021369_ ORIGINAL _ APPROVAL - PKB

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-369

Trade Name: Codeprex Pennkinetic Extended-Release Suspension

Generic Name: Codeine polistirex and chlorpheniramine polistirex

Sponsor: Celltech Pharmaceticals, Inc.

Approval Date: June 21, 2004

Indications: Provides for 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

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Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

APPROVAL LETTER

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 31710
Rochester, NY 14603-1710

Attention: Norman D. LaFrance, M.D.
Sr. Vice President, Medical and Regulatory Affairs

Dear Dr. LaFrance:

Please refer to your new drug application (NDA) dated and received April 13, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension.

We acknowledge receipt of your submissions dated June 19, July 13, August 3 and 24, October 12, November 8, and December 5, 2001, January 3, February 21 and 25, May 10, June 26, August 22 and 23, and September 2 and 27, 2002, April 25, June 9 and 16, August 11 and 18, September 25, and December 19, 2003, and June 4, 7 and 14, 2004.

The December 19, 2003, submission constituted a complete response to our February 13, 2002, action letter.

This new drug application provides for the use of Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension for the 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.

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

The final printed labeling (FPL) must be identical to, except for including the revisions indicated, the enclosed labeling (text for the package insert) and submitted labeling (immediate container label submitted June 14, 2004). These revisions are terms of the NDA approval. Marketing the product(s) before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format (pdf) effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that the labeling

content must be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for children under 6 years of age until June 22, 2007.

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

1. Deferred pediatric study under PREA for the treatment of 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 in pediatric patients under 6 years of age.

   Final Report Submission: June 22, 2007.

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

We remind you of your postmarketing study commitment in your submission dated June 4, 2004. This commitment is listed below.

2. Conduct two in vitro genetic toxicity tests (ICH Q3A) to assess the genotoxic potential of (b)(4)------

   - If genotoxicity tests are negative, a new specification for (b)(4)----- could be qualified by a 28-day toxicology study in the most appropriate species.
   - If(b)(4)------ is genotoxic, levels of b)(4)------ in the drug product should be (b)(4)---------- This may require the development of a more sensitive method for (b)(4)----- within this same time frame. Alternatively, additional testing could be performed in consultation with the Division to permit a higher level.

Protocol Submission:	received June 4, 2004
Study Start:	Upon receipt of Agency comments on proposed protocol
Final Report Submission:	by December 22, 2004

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be

prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

We also remind you of Chemistry, Manufacturing and Controls (CMC) agreements submitted June 4, 2004, and as listed below.

3. (b)(4)----------

4. ----------

5. (b)(4)----------

6. ----------

7. ----------

8. ----------

In your December 19, 2003, submission, you also agreed to perform the following.

9. (b)(4)----------

10. ----------

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary & Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified. Resubmit the updated methods validation package in duplicate, incorporating the agreed upon changes to drug substance and drug product specifications (acceptance criteria and test methods).

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

If you have any questions, call 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

Enclosure: Package Insert with minor edit

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
6/21/04 04:58:46 PM

Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

APPROVABLE LETTER

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 31710
Rochester, NY 14603-1710

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

Dear Mr. Morgan:

Please refer to your new drug application (NDA) dated April 13, 2001, received April 13, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Codeprex (codeine and chlorpheniramine) Extended Release Suspension.

We acknowledge receipt of your submissions dated June 19, July 13, August 3 and 24, October 12, November 8, and December 5, 2001, and January 3, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, it will be necessary for you to address the deficiencies listed below.

A major concern raised in our review is the assurance that you can produce a bioequivalent drug product over time. Substantial reductions in release rate of both batches used in clinical studies and stability batches for codeine and chlorpheniramine were noted over time. Our suggestions to address this and numerous other concerns follow. Please note, however, that if you need to develop a new formulation to improve your product's stability, you may also need to repeat comparative bioavailability/bioequivalence studies, depending on the level of formulation change.

