

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207975Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207975

SUPPL # n/a

HFD # 170

Trade Name **VANTRELA ER tablets**

Generic Name **hydrocodone bitartrate extended-release tablets**

Applicant Name **Teva Branded Pharmaceutical Products R & D, Inc.**

Approval Date, If Known 1/17/17

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 questions 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)(1)

b) 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:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

d) 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 Written 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#	020716	Vicoprofen (hydrocodone and ibuprofen)
NDA#	206627	Hysingla (hydrocodone)
NDA#	202880	Zohydro ER (hydrocodone)
NDA#	022279	Hycofenix (hydrocodone, guaifenesin, and pseudoephedrine)
NDA#	205474	Obredon (hydrocodone and guaifenesin)

And various other NDA and ANDAs.

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.)

☒ **N/A** YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 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 NDAs 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:

3079: *A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 15 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Osteoarthritis or Low Back Pain Who Require Opioid Treatment for an Extended Period of Time*

3103: *A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 30 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time*

1085: *A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Abuse Potential of the Hydrocodone Bitartrate Extended-Release Tablet in Healthy, Nondependent, Recreational Opioid Users*

10032: *A Single-Dose, Double-Blind, Randomized Crossover Study to Assess the Intranasal Pharmacokinetics, Abuse Potential and Safety of CEP-33237 in Healthy, Nondependent, Recreational Opioid*

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 ☒

Investigation #3 YES ☐ NO ☒

Investigation #4 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 ☒

Investigation #3 YES ☐ NO ☒

Investigation #4 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"):

3079: *A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release*

3103: *A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 30 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time*

10032: *A Single-Dose, Double-Blind, Randomized Crossover Study to Assess the Intranasal Pharmacokinetics, Abuse Potential and Safety of CEP-33237 in Healthy, Nondependent, Recreational Opioid*

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 #2 (Study # 3103) !
IND # 105587 **YES** ☒ ! NO ☐
! Explain:

Investigation #3 (Study # 1085)

IND # 105587 **YES** ☒ **! NO** ☐

! Explain:

Investigation #4 (Study # 10032)

IND # 105587 **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 ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! 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:

=====

Name of person completing form: Kimberly Compton
Title: Sr. Regulatory Project Manager
Date: 11/7/15, updated 8/22/16, updated 1/10/17

Name of Division Director signing form: Sharon Hertz, MD

Title: Director, DAAAP (See electronic signature block)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KIMBERLY A COMPTON
01/16/2017

SHARON H HERTZ
01/17/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207975	NDA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: VANTRELA ER Established/Proper Name: hydrocodone bitartrate Dosage Form: extended-release tablets		Applicant: Teva Branded Pharmaceutical Products R & D, Inc.
RPM: Kim Compton		Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>10/23/15</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☒ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☒ MedGuide
☐ Communication Plan
☒ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s): AP, 1/17/17

Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	3/2/15
• Review(s) <i>(indicate date(s))</i>	2/25/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☒ None DMEPA: ☐ None 3/12/15 DMPP/PLT: ☐ None 4/27/16 and 9/30/15 OPDP: ☐ None 12/13/16 and 10/2/15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	2/20/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, Center Director's Exception for Review memo <i>(indicate date)</i>	
• If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics (<i>approvals only</i>)	
- Date reviewed by PeRC <u>9/9/15</u> - If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Various
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 9/15/11; 7/23/14
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 7/14/10
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
Date(s) of Meeting(s)	6/7/16
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 1/17/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 1/13/17
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 15
Clinical	
❖ Clinical Reviews	
Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical review(s) (<i>indicate date for each review</i>)	12/18/15
Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See pages 24-26 of Clinical Rvw
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None 10/19/15 and 1/12/17 (DPMH)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A 9/28/15
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	12/19/16 1/12/17 (memo) ☐ None 12/22/16 and 11/13/15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 9/11/15
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review 9/28/15
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 9/9/15 and 9/11/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 9/17/15 and 9/23/15
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ No separate review 1/13/17
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 1/11/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None 9/18/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>) ☒ N/A
Finalize 505(b)(2) assessment	☐ Done ☒ N/A
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>) ☒ N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

KIMBERLY A COMPTON
01/19/2017

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, January 06, 2016 10:53 PM
To: Douglas Harnish
Cc: Compton, Kimberly
Subject: RE: Pediatric PMR for Vantrela

Hi Doug,

The team has the following comments that relate to our TC on the Pediatric study tomorrow:

These comments pertain to your pediatric program and Protocol C33237-CNS-10019, “An Open-Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Hydrocodone Bitartrate Extended-Release Tablet (CEP-33237) in Patients 7 To 17 Years of Age Requiring Opioids for the Treatment of Pain.”

As written, the protocol is not acceptable for the following reasons:

1. The patient population is not adequately defined:

- a. The protocol defines opioid-experienced as, [REDACTED] (b) (4)
[REDACTED] This definition is inadequate for identifying opioid-tolerant patients.

Amend the protocol as follows:

- Patients must be opioid tolerant, defined as having been treated with opioids for at least the 5 consecutive days prior to dosing and having tolerated the therapy, as demonstrated at the start of study drug dosing by:
 - (a) A normal respiratory rate for age,
 - (b) Pulse oximetry (SpO₂) ≥ 92% on room air, and
 - (c) No significant (grade 3 or 4) opioid-induced somnolence (UMSS)
- Define the dose range that subjects must be taking for the 48 hours prior to start of study drug dosing. The minimum daily dose should be equivalent to the minimum daily dose for which your product can be studied based on the available strengths of your product. Provide a rationale for the maximum dose that subjects can be taking as well. A table to convert the daily dose of prior opioid medications to the daily dose of Vantrela should be provided in the protocol.

- b. [REDACTED] (b) (4).

Amend the protocol as follows:

Patients who have had surgery within five days prior to the first dose of study drug should be excluded from the study.

c.

(b) (4)

Amend the protocol as follows:

(b) (4)

2. The study design, duration of treatment, and number of patients are inadequate to obtain sufficient safety information. The protocol as currently written is primarily a PK study and does not adequately assess safety.

- a. Treatment for (b) (4) is inadequate to adequately assess safety.

Amend the protocol as follows:

Treatment should be for a minimum of 2 weeks. You should attempt to enroll patients who will require opioids for 2-4 weeks. An additional safety study would be acceptable to provide the required longer duration treatment period.

- b. We do not consider (b) (4) patients sufficient to characterize safety in patients ages 7 to 17 years old.

Amend the protocol as follows:

A minimum of 50 patients should be studied in the 7-11 years age group and a minimum of 125 should be studied in the 12-17 years age group.

- c. We note that there is no provision for dose titration based on efficacy or tolerability.

Amend the protocol as follows: Dose increases and decreases should be allowed.

- d. It does not appear that opioid medications are allowed for rescue if appropriate analgesia is not achieved.

Amend the protocol as follows:

Supplemental opioid and nonopioid pain medication should be permitted for rescue and data on use of rescue must be collected and analyzed.

3. Patients (b) (4) which is inadequate to assure safety with multiple dosing.

Amend the protocol as follows: Patients should be monitored until steady state is achieved.

4. It appears that worst pain intensity will be recorded (b) (4) We also note that you plan to use the Wong-Baker FACES Pain Rating Scale (WBS).

Amend the protocol as follows:

Pain assessments should occur with both AM and PM dosing. We recommend for children 12 to 17 years old also using an 11-point NRS for pain.

Additional Clinical Recommendations:

1. Attempt to enroll as many patients as possible with cancer-associated pain.
2. Carefully document the primary reason for chronic opioid treatment in the CRF.
3. Carefully collect information about what rescue medications are used, including dose and frequency of use.

Clinical Pharmacology Comments:

We note that your product's clinical pharmacology and biopharmaceutics program has data from only traditional PK data from bioavailability studies (without a population PK model) in adults. You must justify that a given dose selected for use in a specific age group (7- <12 yrs and $\geq$ 12-17 years) has reasonable chance to "achieve plasma opioid exposure (AUCss or Cminss, etc.) that is comparable to adults. This may be accomplished by integrating PK data from different bioavailability studies and evaluating data for any trend or difference in exposure in adult subject with lower bodyweight compared to heavier subjects (allometry).

