug product is not consistent with the current final antihistamine monograph (21 CFR 341.72). At this time, FDA would not grant the indication for cold on this basis.

4. Discussions to finalize the combination monograph are currently ongoing in the Division of Over-the-Counter Drug Products (DOTCDP). Because the combination monograph has not been finalized, the Division cannot assure the sponsor that an adequate demonstration of bioequivalence to monographed doses of immediate release codeine/chlorpheniramine product will be sufficient for approval based on the monograph determination of safety and efficacy for the combination. The Division agreed to follow up with the DOTCDP on current monograph discussions regarding codeine/chlorpheniramine combination products.

Clinical Addendum, October 5, 1998

Information provided by Gerald Rachanow in DOTCDP on October 1, 1998 clarified issues regarding items # 2 and # 4 above (clinical section). The proposed product would not be allowed under current DEA regulations (Section 1308.15 (c) (1)) to be marketed as an OTC product. Currently, DOTCDP expects that the proposed codeine/chlorpheniramine doses will remain in Category I in the final combination monograph (FM), as they are in the tentative final monograph. However, the FM may not be completed until the spring of 1999. Until its finalization, its contents cannot be confirmed.

Drs. Meyer and Johnson and Mr. Hilfiker relayed this information to the sponsor by telephone on October 5, 1998. They conveyed that the ability of the proposed product to rely on the determination of safety and efficacy in the OTC monograph would be dependent on the findings in the FM and on the sponsor's ability to show "bioequivalence," as defined by Dr. Uppoor in the EOP2 meeting. The sponsor questioned whether "they could proceed." They were told that IND 54,892 was not on clinical hold, the sponsor clarified their intention to submit modified protocols.

Attachments: (1) Opening Presentation, Medeva (HARD COPY ONLY)
(2) Clinical Pharmacology & Biopharmaceutics Comments, FDA (HARD COPY ONLY)
(3) Clinical Comments, FDA (electronic, page 11)

cc: Original IND 54,892
HFD-570/Division files
HFD-570/Hilfiker
HFD-570/Schumaker
HFD-570/Johnson/10-6-98
HFD-570/Meyer/10-6-98
HFD-570/Shah/10-16-98/10-19-98/10-21-98
HFD-570/Poochikian/10-19-98
HFD-570/Pei/10-5-98
HFD-570/Sun/10-5-98
HFD-570/Uppoor/10-1-98

Drafted by: HFD-570/David Hilfiker/9-29-98
C:\my_documents\I54892\98-09-28.min.doc

Initialed by: HFD-570/Gillespie/10-1-98

MEETING MINUTES

ATTACHMENT 3

MEDEVA PHARMACEUTICALS
EOP2 MEETING
CODEINE / CHLORPHENIRAMINE POLISTIREX

SEPTEMBER 21, 1998

CLINICAL COMMENTS

1. **BASIS OF APPROVAL**

   - **BIOEQUIVALENCE TO APPROVED REFERENCE**
     OR
   - **DEMONSTRATION OF CLINICAL SAFETY AND EFFICACY**

2. **PIVOTAL STUDIES SHOULD BE CONDUCTED WITH TO-BE-MARKETED FORMULATION**

3. **MARKETING STATUS (RX VERSUS OTC)**

   - **BIOEQUIVALENCE TO OTC PRODUCT**
   - **CONCENTRATION OF CODEINE IN FORMULATION**
   - **INCLUSION IN OTC MONOGRAPH**

4. **OTC MONOGRAPH ISSUES**

   - **SR PRODUCTS, POLISTIREX ARE NOT IN MONOGRAPH**
   - **PROPOSED COLD INDICATION IS NOT IN FINAL ANTIHISTAMINE MONOGRAPH (CFR ϕ 341.72)**
   - **TENTATIVE FINAL COMBINATION MONOGRAPH**
   - **PEDIATRIC DOSING**