Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

CHEMISTRY REVIEW

Chemist NDA Review

REVIEW OF CHEMISTRY MANUFACTURING & CONTROLS

NDA No.: N 21369
CHEM. REVIEW: #1

REVIEW COMPLETION DATE: January 18, 2002
REVIEW CHEMIST: Vibhakar Shah, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	COMMENT
Original Submission*	April 13, 2001	April 13, 2001	April 18, 2001	19 CMC Volumes
Amendment (BZ)*	August 03, 2001	August 06, 2001	August 06, 2001	Stability data in electronic format
Amendment (BC)*	November 08, 2001	November 16, 2001	November 19, 2001	
Amendment (BC)*	January 03, 2002	January 10, 2002	January 16, 2002	

* **Subjects of this review**

NAME & ADDRESS OF APPLICANT:

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

Tel: (716) 475-9000
Fax:

DRUG PRODUCT NAME:

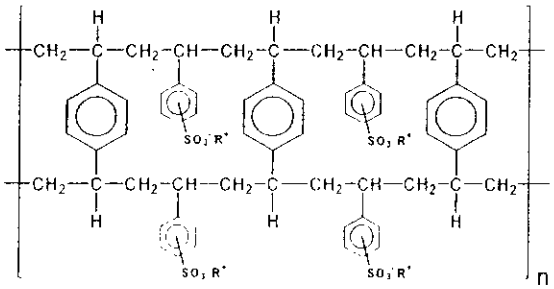
Proprietary: Codeprex™ Extended Release Suspension
Nonproprietary/USAN: Codeine polistirex/chlorpheniramine polistirex Extended Release Suspension
Code Name/#: Not applicable
Chemical Type/Therapeutic Class: **4S**
NDA Type: **505 (b)(2)**

PHARMACOLOGICAL CATEGORY:

Indication: Cough and upper respiratory symptoms associated with allergy or a cold
Dosage Form: Oral suspension
Strengths: 40 mg codeine and 8 mg chlorpheniramine per 10 mL (2 teaspoons)
Daily Dose/Maximum Daily Dose:
Adults & adolescents (ages ≥12 yr): 10 mL every 12 hours, not to exceed 20 mL (4 teaspoonfuls in 24 hours)
Children (Ages 6-12 yr): 5 mL every 12 hours, not to exceed 10 mL (2 teaspoonfuls in 24 hours)
Route of Administration: Oral

Dispensed as: Rx ☒ OTC ☐
SPECIAL PRODUCTS: Yes ☐ No ☒

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



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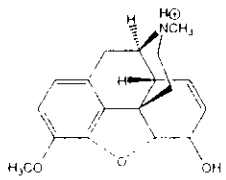
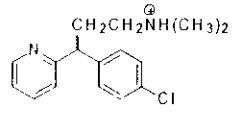


Codeine cation



Chlorpheniramine cation

Codeine polistirex and chlorpheniramine polistirex (USAN 2000, p 155, p 186)

Name: Sulfonated styrene-divinylbenzene copolymer complexed with (5 α, 6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol and 2-[p-chloro- α-(-2-dimethylamino) ethyl]-benzyl pyridine

Molecular Formula: None available/Not applicable **CAS Registry No**: None available

Molecular Weight: None available/Not applicable

SUPPORTING DOCUMENTS:

A. DMFs:

DMF/Type	DMF Holder	Subject	LOA Date	Status	Reference/Comment
DMF Type II			11-04-1997	**Inadequate**	Refer to p 13 of this Review. Information requested.
DMF Type II			10-23-1997	**Inadequate**	Refer to p 19 of this Review Information requested.
DMF Type II			05-25-1998	**Inadequate**	Refer to p 22 of this Review Information requested.
DMF Type III			03-26-2001	**Inadequate**	Refer to p 79 of this Review Information provided in NDA hence considered adequate.
DMF Type III			02-28-2001	**Inadequate**	Refer to p 79 of this Review Information provided in NDA hence considered adequate.
DMF Type III			02-09-2000	Inadequate	Refer to p 82 of this Review Information requested.
DMF Type III			11-22-2000	**Inadequate**	Refer to p 82 of this Review Information provided in NDA hence considered adequate.
DMF Type III			02-16-2000	**Inadequate**	Refer to p 82 of this Review Information provided in NDA hence considered adequate.
DMF Type IV			11-21-2000	**Inadequate**	Refer p 50 of this review. Deficiency Letter issued, 01-10-2002.
DMF Type III			02-22-2000	**Inadequate**	Refer to p 82 of this Review Information provided in NDA hence considered adequate.
DMF Type III			01-26-2001	**Inadequate**	Refer to p **Error! Bookmark not defined.** of this Review Information provided in NDA hence considered adequate.
DMF Type III			01-30-2001	**Inadequate**	Refer to p 86 of this Review Information provided in NDA hence considered adequate.
DMF Type III			02-01-2001	**Inadequate**	Refer to p 85 of this Review Information provided in NDA hence considered adequate.
DMF Type III			03-13-2001	**Adequate**	Refer to p 90 of this review Letter issued, 01-10-2002.