Thereafter, evaluate the PK of Vantrela in pediatric patients in either of the two settings described below:

1. Single dose opioid substitution strategy: Single dose PK studies cannot be done in pediatric patients due to ethical concerns. However, pediatric patients already receiving an opioid IR or ER product may receive a single dose of the Vantrela for traditional or Rich Sampling Plan to evaluate single dose PK of the ERLA product. This strategy should be used if the Vantrela PK is known to be linear and dose-proportional (in adults) and therefore single dose PK can be predictive of multiple dose PK. The single dose PK data must be used, by nonparametric superposition or compartmental methods, to predict doses required in pediatric patients to "achieve plasma exposure comparable to adult subjects".
2. Multiple dose study: Opioid-tolerant (as previously defined) pediatric patients that may require Vantrela use for more than two weeks may be dosed up to steady-state (as known in adults) where traditional or rich blood sampling scheme may be applied. Justification of blood samples during absorption phase, peak plasma (Cmax) levels, and in the elimination phase (to calculate AUC0-tau/AUCss) should be based on adult PK data. The goal of such a multiple dose PK study is to confirm that the dose selected in pediatric patients will have reasonable chance that the pediatric plasma exposure is comparable to previously noted adult plasma exposure with an appropriate dose.

We will speak with you tomorrow afternoon.

I will archive a copy of this email so our comments are contained in the NDA record.

Thanks

Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

Addiction Products

301-796-1191

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/s/

KIMBERLY A COMPTON
01/06/2016

From: Compton, Kimberly
Sent: Friday, December 16, 2016 2:53 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: Vantrela REMS

HI Doug,

Our OSE/DRISK colleagues asked me to forward the below to you. Please let me know if you have any questions on what they are looking for/timing, etc.

In reference to your July 22, 2016, REMS submission for Vantrela ER (NDA 207975) and as a follow-up to the Division of Risk Management's (DRISK's) comments related to the REMS on November 15, 2016, DRISK has the following comments:

On September 30, 2016, the Agency approved a REMS modification for the Extended-release and Long-acting (ER/LA) Opioid Analgesic REMS. As a result of that modification, the approval of a new NDA product does not impact the ER/LA REMS document and REMS appended materials. Therefore, you must officially submit the currently approved versions of the ER/LA REMS document and REMS appended materials, which are attached to this email.

You must also submit the most current ER/LA Opioid Analgesic REMS Supporting Document. You must contact the RPC to request the most current version of the REMS Supporting document.

Finally, you must submit separate WORD documents that include Vantrela ER's product specific information which will be included in the *FDA Blueprint for Prescriber Education* table titled "**Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)**" located only on the FDA website under a static URL link
(
<http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf>
).

We have attached the July 22, 2015, version redlined to reflect the current agreed upon prescribing information for Vantrela ER. Officially submit both a redlined and clean WORD document of the Vantrela ER Product Specific Information (attached to email).

To summarize, in order for the Agency to continue our review of your application, officially submit the following materials as an amendment to your application by COB on December 19, 2016:

1. Compiled REMS Document and REMS Appended materials (Clean, PDF)- attached to email.
2. Vantrela Product Specific information, (redlined, WORD) - attached to email.

3. Vantrela Product Specific information, (clean, WORD) - attached to email.
4. REMS Supporting Document (Clean, WORD)

Thanks,

Kim

Kimberly Compton

Kimberly Compton, RPh

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

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KIMBERLY A COMPTON
01/06/2017

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, January 05, 2017 6:01 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: Vantrela PI

Hi Doug,

Attached, please find the latest version of the Vantrela PI with our edits shown. These mostly reflect the recent opioid SLC, with a few other items mixed in (such as the carci language, etc.)

Please let me know if Teva has any questions.



IN 2017-01-05 19:11:00
from 11-15-17/John...

As before, please accept any changes Teva is OK with and return a tracked version to me via email of any counterproposals/comments, outstanding issues, etc.

Thanks
Kim

Kimberly Compton
Kimberly Compton, RPh
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
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KIMBERLY A COMPTON
01/06/2017

For Internal Use Only

Meeting Request Denied Form**

(Use this form to document the meeting denied via telephone.)

Complete the information below and check form into DARRTS

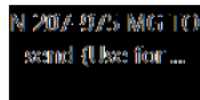
Application Type/Number	NDA 207975
Meeting Type/Code	Type A
DATE Meeting Denied (per communication with requester)	9/30/16
Reason for Denial	The request is directed to the Agency Chief Counsel, Elizabeth Dickinson, and not the Division. The request is to meet with the Office of Chief Counsel and so the Division will not entertain this request and leaves it to the OCC to determine how to proceed in this matter.
Project Manager	Kim Compton

Any follow-up letter must be checked into DARRTS as an advice letter, **NOT as a meeting request denial letter.

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/s/

KIMBERLY A COMPTON
10/01/2016



Study/Trial Completion:

MM/DD/YYYY

Final Report Submission:

MM/DD/YYYY

If there are any additionally required nonclinical PMRs, Matt or I will send those to you as they are decided.

Thanks and see you tomorrow,
Kim

Kimberly Compton

Kimberly Compton, RPh
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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KIMBERLY A COMPTON
06/06/2016

Compton, Kimberly

From: Compton, Kimberly
Sent: Saturday, September 26, 2015 12:51 AM
To: douglas.harnish@tevapharm.com
Subject: RE: PMRs for Vantrela

Hi Doug,

Apparently in my haste to get this out to you this afternoon, I missed one of the ER/LA std PMRs. I am including it here:

(b) (4)

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

Apologies.

Thanks
Kim

From: Compton, Kimberly
Sent: Friday, September 25, 2015 5:19 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: PMRs for Vantrela

Hi Doug,

As I am sure you are aware, if approved, Vantrela, being an ER/LA, will need to have the same PMRs as the other drugs in the class.

Therefore, while we will have more, product specific PMRs to discuss shortly, for the time being we would like to share the std ER/LA PMRs and timelines with you and get Teva's agreement to them.

They are listed below:

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014

Study Completion: 08/2015

Final Report Submission: 11/2015

(b) (4)

We will be encouraging all ER/LA sponsors to work together on the above PMRs with the holders of other approved NDA applications for ER/LA opioids on these studies to provide the best information possible. The milestones noted above reflect those that were specified at the time the study requirements were issued for the class of ER/LA opioid analgesics

Also, later today, I will be sending you a first draft of the Vantrela PI with some of our edits.

Thanks

Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

Addiction Products

301-796-1191

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/s/

KIMBERLY A COMPTON
09/26/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, November 04, 2015 4:52 PM
To: Douglas Harnish
Cc: Compton, Kimberly
Subject: RE: PMRs for Vantrela

HI Doug,

I have a few more PMRs cleared to send. They are below. Please review and if Teva can accept them and the dates as is, please submit an amendment to the application indicating Teva agrees to them. If you need to clarify anything, or change any dates, please let me know.

(b) (4)

2. PMR/PMC Description: Conduct a study evaluating single-dose pharmacokinetics of Vantrela ER tablet in subjects with mild and severe hepatic impairment.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	04/04/2016
Study/Trial Completion:	04/02/2018
Final Report Submission:	10/01/2018

3. PMR/PMC Description: A multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of hydrocodone bitartrate without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of hydrocodone bitartrate.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	04/2016
Study/Trial Completion:	04/2017
Final Report Submission:	10/2017

(b) (4)

5. PMR/PMC Description (PREA): Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Vantrela ER in patients from ages seven to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/2015
Study/Trial Completion:	06/2020
Final Report Submission:	12/2020

(b) (4)

(Please let me know via email if you just amend the NDA and don't need any changes/clarifications.)

Thanks

Kim

From: Douglas Harnish [<mailto:Douglas.Harnish@tevapharm.com>]

Sent: Saturday, September 26, 2015 7:59 AM

To: Compton, Kimberly

Subject: Re: PMRs for Vantrela

Thanks. Wondered what happened to that one

Sent from my iPhone

On Sep 26, 2015, at 12:51 AM, Compton, Kimberly <Kimberly.Compton@fda.hhs.gov> wrote:

Hi Doug,

Apparently in my haste to get this out to you this afternoon, I missed one of the ER/LA std PMRs. I am including it here:

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission: 08/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

Apologies.

Thanks
Kim

From: Compton, Kimberly
Sent: Friday, September 25, 2015 5:19 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: PMRs for Vantrela

HI Doug,

As I am sure you are aware, if approved, Vantrela, being an ER/LA, will need to have the same PMRs as the other drugs in the class.

Therefore, while we will have more, product specific PMRs to discuss shortly, for the time being we would like to share the std ER/LA PMRs and timelines with you and get Teva's agreement to them.

