CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208085Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 109251

MEETING MINUTES

ECI Pharmaceuticals, LLC
5311 N.W. 35th Terrace
Fort Lauderdale, FL 33309

Attention: John S. Copanos, CEO/President

Dear Mr. Copanos:

Please refer to your Pre-Investigational New Drug Application (PIND) file for hydrocodone and guaifenesin.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2011.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	February 25, 2011; 1:00-2:00 PM EST
Meeting Location:	White Oak 22; Conference Room 1419
Application Number:	109251
Product Name:	Hydrocodone and Guaifenesin IR Solid Oral Dose
Indication:	Symptomatic relief of cough, to (b) (4) loosen (b) (4)
Sponsor/Applicant Name:	ECI Pharmaceuticals, LLC
Meeting Chair:	Lydia Gilbert-McClain, M.D., Deputy Division Director
Meeting Recorder:	Philantha M. Bowen, MPH, RN., Sr. Regulatory Management Officer

FDA ATTENDEES

Office of Drug Evaluation II

Lydia Gilbert-McClain, M.D., Deputy Division Director, Division of Pulmonary, Allergy, and Rheumatology Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Durmowicz, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Xu Wang, M.D., Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drug Quality Assessment

Alan Schroeder, Ph.D., Acting Quality Lead, Division of New Drug Quality Assessment III, Branch VIII

Office of Clinical Pharmacology

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

SPONSOR ATTENDEES

ECI Pharmaceuticals

John S. Copanos, CEO/President

Solomon Goll, MS, MBA, Director of Quality

Consultants

(b) (4) Regulatory and Toxicology Consultant

(b) (4)., Regulatory Consultant, Quality Regulatory Consultants

Elaine B. Taylor, Senior Regulatory Consultant, Regulatory Consulting & Submissions, Kendle International, Inc.

Kathryn Wekselman, Ph.D., RN, Director, Regulatory Consulting & Submissions, Kendle International, Inc.

1.0 BACKGROUND

ECI Pharmaceuticals submitted a meeting request dated June 23, 2010. Upon review of the briefing document submitted on August 21, 2010, the Division cancelled the meeting, but provided preliminary comments in a facsimile dated September 21, 2010. ECI submitted a subsequent meeting request and package dated December 16, 2010, which included previously addressed questions; however, requested that the Division provide responses to only the questions in bold font. In a facsimile dated February 24, 2011, the Division responded to only the bolded questions, thus numbered accordingly, in ECI's briefing document.

ECI's requested a Pre-IND meeting to obtain the Agency's guidance on their drug development program for a hydrocodone/guaifenesin immediate release product and the necessary requirements and studies to support a 505(b)(2) NDA.

For the purposes of this meeting, ECI provided the Agency with the questions that warranted further discussion and clarification at the meeting. During the meeting, ECI presented their comments and questions as written in the attached document (refer to Section 5.0 of the Meeting Minutes). Any discussion that took place at the meeting is captured in section 2.0 including any changes in our original position. ECI's questions are in ***bold italics***; FDA's response is in *italics*; and the discussion is in normal font.

2.0 QUESTIONS AND DISCUSSION

2.1 Regulatory/Clinical

QUESTION 2:

Is the Agency in agreement with Tussigon as the reference listed drug for hydrocodone?

FDA Response:

Yes, we concur.

Discussion:

There was no discussion on question 2.

QUESTION 3:

Is the Agency in agreement with ECI relying on the OTC monograph for the efficacy and safety of guaifenesin in their drug product?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 3.

2.2 Non-clinical

QUESTION 6:

Does the Agency confirm that no additional non clinical studies are needed for this hydrcodone/guaifenesin drug product providing that the total intake, with the exception of (b) (4) for impurities and degradants with structural alerts does not exceed (b) (4) mcg/day and the levels of impurities and degradants do not exceed the ICH Qualification Thresholds for drug substances [ICHQ3A (R2) and drug product ICH Q3B (R2)]?

FDA Response:

We agree that no additional nonclincal studies are required, provided that the total intake, with the exception of (b) (4), for impurities and degradants with structural alerts, does not exceed (b) (4) mcg/day and the levels of impurities and degradants do not exceed the ICH Qualification Thresholds for drug substances [ICHQ3A (R2) and drug product ICH Q3B (R2)].

Discussion:

There was no discussion on question 6.

2.3 Clinical Pharmacology/Clinical

QUESTION 7:

ECI Pharmaceuticals plans to conduct a single dose, 4-way crossover comparative bioavailability/bioequivalence study that will include an evaluation of the food effect. Does the Agency agree that this study will:

- ***a. establish the necessary bridge to the hydrocodone RLD?***
- ***b. establish the necessary bridge for the guaifenesin component?***
- ***c. meet the requirements for evaluating a food effect for this drug product?***

FDA Response:

Your proposed studies will be adequate to support the NDA filing. Whether the results are acceptable will be a review issue. We noticed a (b) (4) *day washout period in your proposal. We recommend that you provide adequate data to support that the washout time is long enough, such that there is no carryover effect in this 4-way cross-over study.*

Discussion:

ECI requested that the Division clarify the concern regarding the (b) (4) day washout period, as well as provide insight into the type of data that would be needed to support this specific period. At this time, the Agency does not have a specific requirement regarding the length of a washout period, since this depends on the half-life of the drug. If ECI is able to provide sufficient data to support that no drug carryover exists during the proposed washout period, then their approach may be acceptable; however; this will be a NDA review issue.