1. The following comments pertain to the acceptance specifications of codeine phosphate.

   a. Provide a formal documentation/agreement between ——— and Celltech, which supports your assertion that in addition to current compendial testing, ——— will test every lot of codeine phosphate that is supplied to Celltech for residual solvents ——— and all impurities (individual specified impurity, individual unspecified, total unspecified impurities, and total impurities). Accordingly, provide the test results on an accompanying certificate of analysis (COA). Please note that similar documentation should also be submitted by ———to their Drug Master File (DMF) ———

   b. Additionally, include specifications (acceptance criteria and test methods) for residual solvents ——— and all impurities (individual specified impurity, individual unspecified, total unspecified impurities) in the acceptance specifications for codeine phosphate.

c. Any impurity at or greater than 0.1% w/w in codeine phosphate needs to be identified and qualified. At their currently proposed levels all identified impurities need to be qualified and all individual specified (other known) impurities need to be identified and qualified. Alternatively, reevaluate and tighten the proposed acceptance criteria accordingly for all identified impurities, individual specified (other known) impurities, total unspecified impurities and total impurities to be reflective of the data provided in the NDA as well as in the DMF.

d. Tighten the proposed acceptance criteria for residual solvents ——— to be reflective of the data provided in the NDA as well as in DMF —

e. Verification of the test results provided on the COA for all attributes of codeine phosphate should be performed periodically. The frequency of testing should be reflective of the lots of codeine phosphate procured annually and should be included in the specification document.

f. Provide detailed information on the container-closure system (CCS) that is being used for the storage of codeine phosphate (e.g., quantitative composition for the container, closure, liners, inner seal, desiccant, and references to applicable food additive regulations for their intended use), if it differs from the CCS in which it is shown to be stable and shipped by ———

g. Please note that the holder of the DMF ——— has been recently issued a letter for their product, ——— in support of your application.

2. The following comments pertain to the acceptance specifications of chlorpheniramine maleate.

a. Provide a formal documentation/agreement between —— and Celltech, which supports your assertion that in addition to current compendial testing, —— will test every lot of chlorpheniramine maleate that is supplied to Celltech for residual solvents ——— and all impurities (individual specified impurity, individual unspecified, total unspecified impurities, and total impurities). Accordingly, provide the test results on accompanying certificate of analysis (COA). Please note that similar documentation should be submitted by —— to their DMF —

b. Additionally, include specifications (acceptance criteria and test methods) for residual solvents (——— and all impurities (individual specified impurity, individual unspecified, total unspecified impurities, and total impurities) in the acceptance specifications for chlorpheniramine maleate.

c. Any impurity at or greater than 0.1% w/w in chlorpheniramine maleate needs to be identified and qualified. At their currently proposed levels all identified impurities need to be qualified and all individual specified (other known) impurities need to be identified and qualified. Alternatively, reevaluate and tighten the proposed acceptance criteria accordingly for all identified impurities, individual specified (other known) impurities, total unspecified impurities and total impurities to be reflective of the data provided in the NDA as well as in the DMF.

d. Tighten the acceptance criteria proposed for the residual solvents, ——— to be reflective of the data provided in the NDA as well as the in DMF ——.

e. Verify the test results provided on the COA for all attributes of chlorpheniramine maleate periodically. The frequency of testing should be reflective of the lots of chlorpheniramine maleate procured annually and should be included in the specification document.

f. Provide detailed information on the container-closure system (CCS) that is being used for the storage of chlorpheniramine maleate (e.g., quantitative composition for the container, closure, liners, inner seal, desiccant, and references to applicable food additive regulations for their intended use), if it differs from the CCS in which it is shown to be stable and shipped by ——.

g. Please note that the holder of DMF ——— has been recently issued a letter for their product, ——— in support of your application.

3. The following comments pertain to ———

a. In order to ensure consistent quality of all incoming lots of ——— provide appropriate acceptance specifications for —— *content and impurities (volatile/non-volatile)* of ——— and support the proposed specifications with adequate data (e.g., batch data, COA etc.). If —— *content* of the —— can be inferred from the ——— *capacity*, provide such information/calculation as part of the test method.

b. Provide clarification of whether the test method(s) used for the determination of —— —— is compendial. Otherwise, submit the test method(s) for the determination of —— ——— as part of the specifications. Note that the limits proposed for ——— are not reflective of the data available in the DMF.

c. As applicable, provide numerical values for the test attributes rather than "pass" or complies."

d. Note that the holder of ——— has been recently issued a letter for their —— product, ——— in support of your application.