They are listed below:

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We will be encouraging all ER/LA sponsors to work together on the above PMRs with the holders of other approved NDA applications for ER/LA opioids on these studies to provide the best information possible. The milestones noted above reflect those that were specified at the time the study requirements were issued for the class of ER/LA opioid analgesics

Also, later today, I will be sending you a first draft of the Vantrela PI with some of our edits.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
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KIMBERLY A COMPTON
11/05/2015

From: Sullivan, Matthew
To: ["Douglas Harnish"](#)
Cc: [Compton, Kimberly](#)
Subject: NDA 207975 -- Oct 6 Clinical IR
Date: Tuesday, October 06, 2015 11:53:00 AM

Hi Doug –

Here is another request. Can you get back to us by Thursday? If you can send me an email when you've completed it, I'd appreciate it.

Thanks
Matt

Complete the following two tables for each of the following: 1) Study 3079, 2) Study 3103, and 3) the pooled data from the two studies. Repeat for each of the QT-interval correction methods that you have employed.

Table: Number of Patients with QTc Change-from-Screening > 30 msec

Optimal Dose from the Open-Label Titration Phase	Vantrela ER Group N=? (%)	Placebo Group N=? (%)
15 mg bid		
30 mg bid		
45 mg bid		
60 mg bid		
90 mg bid		
All doses		

Table: Number of Patients with QTc Change-from-Screening > 60 msec

Optimal Dose from the Open-Label Titration Phase	Vantrela ER Group N=? (%)	Placebo Group N=? (%)
15 mg bid		
30 mg bid		
45 mg bid		
60 mg bid		
90 mg bid		
All doses		

Thanks,
Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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MATTHEW W SULLIVAN
10/06/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Saturday, September 26, 2015 10:17 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: Vantrela PI

Hi Doug,

Sorry I didn't get this out you yesterday, was waiting on one more piece which came today.

Attached, please find our first pass with the PI edits. We are still working on a few sections in general (which I tried to mark for you) and on the whole PI in general. It has not been reviewed by Sharon yet and so should only be considered as our opening of labeling negotiations.

Please review with your team and accept the changes you are OK with and track any new ones you make, then send us back a WORD copy showing that no later than next Thur Oct 1 so we can work on it some more and then get it back to you again.

Also, we have our OPDP and Pt Labeling folks still working on the MG and will send you their comments too as soon as they are available.

Please let me know if you have any questions.



IN 2017 09/26/15 10:10
FROM 9/24/15...
SUBJECT: Vantrela PI

You already have DMEPA's Carton and Container comments (sent via email on 9/21/15), so please send the revised versions of those back as soon as possible as well.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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KIMBERLY A COMPTON
09/26/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, September 21, 2015 2:52 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: C & C labeling comments for Vantrela

Hi Doug,

The DMEPA group in OSE has reviewed the carton and container (C & C) labeling proposed for Vantrela and has the following comments:

Container Labels (all strengths)

1. Add the statement, "Swallow tablets whole. Do not cut, break, chew, crush, or dissolve." to the principal display panel to mitigate the risk of wrong technique errors. Add this statement above the statement, "Dispense the accompanying Medication Guide to each patient." Decrease the size of the statement, "Dispense the accompanying Medication Guide to each patient" and remove the (b) (4) from the principal display panel to accommodate the addition of the statement.
2. Increase the size of the strength statement. Decrease the size, remove the (b) (4) background, and change the font color to black for the net quantity statement. As currently presented, the strength does *not* appear more prominent than the net quantity statement. From post marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity and prominence to the strength statement.
3. (b) (4) the modifier "ER." Use the same font size and color for the modifier "ER" as the rest of the proprietary name. The modifier "ER" is an important indicator of the extended-release dosage form and as currently presented, it appears smaller and in a different color than the rest of the proprietary name, which could lead to medication errors if it is over looked.
4. Revise the presentation of the proprietary name from all lower case letters "tradename" to title case "Tradename" to improve readability. We recommend using title case because words written in all lower case letters are less legible than words written in title case.
5. Ensure lot number is present on the immediate container per 21 CFR 201.10(i)(1).
6. Ensure expiration date is present on the immediate container per 21 CFR 201.17.
7. Revise the middle four digits of the NDC numbers to ensure that they are not sequential among the different strengths. Traditionally, healthcare providers use the middle four digits to check the correct product, strength, and formulation. The similarity of the NDC numbers has led to selecting and dispensing of the wrong strength and wrong drug. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668).

Please make the requested changes and submit revised C & C via the EDR as soon as possible so we can do a review to ensure it fulfills our requests.

Thanks

Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

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KIMBERLY A COMPTON
09/21/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, September 03, 2015 5:05 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: Request for N 207-975

Hi Doug,

The audiology expert that is looking at the audiometry analysis for us has the following request:

Conduct additional analyses on the pure tone audiometry data and adverse events associated with vestibular function in order to adequately address our concerns about the potential for ototoxic effects from hydrocodone use.

1. In both clinical studies (3079 and 3103), conventional pure tone audiometry (500-8000 Hz) was performed before and after the open-label titration period (Visit 2 to Visit 3 or 7), and before and after the double-blind treatment period (Visit 7 to Visit 12). Mean hearing threshold changes from baseline to final values after the open-label titration or double-blind treatment period) ranged -2.6 to 1.3 dB for Clinical Study 3079 and -2.4 to 0.5 dB for Clinical Study 3103 across conventional frequencies of 500-8000 Hz. We acknowledge that the reported mean threshold changes are minimal and clinically insignificant. However, all thresholds are compared before and after the open-label titration/double-blind treatment period. Based on the box plot of threshold changes reported in Graph 5 (Clinical Study Report 3103) and Figure 3 (Clinical Study Report 3079), it appears that the standard deviations around the mean thresholds are much larger at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period (e.g., at 4000, 6000, and 8000 Hz testing frequencies in Graph 5, Clinical Study Report 3103). It is unknown whether there are any significant mean threshold changes from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., from the baseline of the open-label titration period (Visit 2) to the final assessment of the double-blind study period (Visit 12). We believe this is an important data analysis to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing.

Request for Additional Analysis

Conduct additional analysis on the pure tone audiometry data to compare the hearing thresholds values between Visit 2 and Visit 12 for both 3079 and 3103 clinical studies in order to adequately support there is no significant signal of acute decrements in hearing in the population studied, during the time course of the study, and under the dosage conditions studied.

2. In both clinical studies (3079 and 3103), individual clinically significant hearing changes are reported in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound (Table 63 and 63 in Clinical Study Report C33237/3079; Table 73, 74, and 75 in Clinical Study Report C33237/3103). Overall, the proportions of patients having at least 1 clinically

significant change in hearing during the study were comparable between the hydrocodone and placebo treatment groups during both open titration period and double-blind study period.

Please address following issues:

- a. For those patients who participated in both the open-label titration and double-blind treatment periods, relatively more clinically significant changes in hearing were reported during the double-blind treatment period compared with the open-label treatment period (Table 74 and 75 in C33237/3103 Clinical Study Report). Again this is related to the observation of larger standard deviations around the mean thresholds at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period at 4000, 6000, and 8000 Hz testing frequencies reported in Graph 5 (C33237/3103 Clinical Study Report). It is unknown whether there are any significant individual clinically significant threshold changes between the hydrocodone and placebo treatment groups from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., from the baseline of the open-label titration period (Visit 2) to the final assessment of the double-blind study period (Visit 12). We believe this is an important individual data analysis to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing.

Request for Additional Analysis

For both 3079 and 3103 clinical studies, conduct further analysis on the individual clinically significant hearing changes from Visit 2 to Visit 12 and report if there is any significant difference in individual clinically significant hearing changes between the hydrocodone and placebo treatment groups for those patients who participated in both the open-label titration and double-blind treatment periods.

- b. You report the clinical significant hearing changes in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound. We acknowledge that the proportions of patients having at least 1 clinically significant change in hearing during both open titration period and double-blind study period were comparable between the hydrocodone and placebo treatment groups. However, the magnitude (i.e., dB shift) of clinical significant hearing changes is not reported for individual subjects. Hearing loss associated with hydrocodone use is typically severe degrees of hearing loss with a rapid onset. It is unknown whether there are any clinical significant hearing changes that have the similar characteristics of hearing loss associated with hydrocodone use.

Request for Additional Analysis

Provide a summary of the results, analyses, and interpretation on the magnitude of clinical significant hearing changes for individual subjects for both 3079 and 3103 clinical studies.