Date Format: MM-DD-YYYY

B. INDs/NDAs:

The following Investigational New Drug Application (IND) has been specified by the applicant in support of this application.

IND 54892 Dec 22, 1997 Codeine Polistirex/Chlorpheniramine maleate Extended Release suspension

RELATED DOCUMENTS (if applicable):
The following NDAs involving similar drug release mechanism for a single drug substance or combination of two drug substances, are approved by the Division of Pulmonary and Allergy Drug Products (HFD-570).

NDA #	Status	Date	Sponsor	Drug Name
19111	AP	Dec 31, 1987	Celltech Pharm.	Tussionex extended release suspension (hydrocodone polistirex, chlorpheniramine polistirex)
18658	AP	Oct 08, 1982	Celltech Pharm.	Delsym extended release suspension, (Dextromethorphan polistirex)

CONSULTS:

Consult	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	07- 17 - 2001	Acceptable 01-16-2002	Refer to p 107 of this review.
2. Microbiology (HFD-160)		Not required.	Refer to p 91 of this review.
3. Pharmacology (HFD-570)		-	Consult to evaluate proposed specification for impurities is **withheld** until all issues related to these impurities are resolved . Refer to p 66 of this review.
4. Biometrics		-	Withheld until issues pertaining to dissolution specification are resolved. Refer to p 105 of this review.
5. Methods Validation		Pending	See p 106 of this review.
6. Labeling & Nomenclature (OPDRA/HFD-400)	08-14-2001	pending	Refer to **section VI**/p 107 of this review
7. Environmental Assessment	-	Acceptable	Applicant has claimed categorical exclusion for the requirement of EA under 21 CFR § 25.31(a) Refer to p 106 of this review (v18, p 4-5365 of the submission).

CR = Chemist Review; Date format: MM-DD-YYYY

REMARKS/COMMENTS: See attached Review Notes

CONCLUSIONS & RECOMMENDATIONS:

Several CMC deficiencies have been found in this NDA 21369 and other supporting drug master files. Pertinent DMF holders have been notified of comments respective to their products. Consequently, the NDA 21369, submitted by Celltech Pharmaceuticals, Inc. for Codeine polistirex/chlorpheniramine polistirex Extended Release Suspension can not be approved until all the CMC issues contained in the draft letter and supporting DMFs are resolved. The comments which are listed on page 109 of this review should be forwarded to the applicant.

Vibhakar J. Shah, Ph.D.
Review Chemist, DNDCII (HFD-820)

cc:

☒ Org. NDA 21369	☒ HFD-570/Chemist/VShah	☒ HFD-570/TL/Gpoochikian
☒ HFD-570/Division File	☒ HFD-570/CSO/CYu	

R/D Init by: GPoochikian/
Document: n21369CR1.doc (Total pages = 122)
Filename: C:\C-5053847(E)\CMCReviews\NDAs\N21369\n21369CR1.doc

NOT APPROVABLE

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

CHEMISTRY REVIEW

NDA 21369

Codeprex® (codeine polistirex and chlorpheniramine polistirex) Extended Release Suspension

Celltech Pharmaceuticals, Inc.