4. The following comments pertain to drug product formulation intermediates.

a. Provide a target coating level for coated codeine polistirex in the master production record in order to assure batch to batch reproducibility, especially, in terms of release rate and bioavailability for codeine. Alternatively, demonstrate with appropriate data (in-vivo and in-vitro) that change in coating levels within —— of coating range has no effect on the release rate profile and bioavailability profile of codeine.

b. Tighten the acceptance criteria proposed for ——— individual unspecified impurities (——) and total unspecified impurities —— and total related substances —— to be reflective of the release (13 lots, v3, p 40501) and stability data (3 lots, v4, 40941) provided for PEG 3350 treated codeine polistirex.

c. Revise the proposed acceptance criteria for codeine assay to be reflective of — of the theoretical assay value of codeine bound to ~~~ resin (e.g., ———), rather than the — of the average assay value for codeine from 13 lots of PEG 3350 treated codeine polistirex.

d. Provide a clarification and supportive data for the hold-time and/or storage, if any is intended, for the coating solution prior to its use in the preparation of coated codeine polistirex.

e. Tighten the acceptance criteria proposed for ——— individual unspecified impurities, total unspecified impurities and total related substances (total impurities) to reflect the release data (10 lots, v3, p 40679) and stability data (5 lots, v4, 40969) provided for coated codeine polistirex.

f. The acceptance criteria proposed for residual solvents (NMT ——— combined both for ——————— are not reflective of the release data provided for coated codeine polistirex (10 lots, v3, p 40679). Tighten the acceptance criteria accordingly, e.g., NMT ———

g. The particle size acceptance criteria proposed for coated codeine polistirex, using ± 6 standard deviation (SD) values of the combined average % retained on ——— and through ——— sieves are not reflective of the particle size distribution (PSD) data provided on 15 lots of coated codeine polistirex (v4, pp. 40681-40685). The data indicate inadequate control and poor assurance for the reproducibility of the process. Particle size range derived using combined average % ± 2 SD may be more appropriate and reflective of the data and the process. Tighten the particle size acceptance criteria for coated codeine polistirex accordingly.

h. The codeine release rate proposed for coated codeine phosphate is too wide and is unacceptable. It is reflective of an entire coating range ——— that is applied rather than a target coating level that should be applied for the manufacture of coated codeine polistirex. Provide a codeine release rate that is reflective of a target coating level for coated codeine polistirex and support it with appropriate data. Alternatively, provide with appropriate *in vivo* data that bio-availability of codeine follows a characteristic of extended release profile over time and remains comparable irrespective of coating level range (—— ~~~) utilized for the manufacture of coated codeine polistirex.

i. Provide updated stability data for coated codeine polistirex and explain any trend, if observed, for the codeine release rate. As for the proposed acceptance criteria for codeine release rate refer to comment 4.h. above.

5. The following comment pertains to the proposed HPLC method for the assay of codeine and codeine related compounds in PEG 3350 treated codeine polistirex.

To ensure accurate quantitation of codeine and its impurities, provide a resolution factor (e.g., NLT 2.0) as a system suitability requirement between the two closest peaks eluting in the chromatogram (e.g., codeine ———————

Figure 14, v3/p 40582, Report TA 99021; Figure 13, v4/p 70775, Report TA 99022). Also provide codeine-related impurities in the system suitability solution for routine sample analysis. Revise and resubmit the method with relevant chromatograms and chemical structures of all the impurities as a part of the method.

6. The following comments pertain to the drug product formulation.

   a. Provide label claim in terms of the drug substances, codeine polistirex and chlorpheniramine polistirex that are equivalent to codeine and chlorpheniramine per 10 mL respectively, e.g., each 10 mL of the suspension contains x mg of codeine polistirex (equivalent to 40 mg of codeine) and y mg of chlorpheniramine polistirex (equivalent to 8 mg of chlorpheniramine).

   b. Note that the holder of DMF [redacted] has been issued a letter dated January 10, 2002, for their product, [redacted] in support of your application.

7. The following comment pertains to in-process controls and manufacturing operations of the drug product.

   Provide acceptance criteria for the in-process tests, assay (both for codeine and chlorpheniramine) and [redacted] at the completion of manufacturing process. Revise the master batch record BX826-01 to include specific instructions for in-process tests and document the test results within the batch record (Refer to step 48, v5, p 41317). Likewise, revise packaging batch record PX-82668-01 to include in-process tests.

8. The following comments pertain to the drug product specifications.

   a. Provide the analytical sampling plan (i.e., number of samples tested, individual/composite samples specified, number of replicate analysis per sample) and procedures implemented to ensure lot to lot quality of the drug product through its shelf life.

   b. The lower limits proposed for the assays of methylparaben [redacted] and propylparaben [redacted] through stability are not reflective of the stability data provided (v18, pp. 45082-45083). Revert these limits back to their respective release limits, i.e., [redacted] and [redacted] for methylparaben and propylparaben respectively.

   c. Revise the proposed limit for *total aerobic microbial count* to reflect the release and stability data provided in the submission, e.g., less than 100 cfu/g.

   d. Report actual numerical values rather than using phrases such as "meets," "complies," or "passes" for all quantifiable attributes of the drug product, e.g., 'L,' 'a' and 'b' values for color test criteria in the stability data.

e. The following comments pertain to the particle size specifications of the drug product.