3. Typically the ototoxic effect of drug use is associated with hearing or vestibular function. You provide pure tone audiometry data to support no significant signal of acute decrements in hearing after hydrocodone use. However, you do not provide a separate report about the data analyses on vestibular function to evaluate whether there is any impact on vestibular function after the

hydrocodone use. Instead you report adverse events associated with vestibular function (e.g., dizziness, vertigo).

Request for Summary

Provide a cumulative summary and your interpretation of the percentage of subjects with confirmed treatment-emergent adverse events related to vestibular function (e.g., dizziness, vertigo, vestibular disorder etc.) for both 3079 and 3103 clinical studies in order to adequately support a finding of no significant signal of acute decrements in vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied.

We need a reply no later than the end of next week (Fri Sept 11) in order to stay on target for wrapping up this NDA on time. Please let me know if you anticipate any problem replying by then.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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KIMBERLY A COMPTON
09/09/2015



NDA 207975

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Douglas C. Harnish, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Dr Harnish,

Please refer to your original New Drug Application received December 23, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CEP-33237 (Hydrocodone Bitartrate ER) tablet, 15, 30, 45, 60 and 90 mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 8, 2015.

Provide the following information/data by Tuesday (9/8/2015) to support the ER claim for you product: Hydrocodone Bitartrate Extended Release Tablets:

The input and output files for the simulation of the steady state PK, including the Phoenix WinNonlin project file. Note that ER claim should meet the requirements stated under CFR 325.25f.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Steven Kinsley -S

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Steven Kinsley -
S, 0.9.2342.19200300.100.1.1=2001720189
Date: 2015.09.03 15:02:50 -04'00'

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, August 24, 2015 10:46 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: IR for N 207975

Hi Doug,

I just got an information request from the stats folks for N 207975. It is listed below. They would like a reply no later than next Monday, 8/31/15.

1. In your response to Question 7 of our June 15, 2015, emailed information request, you state that deltaP based on the observed data is 1.05. Tell us how you arrived at this number, and provide the mean WPI at baseline and week 12 for the 12 subjects in the placebo group with an off-treatment week 12 WPI value.
2. For trial 3079, provide results from an analysis of WPI change at week 12 which excludes subjects whose successful pain relief dose was 15 mg. Repeat this analysis by levels of opioid status. Provide the SAS program code used for these analyses.
3. In Section 11.4.1.3 of the CSR for trial 3103, describe how you calculated the number of subjects that used rescue medication and provide your SAS program code.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
08/24/2015



NDA 207975

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Douglas C. Harnish, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Dr. Harnish,

Please refer to your original New Drug Application received Tuesday, December 23, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CEP-33237 Hydrocodone Bitartrate ER tablets in 15, 30, 45, 60 and 90 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Friday, August 14, 2015.

1. With regard to the PSD specification of the coated granule, we recommend including an upper limit for % particles retained on (b) (4). Submit updated documents.
2. You updated Content Uniformity in 3.2.P.5.2 to include (b) (4). Please provide method detail for (b) (4) for different strengths, number of samples taken at the sampling location, sample preparation and sample solution concentration and the calculations. We recommend the following (b) (4) specification: Mean of Sample Assay is (b) (4) % of label potency, RSD NMT (b) (4) %.
3. You have provided data from one batch for assay of the (b) (4) samples, their corresponding coated granules and the (b) (4). To better control the process we recommend including a routine (b) (4). Submit revised documents.
4. The API loading in the drug product is low; the submitted (b) (4) data shows variation over a wide range and appears to be dependent on sample size. Use of stratified sampling method to ensure content uniformity, in addition to the (b) (4) test, is highly recommended. Please

provide description of stratified sampling and the method of analysis including acceptance criteria in the analytical section of the NDA submission.

5. You have suggested that change in [REDACTED] (b) (4) [REDACTED] resulted in a change in the drug product dissolution profile. You have included an additional acceptance criterion to assess the [REDACTED] (b) (4) of this excipient. In this regard:
- a. Justify the proposed acceptance criterion.
 - b. What is the retest date for this excipient?
 - c. Please discuss whether each lot should be tested for this criterion to ascertain lot suitability to manufacture.

Sincerely,

**Steven
Kinsley -S**

Steven Kinsley, Ph.D.

Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -S
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Date: 2015.08.03 08:16:38 -04'00'



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207975

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Douglas H. Harnish, Ph.D.
Teva Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Dear Dr. Harnish:

Please refer to your original New Drug Application received December 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for hydrocodone bitartrate extended-release, abuse deterrent, oral tablets in 15, 30, 45, 60, and 90 mg strengths.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your supplement. Please submit your response prior to COB July 21, 2015.

Please provide data for the following:

- Volume of pure ethanol (95%, 190 proof) required for extraction of at least 80 % of drug from manipulated drug product(s) under various experimental conditions e.g. extraction using pure ethanol at room temperature and ~60-70°C with and without agitation.
- Simple extraction studies using media containing ethanol above 40 %v/v and up to 95% v/v.
- Extraction studies with water and applesauce, after microwave heating of manipulated and intact drug product(s).
- Multiple-step extraction studies using manipulated drug product(s), following a sequence of steps as described below and/or any other method deemed relevant for the extraction of hydrocodone:
 - Extract physically manipulated drug product(s) with pure ethanol (95%, 190 proof) under hot conditions (~60-70°C).
 - Separate undissolved (b) (4), by filtration from the hot ethanol extract.

- Separate (b) (4) by precipitation from filtered extract by addition of hot water while stirring slowly, maintaining the temperature of the extract above 70°C.
- Separate (b) (4) by phase separation and/or solidification upon cooling.

Sincerely,

Steven Kinsley -

S

Steven Kinsley, Ph.D.

Regulatory Business Project Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley - S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Steven Kinsley - S,
0.9.2342.19200300.100.1.1=2001720189
Date: 2015.06.29 08:34:21 -04'00'

Kinsley, Steven

From: Douglas Harnish <Douglas.Harnish@tevapharm.com>
Sent: Thursday, July 02, 2015 12:50 PM
To: Kinsley, Steven
Cc: Matt Sheehan
Subject: RE: Correspondence

Steven

We have a clarification Question for FDA regarding this Information Request

Drug Product, Question 1: "Provide the (b) (4) data for your batches and include the details of the analytical method and validation data to support your results".

Request for Clarification:

(b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4)

Does the Agency require information beyond that provided in the NDA?

Thanks
Doug

From: Kinsley, Steven [<mailto:Steven.Kinsley@fda.hhs.gov>]
Sent: Tuesday, June 23, 2015 12:44 PM
To: Douglas Harnish
Subject: Correspondence

Dear Dr. Harnish,

Please find the attached Information Request for NDA 207975. The response is required by July 14th, 2015. Please note the change in Regulatory Business Project Manager; all CMC correspondence should be now be addressed to me.

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
2240-402-2773

MEMORANDUM OF TELECONFERENCE

Teleconference Date: 6/10/15

Application Number: 207975

Product Name: Vantrela ER (hydrocodone ER)

Sponsor/Applicant Name: Teva

Subject: PREA status

FDA Participants : John Feeney (CDTL), Kim Compton (PM)

Sponsor/Applicant Participants: Doug Harnish (Regulatory Affairs) and others

BACKGROUND: It was stated in the 74-day letter issued to the firm that PREA did not apply to this NDA. However, it was determined this was an error and that PREA was triggered by this NDA. The firm was contacted to clarify this.

DISCUSSION: Dr Feeney and I spoke to the firm and they indicated that they assumed the statement to be an error and had continued their pediatric development program as previously discussed and agreed with the Agency in the iPSP.

ACTION ITEMS: No further action is needed at this time.

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/s/

KIMBERLY A COMPTON
06/19/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, June 15, 2015 6:30 PM
To: douglas.harnish@tevapharm.com
Cc: Compton, Kimberly
Subject: N 207-975 request from stats

HI Doug,

The stats team has the below requests for N 207975.

The following requests are based on our preliminary review of your primary efficacy analysis for trial 3103:

- Clarify the estimand or causal effect of CEP-33237 you are attempting to estimate in your primary analysis. We could not locate it in your CSR, protocol, or SAP. In your response, also discuss:
 - Whether the trial design supports estimating the causal effect of interest. For example, if you are interested in the effect when everyone could adhere to randomized therapy to week 12 (contrary to some not being able to), the trial design did not ensure subjects would adhere to study drug for the entire duration.
 - Why you consider the causal effect of interest to be clinically meaningful/relevant overall and to the experiences of all randomized subjects in the trial.