Vibhakar Shah, Ph.D.
Division of Pulmonary and Allergy Drug Products
HFD-570

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-369

2. REVIEW Number: 2

3. REVIEW DATE: June 16, 2004

4. REVIEWER: Vibhakar Shah, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	April 13, 2001
Amendment (BZ)	August 03, 2001
Amendment (BC)	November 08, 2001
Amendment (BC)	January 03, 2002
Chemistry Review –1	January 21, 2002
Approvable Letter	February 13, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment (AZ)	December 19, 2003
Amendment (BZ)	June 04, 2004
Amendment (BC)	June 07, 2004

7. NAME & ADDRESS OF AP7PLICANT:

Name: Celltech Pharmaceuticals Inc.
Address: 755 Jefferson Road
P.O. Box 31766
Rochester, NY 14603-1766
Representative: Mary Evelyn Towne
Telephone: (716) 475-9000; Fax: 585-272-3952

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: Codeprex™ Extended Release Suspension

b) Non-Proprietary Name (USAN): Codeine polistirex and chlorpheniramine polistirex extended release suspension

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) of the FD&C Act

10. PHARMACOL. CATEGORY: Antitussive (Codeine), Antihistamine (chlorpheniramine)

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 20 mg codeine and 4 mg chlorpheniramine per 5 mL (1 teaspoon)

13. ROUTE OF ADMINISTRATION: Oral

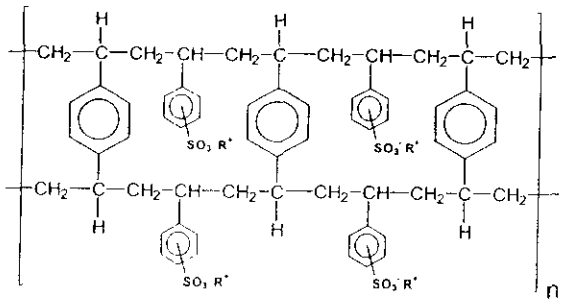
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Sulfonated styrene-divinylbenzene copolymer complexed with (5α, 6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol and 2-[p-chloro-α-(-2-dimethylamino) ethyl]-benzyl pyridine



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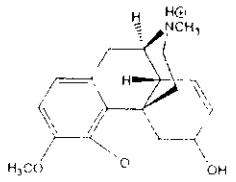
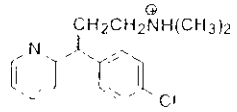


Codeine cation



Chlorpheniramine cation

Chemistry Review Data Sheet

Codeine polistirex and chlorpheniramine polistirex (USAN 2000, p 155, p 186)

Molecular Formula: None available/Not applicable **CAS Registry No:** None available
Molecular Weight: None available/Not applicable

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS[3]
	II			1	**Adequate**	See p 21 of this Review
	II			3	**Adequate**	See p 28 of this Review
	II			1, 3	**Adequate**	See p 31 of this Review
	III			1, 4	**Adequate**	See p 79 of this Review
	III			1, 4	**Adequate**	See p 79 of this Review
	III			1, 4	**Adequate**	See p 82of this Review
	III			-	-	No longer used
	III			1, 4	**Adequate**	See p 82 of this Review
	III			1, 4	**Adequate**	See p 82 of this Review
	III			3, 4	**Adequate**	See p 82 of this Review
	IV			1	**Adequate**	See p 42 of this Review
	III			1	**Adequate**	See p 82of this Review
	III			1, 4	**Adequate**	See p 87 of Chem.Rev-1
	III			-	-	No longer used
				-	-	No longer used
	III			1	**Adequate**	See p 84 of this Review

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 54892	Celltech	Codeine Polistirex/Chlorpheniramine maleate Extended Release suspension	-	Dec 22, 1997	-

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	19111	Celltech Pharm.	Tussionex (hydrocodone polistirex, chlorpheniramine polistirex) extended release suspension, Approved
NDA	18658	Celltech Pharm.	Delsym (Dextromethorphan polistirex) extended release suspension

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Expiration dating period evaluation	-	-	None initiated as the requested 18M expiry dating period is supported by real-time stability data.
EES	Prior Approval GMP Inspection	01-23-2004	Acceptable 04-28-2004	All facilities were found acceptable by OC (HFD-322) from GMP perspective
Pharm/Tox	Safety evaluation of [redacted] at NMT [redacted] in the drug product	04-22-2004	Complete T. Robison 05-21-2004 06-09-2004	Per Division's recommendation Celltech has agreed to qualify [redacted] as phase IV studies. Refer to p 58 & 95 of this review
Bio-pharm	-	-	-	-
DMETS/LNC (HFD-420)	Codeprex ® Trade name and Labeling	02-12-2004	Acceptable Charles Hoppes	Refer to DMETS Rev. dated 04-28-04 by Charles Hoppes (HFD-420)
Methods Validation	Verification of the test methods	Pending	-	To be forwarded to FDA Lab subsequent to the NDA approval
EA	Categorical exclusion as per 21CFR25.31(a)		Acceptable	See p 106 of Chem. Rev-1 for this NDA
Microbiology	-	-	-	Not required