(1) The proposal not to include particle size specification and control particle size distribution (PSD) as part of the drug product specifications is not acceptable. The extent of PSD data available in support of this proposal is limited to only 5 lots of the drug product (8027-121A, CL-99025A, CL-99026A, CL-99034A, CL-99035A), all of which are — of the commercial batch (—). Because of the observed differences (variation in data, no consistent trend) between these lots at each time point, they are not adequate to predict any trend(s) in PSD that may occur in the commercial batches. Additionally, take into consideration what will happen to the PSD on scale up (—) to commercial batch production, if PSD is not controlled tightly, as well as what effect, if any, that may be exerted on the extended release characteristics of codeine and chlorpheniramine both *in vivo* and *in vitro*. Consequently, provide appropriate particle size acceptance criteria and documentation of PSD control throughout the expiry of the drug product to ensure a consistent release profile of codeine and chlorpheniramine.

(2) As indicated in the report TA 00109, the particle size analysis by microscopy is inherently error-prone (due to, i.e., sampling, instrumentation, analyst) and very likely to introduce variation/scatter in PSD data. Additionally, it is not clear whether the variation observed in PSD data (%SD) is due to the method or the drug product. Investigate and identify the causes of the observed variability in PSD data and take appropriate measures to rectify them. Consider using more reliable and sensitive particle size analyzers that function on a quantitative approach for monitoring and controlling the PSD of a drug product.

f. The following comments pertain to the related substances (impurities) of the drug product.

(1) One photostability study result, — observed for — (Lot CL99025A, —glass bottle) does not justify the proposed acceptance criterion, NMT —, especially, when it is found at or below —, at all storage conditions while packaged in the proposed commercial container closure, an amber — bottle, for this drug product. Tighten the acceptance criteria for — to reflect its release and stability data.

(2) Given the fact that the process impurities related to codeine phosphate and chlorpheniramine maleate are not included/accounted in the total impurities of the drug product, the proposed acceptance criterion for total impurities, NMT — is not justified, especially, when it is found at or below (—, at all storage conditions. Tighten the proposed acceptance criteria for total impurities to be reflective of its release and stability data, e.g., —

(3) The proposed acceptance criteria for individual unspecified impurities (known, unknown) are not justified in view of their levels observed at release and all storage conditions (below quantifiable limit to —). Tighten the proposed acceptance criteria for individual unspecified impurities (known, unknown), to be reflective of their release and stability data.

(4) Note that any impurity (degradant) related to codeine in the drug product needs to be identified and qualified at or greater than —— , whereas, any impurity (degradant) related to chlorpheniramine in the drug product needs to be identified at or greater than — , and qualified at or greater than —— As a result, "individual unspecified impurity (no other known)" at its proposed level, —— needs to be identified and qualified and "individual unspecified (unidentified)" at its proposed level, —— , needs to be identified. Alternatively, you may consider revising the proposed acceptance criteria for these unspecified impurities.

g. The following comments pertain to codeine and chlorpheniramine release rates in the drug product.

(1) The proposed acceptance criteria for the dissolution of codeine and chlorpheniramine are not justified on the basis of *in vitro- in vivo* correlation (IVIVC) data provided only at release. Provide appropriate IVIVC data for all lots (containing different coating levels of coated codeine polistirex) beyond their release through shelf-life of the drug product to demonstrate that the percent decrease observed for codeine and chlorpheniramine release remain bio-equivalent with time (3, 6, 9, 12, 18, 24 months) and temperature storage (—— . Alternatively, in absence of such data, the release ranges observed for codeine and chlorpheniramine at release may be used as the dissolution acceptance criteria for codeine and chlorpheniramine respectively.

(2) Provide updated dissolution data for all lots. In addition to providing individual dissolution data, provide dissolution averages at each time point, both for codeine and chlorpheniramine and for all lots. Pool all the dissolution data (individual and average) at each storage conditions for each release time points (1h, 3h, 6h, 12h, 24h). In addition to the paper copy, provide an electronic copy of these data.