Refer to the pages 22-27 of the 2010 National Academy of Science report on missing data for additional considerations/details.

- Describe your clinical and statistical rationale for treating wWPI measured after discontinuing study drug as missing in your primary analysis.
- For subjects that prematurely discontinued study drug, there was no notable difference between their imputed week 12 wWPI value and the wWPI obtained from their last visit on study drug (Table 1). Your imputation approach is found to preserve the between group difference based on measurements taken while on study drug (note that the imputed analysis is based on 1000 imputed datasets). Comment on whether you consider the lack of attenuation appropriate, given these subjects were no longer receiving study drug. In your response, consider the experiences for the 21 subjects with a week 12 wWPI measurement after discontinuing study drug (Table 2).

Table 1. Summary of last value on-treatment and imputed week 12 wWPI for subjects that discontinued study drug

	Hydrocodone N=39 mean	Placebo N=46 mean	Difference: Δ Hydrocodone – Δ Placebo
Baseline	4.6	4.5	
Last visit on study drug	4.4	5.6	-1.3
Imputed wk 12 response	4.6	5.8	-1.3

Table 2. Summary of observed and imputed week 12 wWPI for subjects that stopped study drug early but had a week 12 wWPI measurement

	Hydrocodone ER N=9 mean	Placebo N=12 mean
Last visit on study drug Week 12	4.5	5.7
Imputed response	4.6	5.8
Observed response	5.3	5.5

- For the primary efficacy endpoint provide results from
 - A Wilcoxon rank sum test where subjects that stopped study drug early are assigned the worst rank.
 - A Wilcoxon rank sum test similar to the approach above, except subjects that stopped study drug earlier in the trial are assigned worse ranks than those that stopped study drug later. That is, the subjects that stopped treatment early will receive ranks based on the timing of their discontinuation of study drug, but their ranks will be less than those that adhered to study drug regardless of their wWPI (change) values at week 12.
 - Repeat the above analyses by opioid status (experienced and naïve).
- Conduct and provide results from a tipping-point analysis to evaluate the impact of missing data on the effect of change in wWPI at week 12. For clarification, we do not consider subjects with pain scores at week 12 that were measured after stopping study as missing; pain scores for these patients should not be treated as missing in this investigation. We request your investigation follow the following general algorithm:
 - Generate a large number of imputed datasets (e.g., 100) using multiple imputation
 - For each subject with missing week 12 data:
 - Calculate the average change in wWPI at week 12 across imputed datasets
 - Center the imputed values about the average imputed value
 - For subjects randomized to CEP-33237 (Placebo) add a constant Δ_T (Δ_P) to their imputed values.
 -
 - Analyze the imputed datasets using your primary ANCOVA model. Retain the estimated treatment effect and the upper and lower limits of the 95% confidence interval.
 - Repeat the above steps for different configurations of Δ_T and Δ_P .

The values of Δ_T and Δ_P you should explore are 0 to 1.5 in increments of 0.05, and you should evaluate all 961 possible configurations. Results from the investigation should be summarized and discussed. You may want to consider graphical methods to summarize the data; of particular interest is the point estimate and scenarios where the results are not statistically significant. For the scenarios that lead to non-statistically significant differences, discuss whether you consider the sensitivity parameters could possibly describe the pain scores at week 12 for those that were not measured. Your discussion should consider the experiences for the 21 subjects with a week 12 wWPI measurement after discontinuing study drug (Table 2). Provide the program code and describe specific details of your algorithm (e.g., your imputation model).

Provide the requested material by June 29, 2015.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

Addiction Products

301-796-1191

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/s/

KIMBERLY A COMPTON
06/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207975

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R & D, Inc.
Attn: Douglas C. Harnish, PhD
Director, Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Dear Dr. Harnish:

Please refer to your New Drug Application (NDA) dated and received December 23, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hydrocodone bitartrate extended-release tablets, 15, 30, 45, 60 and 90 mg.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by May 4, 2015 in order to continue our evaluation of your NDA.

A. The Manufacturing Process.

1. The API hydrocodone bitartrate is known to exist in various polymorphic forms; for example, (b) (4). The API used in this NDA is the hydrate form which contains 2.5 moles of water per mole of hydrocodone. Discuss the impact of the drug product manufacturing process on the solid state of the API. If there is any change in the polymorphic form, please comment on its impact on the dissolution profile/PK parameters of the drug product.
2. Provide batch reconciliation for each manufacturing stage.
3. You have provided controlled ranges of the process parameters employed in the manufacture of coated hydrocodone bitartrate (b) (4) granules, and process parameter ranges and in-process controls for the (b) (4) in 3.2.P.3.3 (Table 2-4); provide batch results for all submission batches. Discuss any deviations from the proposed ranges.
4. You have provided in-process control tests and acceptance criteria for coated hydrocodone bitartrate granules in 3.2.P.3.4 (Table 1-2), please include batch results.

Provide results of your study of (b) (4)

(b) (4)

5. Justify not including the (b) (4)

(b) (4)

6. Ethyl Cellulose is used as a (b) (4)

Provide a quantitative breakdown of ethyl cellulose used as (b) (4) for all development batches and final commercial batches. Please also provide dissolution profile comparison for all batches (development and final formulation) with (b) (4)

7. Provide a table of components and composition where the composition is expressed in %w/w.

8. The (b) (4) lactose monohydrate used as an (b) (4) excipient in the manufacture of the drug products, is NF grade and comprises (b) (4)% of the tablet composition. Please discuss the role of (b) (4) this excipient in (b) (4) finished product. Propose an appropriate specification for lactose monohydrate and submit Certificate of Analysis for all lots used in your manufacturing batches.

9. For the (b) (4)

(b) (4)

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

**Ciby J.
Abraham -A**

Digitally signed by Ciby J. Abraham -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000827346,
cn=Ciby J. Abraham -A
Date: 2015.04.13 12:15:27 -04'00'

Ciby J. Abraham, Ph.D.
Application Technical Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207975

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

ATTENTION: Douglas C. Harnish, Ph.D.
Director, Regulatory Affairs

Dear Dr. Harnish:

Please refer to your New Drug Application (NDA) dated and received December 23, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate Extended-release Tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg.

We also refer to your correspondence, dated and received December 23, 2014, requesting review of your proposed proprietary name, Vantrela ER.

We have completed our review of the proposed proprietary name, Vantrela ER and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application, contact Kimberly Compton, Regulatory Project Manager in the Office of New Drugs, at 301796-1191.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/02/2015



NDA 207975

NDA ACKNOWLEDGMENT

Teva Branded Pharmaceutical Products R & D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Douglas C. Harnish, PhD
Director, Regulatory Affairs

Dear Dr. Harnish:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Hydrocodone bitartrate extended-release tablets (CEP-33237)

Date of Application: December 23, 2014

Date of Receipt: December 23, 2014

Our Reference Number: NDA 207975

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling described in 21 CFR 314.50(l)(1)(i), in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 207975** submitted on December 23, 2014 and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and
Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KIMBERLY A COMPTON
01/13/2015



NDA 207975

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Teva Branded Pharmaceutical Products R & D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Douglas C. Harnish, PhD
Director, Regulatory Affairs

Dear Dr. Harnish:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received December 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hydrocodone bitartrate extended-release tablets (CEP-33237).

We also refer to your amendments dated September 30, 2014, and January 13, and February 6, 10, 13, and 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 25, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Provide the Certificate of Analysis for the drug substance batches in section 3.2.S.4.4.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. White space should be present before each major heading in Highlights (HL). There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. There is no white space before each major heading in HL.
2. The same heading for the Boxed Warning (BW) that appears in HL and the Full Prescribing Information (FPI) must also appear at the beginning of the Table of Contents (TOC) in UPPER CASE letters and bolded. The TOC BW title is missing the last word- "Interaction" from the title in the HL's BW.
3. The following heading must be bolded and appear at the beginning of the FPI: "FULL PRESCRIBING INFORMATION". This heading should be in UPPER CASE. Currently, while present, this heading appears on a separate page from the start of the FPI. Adjust the formatting so that it appears on the same page as the start of the FPI.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 28, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Kimberly Compton, RPh, Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
02/28/2015

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, February 09, 2015 12:09 PM
To: Douglas Harnish; Sullivan, Matthew
Cc: Compton, Kimberly
Subject: RE: Meeting minutes follow up questions and status request for Thursdays tcon

HI Doug,

Our responses to the questions you posed are interspersed below.