The Chemistry Review for NDA 21-369

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be **approved** from a CMC perspective with an expiration dating period of 18 months for the drug product stored at controlled room temperature, not to exceed 25°C (77°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Several post-approval agreements have been accepted by the applicant and the Agency (amendment dated June 04, 2004) for continuous improvement and quality assurance of the drug product. These CMC agreements include: to submit a prior approval supplement to finalize

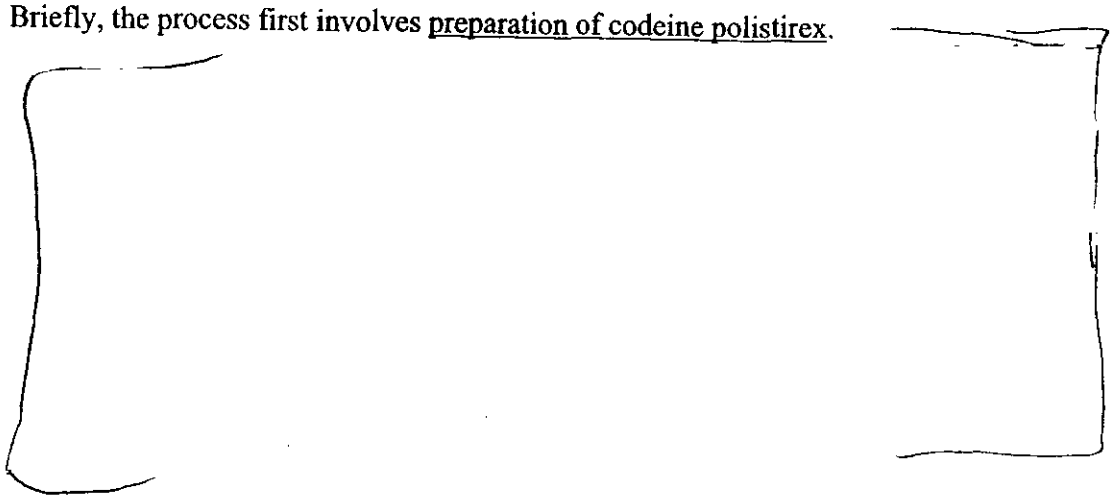
In addition to the agreements of June 04, 2004 amendment, the commitments made by Celltech to be fulfilled as specified within the December 19, 2003 submission and comments listed on page 102 of this review should be communicated to Celltech either in the action letter or in a separate letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Codeprex (Codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension is a pink to purple-pink colored, cherry cream flavored, aqueous oral suspension containing codeine polistirex, chlorpheniramine maleate and excipients. For the extended release characteristics of the suspension, the formulation employs ion exchange resin for the binding of a drug to resin and a water insoluble semi-permeable membrane (ethyl cellulose) coating.

Briefly, the process first involves preparation of codeine polistirex.



Manufacture of Codeine/chlorpheniramine extended-release suspension:

The finished drug product is tested and released by Celltech Pharmaceuticals, Inc., which is also the site where the post-approval stability studies will be conducted.

One of the major review issues focused on the test method and acceptance criteria for drug release from this complex extended release combination drug product. In their 12/19/03 resubmission, the applicant proposed an inappropriate media replacement approach which in effect, for drug release from the cation exchange resin. After substantial discussion with the applicant, the original method was accepted to be used but with more appropriate acceptance criteria.

Another substantial review issue centered around the acceptance criterion for (a degradant) which has a structural alert moiety common to many opiates. Through in-depth discussions with the applicant and in collaboration with the Toxicology review team, it was determined that an 18 month shelf-life is acceptable provided the applicant restrict the storage condition to "Controlled room temperature, not to exceed 25°C (77°F). This risk-based approach ensures the quality and safety of the drug product without increased manufacturing burden or excessively short expiry dating.

B. Description of How the Drug Product is Intended to be Used

The drug product is for oral use only. It is intended 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.

The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours.

The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years.

The drug product is granted an expiration dating period of 18 months with storage at controlled room temperature not to exceed 25°C (77°F).