9. Revise the proposed post-approval stability protocol to include the following and submit the updated stability protocol.

a. Include a commitment to place and test the first three commercial scale drug product lots not only at —— (long term), but also at accelerated (—— and intermediate ——) storage conditions, if needed.

b. Indicate the storage orientations of the product placed on stability.

c. Include particle size testing as an attribute in the stability specifications.

d. Revise the proposed acceptance criteria for the lower assay limits of methylparaben and propylparaben, microbial limits, related substances, and codeine and chlorpheniramine release rates in the stability specifications as indicated by the comments 8.b., 8.c., 8.f., and 8.g. above respectively.

e. Include a commitment to placing adequate numbers of drug product lots on stability that are proportional to the number of lots manufactured per year, instead of the proposed one lot per year.

10. The following comments pertain to the test methods of the drug product.

a. Specify what other brands of analytical columns and guard columns are considered equivalent to the one that has been used and validated (e.g., phenomenex prodigy ODS 3) in each of the HPLC methods used in the analysis of various attributes of the drug substances and the drug product (e.g., for assay of codeine, chlorpheniramine maleate, methylparaben propylparaben and impurities). Provide appropriate validation data to support the equivalency of these "equivalent" columns and guard columns. Alternatively, delete reference(s) to these analytical columns (including guard columns) that have not shown to be equivalent with appropriate validated chromatographic data. This comment also pertains to all chromatographic methods (GC/HPLC) that are used in the analysis of various attributes of the drug substances and the drug product.

b. Justify the use of [redacted] of the drug product on a [redacted]

11. The following comments pertain to the container closure of the drug product.

a. Provide appropriate acceptance criterion for non-volatile residue (USP <661>) extracted in the most discriminating solvent (e.g., [redacted]) from the amber [redacted] bottle to ensure consistent quality of incoming shipments of these bottles. Support the proposed acceptance criterion for the non-volatile residue with adequate data. In the specification document, T066 (v6, p 41379), clearly specify the test attributes performed routinely on each shipment of the bottles and provide a predetermined testing schedule to verify the test results supplied on certificate of compliance accompanying each shipment of the bottle. Provide a certificate of compliance received from the supplier for the shipment of bottles that were used in the packaging of the drug product. Resubmit the revised acceptance specifications for the amber [redacted] bottle.

b. In the specification document C076 for [redacted] cap (v6, p 41391), clearly specify the tests that are routinely performed on each shipment of the caps received. Additionally, as noted in packaging specification, C076 (for the [redacted] cap), the requirement from the supplier of [redacted] cap ([redacted]), "to notify Celltech of any change in bottle mold" appears to be a mistake and needs to be corrected. Resubmit the revised acceptance specifications for the [redacted] cap.

c. Rectify the discrepancy/differences noted between the materials used in the construction of [redacted] label, as provided in the packaging specifications LR929A, LR929B, and the information provided in volume 6, pages 41375-413576 of the submission. Additionally, provide information on overlaminate ([redacted] , leaflet and top label ([redacted] and liner ([redacted] as

referenced in the specification documents. Indicate volume/page reference(s) for this information, if it is provided elsewhere in the submission.

d. Note that the holder of DMF [redacted] has been recently issued a letter concerning to their [redacted] products in support of your application.

12. Note that the statistical evaluation of the release rates both for codeine and chlorpheniramine is appropriate and critical for expiry determination. Consequently, comments pertaining to expiry dating are deferred at this time, until all other issues pertaining to drug product acceptance criteria, especially, codeine and chlorpheniramine release rates, are resolved.

13. The following comment pertains to chlorpheniramine dissolution and *in vitro –in vivo* correlation (IVIVC).

The food effect study data should be used for external validation of the IVIVC. If IVIVC is validated with this analysis, then calculate the plasma concentration time profile using convolution or other appropriate modeling techniques and determine the dissolution specification that will result in a maximal difference of 20 % in Cmax and AUC (i.e., + and – 10 % of the Cmax or AUC of the biobatch).

14. The following dissolution method/specification should be used for codeine.

Method: USP Apparatus II (Paddle), [redacted] rpm
Medium: [redacted]

Time	Biobatch (LotCL00047A) Average (range); n=12	Sponsor's proposal	Agency's recommendation
1	33 [redacted] %	[redacted]	
3	62 [redacted] %		
6	82 [redacted] %		
12	93 [redacted] %		
24	94 [redacted] %		

15. To obtain a longer shelf-life, provide data demonstrating acceptable *in vivo* performance for a batch with a significantly reduced release profile, especially for codeine for the newly requested/proposed shelf-life.