In addition, we are not prepared to address the outstanding question about exclusivity later this week and so I have held a new spot about 2 weeks out (Fri Feb 27 at 2 PM) in the hopes that we will be able to reply by that time. Unfortunately, we do not have really any other days open that week, so I hope that slot works for your team.

Thanks
Kim

From: Douglas Harnish [<mailto:Douglas.Harnish@tevapharm.com>]
Sent: Monday, February 09, 2015 10:36 AM
To: Sullivan, Matthew
Cc: Compton, Kimberly
Subject: Meeting minutes follow up questions and status request for Thursdays tcon

Matt and Kim,

Teva has reviewed the Division's meeting minutes and has the following questions based upon the Division's response (in italics) to our post-meeting question in bold:

1. **If Teva were able to secure the right of reference to the Vicoprofen NDA, thereby having the right of reference to all studies and data used in the original FDA decision to approve Vicoprofen, would the Division consider our current application supplemented with this data a stand-alone 505(b)(1) NDA?**

Based on the right of reference described, the Division would not impose any additional requirements for a possible 505(b)(1) application beyond what would have been required if the Sponsor submitted a 505(b)(2) application referencing FDA's finding of safety and/or effectiveness for Vicoprofen as the listed drug.

Teva would like clarification to this statement:

1. Can the Division confirm that if Teva obtains the right of reference to the Vicoprofen NDA, the combination with Teva's current 207975 NDA application meets the regulatory standards for a 505(b)(1) application.

FDA Response

Yes

The Sponsor would need to confirm that the proposed 505(b)(1) application would not rely on any other data that would make it a 505(b)(2) application.

2. Does “any other data” in the statement above mean reliance on data outside of the Vicoprofen NDA and our 207975 NDA application?

FDA Response

Yes

3. The current prescribing information in our NDA submission includes historic hydrocodone reference labeling recommendations that are also contained in the Vicoprofen PI. Can the Division confirm that use of this historic general knowledge is acceptable for a 505(b)(1) application?

FDA Response

It can be very difficult to confirm that information is general knowledge. For example, information in a text book cannot be assumed to be general knowledge. You must provide a rationale for how such information is considered general knowledge and does not represent reliance on data for which you neither own nor have right of reference.

Also, we have a teleconference scheduled with the Division for this Thursday, February 12th at 4:30 PM. Can you confirm whether we can use this teleconference to discuss the questions we raised above and if the Division is in a position to address the first question posed in our briefing package regarding the scope of the 3 year exclusivity periods granted to Zohydro ER and Hysingla ER?

Thanks

Doug

Douglas C Harnish, PhD
Sr Director Pain & Migraine
Regulatory Affairs Teva
610-727-6246

From: Sullivan, Matthew [<mailto:Matthew.Sullivan@fda.hhs.gov>]

Sent: Wednesday, February 04, 2015 5:43 PM

To: Douglas Harnish

Cc: Compton, Kimberly

Subject: Meeting minutes

Hi Doug –

Attached are the minutes from our 1/15 teleconference.

Let me know if you have any questions.

Matt

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/s/

KIMBERLY A COMPTON
02/09/2015



NDA 207975

ACKNOWLEDGE NDA PRESUBMISSION

Teva Branded Pharmaceutical Products R & D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Douglas C. Harnish, PhD
Director, Regulatory Affairs

Dear Dr. Harnish:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Hydrocodone bitartrate extended-release tablets (CEP-33237)

Date of Submission: September 30, 2014

Date of Receipt: September 30, 2014

Our Reference Number: NDA 207975

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KIMBERLY A COMPTON
10/06/2014



IND 105587

MEETING MINUTES

Teva Branded Pharmaceutical Products R & D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Douglas C. Harnish, PhD
Director, Regulatory Affairs

Dear Dr. Harnish:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food Drug and Cosmetic Act for hydrocodone bitartrate extended-release tablets (CEP-33237).

We also refer to the meeting between representatives of your firm and the FDA on July 23, 2014. The purpose of the meeting was to discuss preparations for submission of a New Drug Application (NDA) for your product.

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

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, RPh
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction 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/Category: Type B, Pre-NDA
Meeting Date and Time: July 23, 2014, at 4:00 PM
Meeting Location: White Oak Bldg 22, Conference Room 1313
Application Number: IND 105587
Product Name: Hydrocodone bitartrate extended-release tablets (CEP-33237)
Regulatory Status: Active IND, pre-NDA, Fast-Track status granted
Proposed Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Sponsor Name: Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair: John Feeney, MD, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Center for Drug Evaluation and Research (CDER)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Teva Representatives	Title
Douglas Harnish, PhD	Director, Regulatory Affairs
Kenneth Bonk	Senior Director, Regulatory Affairs
Valerie Mulligan	Senior Director, Regulatory Affairs CMC
Brad Barnes, PhD	Senior Director, Nonclinical Safety
Matthew Sheehan	Manager, Regulatory Affairs CMC
Richard Malamut, MD	Vice President, Global Clinical Development in Pain
Derek Moe, PhD	Vice President, Drug Delivery
Randal Seburg, PhD	Director, Analytical Development
Mary Bond, MS, MBA	Director, Clinical Pharmacology
Ronghua Yang, PhD	Senior Director, Biostatistics
Jeffrey Martini, PhD	Director, Project Champion, Global Research and Development
FDA	Title
Sharon Hertz, MD	Deputy Director, DAAAP
Robert Levin, MD	Medical Officer, DAAAP
John Feeney, MD	Clinical Team Leader, DAAAP
Dan Mellon, PhD	Supervisory Pharmacologist, DAAAP
Julia Pinto, PhD	CMC Lead, Office of New Drug Quality Assessment (ONDQA), CDER

Yong Hu, PhD	Chemistry Reviewer, ONDQA, CDER
Eric Duffy, PhD	Division Director, Division of New Drug Quality Assessment III, ONDQA
Kelly Kitchens, PhD	Biopharmaceutics Reviewer, ONDQA
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), CDER
Yun Xu, PhD	Team Leader, OCP, CDER
Janice Derr, PhD	Team Leader, Division of Biometrics II
Danny Gonzalez	Risk Management Analyst, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)
Kim Lehrfeld, PharmD	Team Leader, DRISK, OSE
Alex Secora, MPH	Epidemiologist, Prescription Drug Abuse Team, Division of Epidemiology (DEPI), OSE
James Tolliver, PhD	Reviewer, Controlled Substances Staff (CSS)
Silvia Calderon, PhD	Team Leader, CSS
Kim Compton	Sr. Regulatory Project Manager, DAAAP

BACKGROUND

CEP-33237 is an extended-release hydrocodone bitartrate, abuse-deterrent, oral tablet in 15, 30, 45, 60, and 90 mg strengths. The Sponsor intends to submit a 505(b)(2) application that will rely on the Agency's previous findings of safety and efficacy for Vicoprofen (NDA 020716). The Sponsor has proposed that the product be indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

A previous pre-NDA meeting was held between the firm and Division on September 15, 2011, and a Type C Guidance meeting to discuss abuse-deterrent issues related to the product was held on January 23, 2014.

According to the Sponsor, the initial submission of IND 105587 included the initial pharmacokinetic studies to characterize prototype formulations. Four Phase 3 clinical efficacy studies have been conducted with CEP-32337. The first two studies, a double-blind study, C32337/3079, and an open-label extension study, C32337/3080, have been completed. Study 3079 did not demonstrate effective analgesia with regard to average pain intensity (API) for several reasons thought to be related to study design and assay sensitivity issues. Therefore, a second set of Phase 3 studies, double-blind study C32337/3103, and open-label extension study C32337/3104, were designed to incorporate several study design changes in order to provide confirmation of the efficacy of CEP-32337 for the treatment of moderate to severe pain. The final data analyses for the original Phase 3 studies have been completed and submitted to the IND; Study 3103 has recently completed, and Study 3104 is ongoing.

In addition, 18 clinical pharmacology studies have been performed to date to characterize the pharmacokinetics of hydrocodone following administration of CEP-33237. These studies include assessments of the pharmacokinetics of single and multiple doses (up to 90 mg administered every 12 hours) of extended-release hydrocodone tablets and assessments of single-dose pharmacokinetics under various conditions, including when taken with food or alcohol, or when the tablet is crushed. A study to assess the relative abuse potential of the crushed and intact hydrocodone bitartrate extended-release tablet when taken orally by healthy, nondependent, recreational opioid users was performed. Renal and hepatic impairment studies were also conducted in addition to various relative bioavailability and bioequivalence assessments. One additional clinical pharmacology study to assess the intranasal clinical abuse potential of the hydrocodone extended-release tablet has been recently initiated and will be included in the New Drug Application (NDA).