QUESTION 8:

Does the Agency agree that the proposed clinical development program is acceptable for registration and no additional efficacy and safety studies are required for this hydrocodone 5 mg/guaifenesin 400 mg drug product?

FDA Response:

We agree that no additional efficacy and safety studies would be required for the proposed drug product to support efficacy and safety in the adult (18 years of age and older population) , provided that the product demonstrates bioequivalence to the RLDs in clinical pharmacology studies; however, additional studies will be necessary to support efficacy and safety of the product in the pediatric population (Refer to the response to question 13).

Discussion:

There was no discussion on question 8.

QUESTION 9:

Does the Agency agree with the choice of dosage for the hydrocodone/guaifenesin product?

FDA Response:

We agree with the choice of dosage for the adult population (18 years of age and older). Also, refer to the response to Question 13.

Discussion:

There was no discussion on question 9.

2.4 Chemistry, Manufacturing, and Controls

QUESTION 10:

Does the Agency agree that the proposed excipients in the oral tablet formulation are acceptable?

FDA Response: The excipient quantities in the proposed formulation appear to be acceptable. Include the following in your IND submission:

- *A representative certificate of analysis for each excipient. Indicate the specific grade (e.g., K30, (b) (4)) of povidone to be used;*
- *Indicate target weights for each ingredient in your drug product composition rather than only ranges;*
- *The drug product composition appears to vary depending on the source of guaifenesin granules to be used. Submit the exact quantitative composition(s) of the drug product to be used in clinical studies.*
- *Complete compositions of the guaifenesin granules; and*
- *Since the guaifenesin granules (b) (4) full CMC information should be provided for them that is appropriate to the IND phase.*

Discussion:

There was no discussion on question 10.

QUESTION 11:

Does the Agency agree that the Chemistry, Manufacturing and Controls information on the hydrocodone/guaifenesin drug product is adequate to open an IND and conduct a clinical study?

FDA Response:

No, we do not agree. The drug substance DMFs will be evaluated for safety once you provide appropriate letters of authorization and submit the IND. It appears that you have not yet developed your drug product and the information which you have submitted is primarily a discussion of proposed drug development plans. We will evaluate the safety of your proposed drug product once adequate information has been provided as part of your future IND. Refer to the CMC comments which we have previously sent to you in our facsimile dated September 21, 2010. Submit sufficient CMC information as per the above-mentioned comments, to support the safety of your proposed drug product in the IND studies.

Discussion:

(b) (4)

QUESTION 12:

Does the Agency have any additional concerns about the proposed drug product?

FDA Response:

Refer to the response to Question 11.

Discussion:

There was no discussion on question 12.

2.5 General

QUESTION 13:

Does the Agency have any issues that ECI has not addressed in the meeting package with regard to using hydrocodone as an antitussive in this drug product?

FDA Response:

(b) (4)

(b) (4)

QUESTION 14:

Does the Agency have any issues that ECI has not addressed in the meeting package with regard to using guaifenesin as an expectorant in this drug product?

FDA Response:

Refer to the response to Question 13.

Discussion:

There was no discussion on question 14.

QUESTION 15:

Does the Agency have any issues that have not been addressed in the meeting package with regard to the combination of hydrocodone/guaifenesin?

FDA Response:

Refer to the response to question 13.

Discussion:

There was no discussion on question 15.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no action items for this meeting.

5.0 ATTACHMENTS AND HANDOUTS

ECI Pharmaceuticals, in an email correspondence dated February 25, 2011, provided a document containing their rationale and position on selected questions for discussion during the meeting.

From: Taylor.ElaineB@kendle.com

Sent: Friday, February 25, 2011 11:35 AM
To: Bowen, Philantha
Subject: ECI meeting 1 PM today

Dear Ms. Bowen

On behalf of ECI Pharmaceuticals, we would like to provide you with an indiction of the topics we would like to discuss with the Division of Pulmonary, Allergy and Rheumatology Products at the meeting scheduled for 1:00 PM today.

ECI will be requesting clarification of several points in the CMC and clinical areas.

Question 11:

With respect to CMC, ECI would like to clarify several points with regard to batch sizes.

First, is the acceptable batch size affected by the fact that one of the active ingredients is a controlled substance?

Second, since the expected development program for the proposed hydrocodone/guaifenesin drug product is of short duration, ECI would like some clarification of acceptable batch sizes for the NDA.

Last, ECI would like some clarification of packaging requirements of the IND and NDA drug lots, with regard to stability. Will it be required to package each one of the 3 NDA drug lots in all of the commercial packaging configurations?

Question 7:

With respect to the proposed 4-way crossover pharmacokinetic study, the Division commented that the proposed (b) (4) day wash-out period will need to be supported by adequate data. ECI would like some clarification of the Division's concern with the wash-out period, as well as what data would adequately support the wash-out period,

Question 13:

With respect to the Division's comments on pediatric requirements, ECI would like clarification of several points.

(b) (4)

(b) (4)

With respect to the

Elaine B. Taylor

Senior Regulatory Consultant

Regulatory Consulting & Submissions

Kendle International, Inc.

441 Vine Street, Suite 500, Cincinnati, OH 45202, United States

(Phone) 513.345.4097, (Fax) 513.763.7628

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

/s/

PHILANTHA M BOWEN
03/23/2011