C. Basis for Approvability or Not-Approval Recommendation

In the first review cycle, this NDA was recommended an *approvable* action from CMC viewpoint because of its failure to demonstrate consistent dissolution/release profile of codeine and chlorpheniramine on storage (25°C/40% RH) over time (Shelf-life of the drug product). Additionally, from Bio-Pharm review (Young Moon, Choi, Ph.D.) it was noted that the drug product has failed to establish IVIVC for codeine, and to validate the IVIVC for chlorpheniramine.

Since then applicant implemented several improvements in the manufacturing process (see p 37 of this review) including a very narrow target coating range ——— for the coating of PEG-treated codeine polistirex with ethyl cellulose to produce a stable, reproducible and predictable suspension that does not change significantly over time. In addition, the applicant conducted a bio-study (PK/PD) on a commercial scale lot (——— to demonstrate extended release characteristics in-vivo without any dose dumping within first few hours of the administration of the drug product. Applicant also used bio-batch to establish in-vitro dissolution specifications.

Because of implementation of these manufacturing changes and the proposed drug product controls, all issues related to drug product performance, especially with inconsistent dissolution profile during stability studies have been adequately addressed. The stability data show consistent and comparable dissolution/release profile both for codeine and chlorpheniramine between three primary stability lots and one bio-batch. All attributes of the drug product except for the formation of degradation product ——— remain within their respective acceptance criteria range and do not show any significant trend impacting adversely on the performance of the drug product.

As per the Pharm-Tox reviewer, ———is believed to have a genotoxic potential to react to DNA. At this time no information is available on its genotoxic potential. Celltech has committed to conduct safety and qualification studies as phase-IV commitment within 6 months of the NDA approval. In the interim, Pharm-Tox Reviewer has recommended that ——— be

controlled at the lowest possible level in the drug product that is technically feasible, i.e., NMT [redacted] (LOQ). Celltech has agreed to control [redacted] at NMT [redacted] and has revised its acceptance criterion to NMT [redacted] in the drug product. Stability data provided to-date for 3 primary lots (18 months) and one bio-batch [redacted] stored at 25°C/40% RH show that [redacted] remains fairly constant and below [redacted] at all testing intervals. Based on these data, Celltech has requested expiration dating period of 18 months with product storage at 25°C and allowing excursions to [redacted] However, since we do not know the effect of high temp excursions on the rate of production of [redacted] the storage condition may NOT exceed the stability storage condition of 25°C.

Considering the extensive marketing experience of codeine, the intended short-term use of the drug product (e.g., generally less than 7 days), [redacted] being a known impurity of codeine and present at unknown levels in several other (marketed) codeine drug products, and that [redacted] levels remain relatively constant and below LOQ [redacted] through 18 months in this drug product, it is reasonably safe to extend the expiration dating period from [redacted] to 18 months as long as the product is stored at controlled room temperature not to exceed 25°C (77°F).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date:	Vibhakar Shah, Ph.D., June 16, 2004
Chemistry Team Leader Name/Date:	Rik Lostritto, Ph.D., June 16, 2004

C. CC Block

☒ Org. NDA 21369
☒ HFD-570/Division File
☒ HFD-570/Chemist/VShah
☒ HFD-570/CSO/CYu
☒ HFD-570/TL/RLostritto

R/D Init by: R. Lostritto/ _____
Document: N21369CR2 (Total pages = 111)
Filename: C:\CData\CMCReviews\NDAs\N21369\N21369DFS\N21369CR2.doc

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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21369/000**
Stamp: **13-APR-2001** Regulatory Due: **13-FEB-2002**
Applicant: **CELLTECH PHARMS**
755 JEFFFERSON RD
ROCHESTER, NY 146031710

Priority: **3S** Org Code: **570**
Action Goal: District Goal: **15-DEC-2001**
Brand Name:

Established Name:
Generic Name: **CODEINE/CHLORTHENIRAMINE E-R SUSPENSION**
Dosage Form: **SUS (SUSPENSION)**
Strength: **40MG/8MG PER 10 ML**

FDA Contacts:

C. YU	**(HFD-570)**	**301-827-1050**	**, Project Manager**
V. SHAH	**(HFD-570)**	**301-827-1050**	**, Review Chemist**
G. POOCHIKIAN	**(HFD-570)**	**301-827-1050**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 16-JAN-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1314625**
CELLTECH PHARMACEUTICALS IN(
755 JEFFERSON RD
ROCHESTER, NY 146031710

DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **31-DEC-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **31-OCT-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-DEC-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