The Sponsor has stated that their purpose for this Pre-NDA meeting is to obtain concurrence from the Division on the planned contents and analyses to be included in the NDA submission.

The questions from the June 11, 2014, background package are shown below in *italic* font.

On July 18, 2014, the preliminary responses, shown below in **bold**, were issued to the firm via email. The firm provided replies via email on July 22, 2014. Those follow the Division reply to which they pertain in *italic* font. The firm indicated that they would like to discuss Questions 1, 2, 3, 5, 6, and 9. Discussion that took place at the meeting follows those questions in normal font.

DISCUSSION

Regulatory Question

Question 1

Teva would like to submit this NDA on a rolling basis as allowed for fast track designated products. Does the Division agree with the proposed submission schedule for each portion of the NDA and can the Division comment on their ability to initiate review of the NDA components to be submitted in late September?

FDA Response

Yes, we agree with the rolling submission strategy. The proposed submission schedule for each portion of the NDA is acceptable.

Sponsor Response to FDA comments on Question 1 (via July 22, 2014 email)

Based upon the additional CMC experiments requested, the complete module 3 will likely not be ready by the previously suggested September submission date. Would the Division accept the majority of the completed module 3 documents in September followed by a later submission of 2.3 Quality Overall Summary and the additional requested in vitro manipulation reports that Teva plans to include as leaves in p.2.2?

Discussion

The Sponsor stated that it is possible that some of Modules 3 and 4 would not be complete in September if it is determined additional studies are needed and inquired if the Division would accept incomplete modules. The Agency stated that the objective with a rolling review is to be able to start reviewing information as soon as it is available, and so the Agency would try to be accommodating to meet the public health need in this case.

*****Post-Meeting Note**

We remind you that only final reports should be included in modules that are submitted during a rolling review. In accordance with the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>, draft reports should not be submitted.

Question 2

Teva seeks clarification on Agency expectations regarding the post-marketing requirements for extended-release/long-acting opioids. Specifically, can Teva leverage studies that are already being conducted by existing NDA holders (ie, utilize validation studies for postmarketing requirements 2, 3, and 4 in lieu of conducting independent studies and also join ongoing studies to meet postmarketing requirements 1 and 5)?

FDA Response

Yes.

Sponsor Response to FDA Comments on Question 2 (via July 22, 2014 email)

Could the Division further expand on the operational aspects to joining PMR 1 and 5? Have the logistics been elucidated as to how new sponsors join these ongoing studies and begin mining data specific to their product?

Discussion

The Division stated that joining the PMR group that is already working on the extended-release/long-acting (ERLA) opioid PMRs is an acceptable approach for addressing any outstanding PMRs at the time of an action for this product.

Chemistry Questions

Question 3

The proposed approach to setting specifications for the drug substance, (b) (4), and drug product is provided. The proposal includes an overview of CEP-33237 batches used in the development program and a rationale for the selection of batches used to set specifications. In addition, the approach to setting dissolution specifications, based on the guidance provided by the Division at the Type B Meeting held 15 September 2011, is

presented. Does the Division agree that the strategies proposed by Teva for setting specifications are appropriate for hydrocodone extended-release tablets?

FDA Response

The proposed strategies for setting specifications appear reasonable. The acceptability of the specifications will be determined at the time of the NDA review.

The impurities/degradation products should be reported, identified, and qualified in accordance with the ICH Q3A and Q3B guidelines.

The proposed strategy for setting the dissolution specifications appears reasonable. Note the final determination on the acceptability of the proposed dissolution acceptance criteria will be determined during the NDA review process based on the totality of the provided dissolution data. Provide the complete dissolution data (*individual, mean, SD*) for all the batches tested to support your proposed acceptance criteria.

We have the following additional comments regarding the dissolution information that you should provide in your NDA:

1. Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance covering the pH range.
 - b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions used for each test. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable.
 - c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. Report the dissolution data as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
 - c. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (*i.e., ± 10 -20% change to the specification-ranges of these variables*). In

addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

- d. Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA.

- 2. Provide the complete dissolution data (*individual, mean, SD*) used to establish your proposed dissolution acceptance criteria for each batch tested at each time point under the release and stability conditions.**
- 3. We are concerned that your extended-release (ER) product may release its entire contents (“dose dumping”) when used with alcohol, thereby leading to safety concerns. Therefore, we recommend that you conduct a drug-alcohol interaction study with your ER product. We acknowledge that you completed an in vivo drug-alcohol interaction study using your 15 mg strength. You must conduct in vitro dissolution testing in alcohol using the 90 mg strength. In vitro dissolution testing in a range of alcohol concentrations should generally be conducted on the highest strength of the ER product. However, if the release mechanism is different across the different strengths, additional testing on each strength with a different mechanism will be necessary. In such a situation, we recommend that the development program should be discussed with the Agency.**

The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0%, 5%, 20%, and 40%.

- a. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (*pH 1.2, 4.5, and 6.8*) are recommended.**
- b. Report f_2 values to assess the similarity (or lack thereof) in the dissolution profiles.**
 - i. Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first two hours.**
 - ii. Include the complete data (*i.e., individual, mean, SD, comparison plots, f_2 values, etc.*) collected during the evaluation of the in vitro alcohol induced dose dumping study.**

The data from in vitro dissolution testing in alcohol is required prior to filing your NDA.

Sponsor Response to FDA Comments on Question 3 (via July 22, 2014 email)

1. In FDA's response to the dissolution specification strategy, the following statements are made:

- "Provide the complete dissolution data (individual, mean, SD) for all the batches tested to support your proposed acceptance criteria."
- "Provide the complete dissolution data (individual, mean, SD) used to establish your proposed dissolution acceptance criteria for each batch tested at each time point under the release and stability conditions."

Teva plans to submit complete dissolution data (individual, mean, SD) for the 8 batches of drug product that were employed to establish the proposed acceptance criteria. These batches consist of two batches each of 15, 30, and 45 mg strengths and one batch each of 60 and 90 mg strengths, manufactured in the commercial facility. All sampling times in the dissolution profiles will be included for release and stability testing (all stability intervals, long-term and accelerated conditions).

Does the Agency agree that this dataset fulfills its requests above?

Discussion

The Sponsor indicated that the eight batches used to establish the proposed acceptance criteria are clinical batches and commercial batches. The Division stated that it is acceptable for the Sponsor to provide complete dissolution data for the eight batches that they used to propose the acceptance criteria.

2. In FDA's response to the dissolution specification strategy, the following statement is made:

"The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached."

- FDA Guidance for Industry: "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" states that the last time point should be the time point where at least 80% of drug has dissolved or when the plateau of the profile has been reached.
- In previous Sponsor communications with FDA, the Agency agreed with the not-less-than (NLT) (b) (4) % criterion (b) (4) (15 Sept2011 pre-NDA Meeting Minutes, Response to Question 14).

Teva therefore employed the NLT (b)(4)% criterion as a guide for dissolution method development and specification setting.

Does the Agency agree that the previously agreed upon NLT (b)(4)% criterion is appropriate for the dissolution profile specification?

Discussion

The Division stated that NLT (b)(4)% dissolution is acceptable as the acceptance criterion. While NLT (b)(4)% dissolution may be the last time point for the acceptance criterion, the profiles should (b)(4) 85% dissolution, regardless of how many time points are needed. If the profile plateaus at close to 85% (e.g., 84%), that is acceptable as well. The Division wants to know where the dissolution profile plateaus, and noted that the firm should continue sampling until they reach either a plateau or 85% dissolution, whichever occurs first.

3. *FDA requests that in vitro dissolution testing in alcohol using the 90 mg dose strength be conducted and that these experiments employ 0%, 5%, 20%, and 40% alcohol (n=12 replicates).*

During the 15 Sep2011 pre-NDA meeting, Teva proposed to conduct in vitro alcohol dissolution experiments on the commercial formulation at the extreme 0% and 40% ethanol conditions in 0.1 N HCl and that the results would be reported in the NDA, section 3.2.P.2.2.3. The Agency agreed with this proposal (pre-NDA meeting minutes, Question 13).