16. Submit draft labeling incorporating the following comments.

a. Following the example of your approved drug product, Tussionex Extended Release Suspension, revise the DESCRIPTION and HOW SUPPLIED Sections of the proposed labeling for this drug product. Additionally, note that the official names (USAN) for the drug substances are codeine polistirex and chlorpheniramine polistirex, not codeine or chlorpheniramine maleate respectively.

b. Express the amount of codeine polistirex and chlorpheniramine polistirex in a dose in terms of their free base equivalent, e.g., Each teaspoonful (5 mL) of the suspension contains codeine polistirex equivalent to 20 mg of codeine and chlorpheniramine polistirex equivalent to 4 mg of chlorpheniramine.

c. Revise the sentence, [redacted] to "Dispense in a well-closed container, and protect from light."

d. Replace the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection with the following.

Although studies with Codeprex [redacted] to evaluate carcinogenic, mutagenic or impairment of fertility potential have not been conducted, published data are available for the active ingredients.

Codeine

In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 8 and 20 times, respectively, the maximum recommended daily dose for adults and children on a mg/m^2 basis).

Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

Chlorpheniramine

In 2-year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 15 times the maximum recommended dose for adults and children on a mg/m^2 basis).

Chlorpheniramine maleate was not mutagenic in the *in vitro* bacterial reverse mutation assay or the *in vitro* mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the *in vitro* CHO cell chromosomal aberration assay.

In rats and rabbits, oral doses of chlorpheniramine maleate up to approximately 20 and 25 times the human dose on a mg/m^2 basis, respectively, did not impair fertility.

e. Replace the second and third paragraphs of the "Pregnancy: Teratogenic Effects: Pregnancy Category C" subsection with the following.

Codeine

In a study in which pregnant rats were dosed throughout organogenesis, an oral dose of 120 mg/kg/day (approximately 10 times the maximum recommended daily dose for adults on a mg/m^2 basis) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, oral doses up to 30 and 600 mg/kg/day, respectively (approximately 6 and 30 times, respectively, the maximum recommended daily dose for adults on a mg/m^2 basis), produced no adverse developmental effects.

Chlorpheniramine

In studies in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 20 and 25 times the maximum recommended daily dose for adults on a mg/m 2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, an oral dose of 20 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m^2 basis) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed prior to mating with 10 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m^2 basis).

A retrospective study found a small but statistically significant association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

There are no adequate and well-controlled studies in pregnant women. Codeprex ——— should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

f. Replace the first sentence of the fourth paragraph of the OVERDOSAGE Section with the following.

Oral lethal doses of chlorpheniramine maleate were 130, 306 and 198 mg/kg in mice, rats and guinea pigs, respectively (approximately 35, 170 and 150 times, respectively, the maximum recommended daily dose for adults and children on a mg/m^2 basis).

g. The INDICATION AND USAGE Section states that "Codeprex ——— is indicated for the temporary relief of ——— cough, and runny nose, sneezing, itching or the nose or throat, and itchy watery eyes, as may occur with the

common cold, inhaled irritants, hay fever, or other respiratory allergies." [Volume 1.1, page 3.0005]

Your application is being submitted under Section 505(b)(2) of the FD&C Act, and this application relies on the Agency's previous findings of safety and efficacy of the active drugs as described in the appropriate OTC monographs. Therefore, labeling should reflect OTC monograph labeling. The proposed indication and usage section combines OTC monograph language for antitussive and antihistamine drug products. However, the common cold indication is appropriate for the antitussive product, but not for the antihistamine product. An example of acceptable language for this section follows:

> "Codeprex ——————— is indicated for the 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 respiratory allergies, or allergic rhinitis." [21 CFR 341.72, 21 CFR 341.74].

h. 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.

i. The DRUG ABUSE AND DEPENDENCE Section should state that Codeprex is a controlled narcotic in Schedule III of the Controlled Substances Act (CSA).

j. Abuse of Codeprex 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 Codeprex formulation will be listed in C-III, codeine substance is a C-II narcotic. In the subsection on dependence, the words "——————— should be deleted. The warning should state as follows:

> "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."

Please also include in this section a description of neonatal withdrawal (as described earlier in comment "h").

17. Submit draft carton and container label incorporating the following comment.

a. Change the word "DOSAGE" to "———————

b. 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. The expression of strength should 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

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. Additionally, more detailed labeling comments will be provided prior to approval of the application.

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.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/

Marianne Mann
2/13/02 03:20:04 PM
Signing as Acting Director in the absence of Dr. Meyer.