Teva has completed in vitro alcohol dissolution experiments on 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg strength tablets manufactured at the Salt Lake City commercial facility. The testing has been completed in 0.1 N HCl media with 0% and 40% ethanol (n=12 replicates for each condition). These concentrations bracket the intermediate 5% and 20% ethanol conditions. The data demonstrates that no dose dumping occurs and modified release characteristics are maintained.

Teva will include in the NDA the complete data (individual, mean, SD, comparison plots, and f2 values) for the 0% and 40% alcohol experiments on all five strengths.

Does the Agency agree that this dataset fulfills its expectations for assessment of in vitro alcohol dose dumping dissolution, as communicated to Teva at the 15 Sep2011 meeting?

Discussion

The Division still agrees with testing the 0 and 40% ethanol conditions, but recommends that the Sponsor submit the results of in vitro testing on all strengths before the application is submitted, so that if the results are inadequate, additional testing can be initiated as early as possible. The Division noted that, depending on available resources, any data not submitted by the time the final module is submitted (i.e., the start of the user fee goal date “clock”) may not be reviewed and could lead to a Complete Response action.

Question 4

The registration and supportive stability program for CEP-33237 is provided. The current stability program is more extensive than the program discussed during the Type B meeting on 15 September 2011. The program now includes 5 strengths of CEP-33237 tablets (i.e., 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg) and multiple batches produced at the development manufacturing sites as well as the proposed commercial site in (b) (4). Stability data to be available at the time of NDA submission are anticipated to range from 12 to 36 months. The proposed commercial stability protocol, also provided, (b) (4) 15 commercial/validation batches (3 batches each of the 15-mg, 30-mg, 45-mg, 60-mg, and 90-mg tablets).

Does the Division agree that the proposed registration and supportive stability database are sufficient to support NDA review of 5 strengths of the product? In addition, does the Division agree with the suitability (b) (4) approach proposed for the commercial stability protocol?

FDA Response

We agree that the stability database is sufficient to support review of the NDA.

We do not agree with the suitability of the (b) (4) proposed for the commercial stability protocol (b) (4)

Discussion

There was no further discussion on this point.

Question 5

An overview of the in vitro abuse potential program conducted by Teva is provided in Appendix B Section 4.0. The overview addresses the requests for analyses made by the Division during the Type C Meeting on 23 January 2014. Two in vitro manipulation studies are planned that specifically address the following 2 requests:

- to examine simulated intravenous preparation from intact and manipulated tablets*
- to examine simulated intravenous and large-volume extractions on a comparator product (ZOHYDRO™ ER [hydrocodone bitartrate] extended-release capsules, Zogenix, Inc.)*

Proposals for these studies were submitted to the Division for comment on 25 April 2014 (SN0143). Does the Division agree that the 2 proposed studies, in conjunction with the overall in vitro abuse potential program, fulfill expectations discussed in the Type C Meeting on 23 January 2014?

FDA Response

We refer you to our Advice Letter dated June 20, 2014, in which we provided comments regarding the proposed study for simulated intravenous preparation from intact and manipulated tablet and for conducting simulated intravenous and large-scale extractions on the comparator, Zohydro ER.

We remind you to conduct in vitro studies using the to-be-marketed formulation, and we request that you include batch numbers for the lots used in different in vitro studies.

You conducted your large volume extractions using 30 mL of solvent. We encourage you to conduct a subset of extraction studies on intact and manipulated CEP-33237 tablets and Zohydro ER using 100 mL of each of the following solvents: water, acidic solution, and selected aqueous ethanol concentrations (20%, 40%, and 75% ethanol.) Conduct studies at room temperature and elevated temperature under agitated and non-agitated conditions.

Sponsor Response to FDA Comments on Question 5 (via July 22, 2014 email)

1. Teva agrees to conduct the subset of 100-mL extraction experiments requested by the Agency. Teva understands the purpose of these experiments is to assess the feasibility of extraction with intent to ingest. Teva will employ the experimental design in Table 1. The acidic medium, extraction temperatures, and agitation parameters have been chosen to be consistent with previous 30-mL extraction studies conducted by Teva. The two pairs of temperature and agitation conditions have been chosen to bracket extremes.

Table 1: Proposed Subset of 100-mL Extraction Experiments (sampling times to be determined within the range of 5 to 120 minutes)

Test Article	Manipulation	Media (100 mL)	Temperature (Agitation)
CEP-33237 (15 mg and 90 mg strengths) (40%)	Intact	Water	Room temperature (none)
	Coffee Mill	pH 2 phosphate buffer	
	Rotary Abrasion Tool	20% EtOH in water	60°C (500 rpm stirring)
		40% EtOH in water	
		75% EtOH in water	
Zohydro ER (50 mg)	Intact	Water	Room temperature (none)
	Coffee Mill	pH 2 phosphate buffer	
		20% EtOH in water	60°C (500 rpm stirring)
		40% EtOH in water	
		75% EtOH in water	

Does the Agency agree that this subset of experiments is satisfactory for the 100 mL extractions?

Discussion

The Division requested in vitro testing be conducted with readily available solvents such as ethyl acetate or acetone, and an alkaline medium as well. The Sponsor indicated they have completed such studies and the Agency requested that they submit the data.

The Division noted that, if the Sponsor already has data demonstrating that the abuse-deterrent properties of the formulation can be defeated in 30 mL of liquid, there is no need to reproduce the studies using 100 mL of liquid. However, since other abuse-deterrent products have data in 20% ethanol, the Agency would prefer to have data on the performance of the formulation in 20% ethanol as a reference point and for comparison purposes. The Agency stated that, in some situations, it is relevant to evaluate the effect of a larger amount of solvent on the viscosity of the resulting extracts. If the Sponsor finds that the viscosity of the manipulated product in a small volume was too great to administer to subjects in a human abuse potential study, a larger volume should be used. Additionally, the viscosity should be measured and the data submitted.

The Division suggested that the Sponsor prepare a comprehensive table of the testing they plan to submit with a description of why the testing parameters were chosen. This will give the Agency the opportunity to determine if more information is needed. The Agency will provide that feedback separately from the meeting minutes.

2. *In the Advice Letter dated June 20, 2014, the Agency requests that in addition to the experiments conducted in pH 6.3 and pH 10.3 buffers, Teva conduct additional simulated intravenous experiments in water.*
 - *Teva will collect simulated intravenous data for CEP-33237 tablets using water as the extraction medium with sampling times through 30 minutes.*
 - *The additional data will be collected on samples and with conditions presented in Table 2 below, which represent a selected subset of the conditions from the pH 6.3/pH 10.3 study (e.g., only agitation at 150 rpm will be studied, since the no agitation condition generated extraction efficiencies similar to or less than 150 rpm).*

Table 2. Proposed Simulated Intravenous Extractions in Water with Sampling through 30 Minutes^a

Test Article	Manipulation	Medium, Extraction Temperature	Agitation	Sampling Times
Zohydro ER (50 mg)	None (intact beads)	One Condition:	One Condition:	1, 5, 10, 30 min

Test Article	Manipulation	Medium, Extraction Temperature	Agitation	Sampling Times
	Coffee Mill	water at 90°C	150 rpm	
CEP-33237 (15 mg and 90 mg strengths) (40%)	None (intact tablets)	One Condition: water at 90°C	One Condition: 150 rpm	1, 5, 10, 30 min
	Coffee Mill			
	Rotary Abrasion Tool			

^a The pH of water before extraction and of representative solutions after extraction will be measured.

- *Teva will measure and report the pH of the water used for extraction and the pH of representative extracted sample solutions as requested. This additional work will provide data directly comparable to that from the pH 6.3/pH 10.3 study, thus providing a wider pH context for the data.*
- *In addition, all simulated intravenous data previously generated in water as the extraction medium will be included in the NDA. These data include extraction times of 1 and 5 minutes.*

Does the Agency agree that the proposed experiments address FDA's recent advice?

Discussion

Discussion on this and Part 3 of the firm's response to Question 5 were tabled until the firm provides the comprehensive summary.

- In the Advice Letter dated June 20, 2014, FDA requests that Teva conduct multiple-tablet simulated intravenous extraction experiments in 30-50 mL of water to achieve solutions appropriate for intravenous injection. Further clarification on 7 July indicated that intravenous extraction studies should be conducted with the intent of exploring different methods that might produce a solution appropriate for intravenous injection (low viscosity to be injected via a syringe and needle and sufficient concentration of API).*

Teva believes that the dataset for the simulated IV experiments already performed on single tablets adequately characterizes maximizing the concentration of hydrocodone in the lowest volume of solution that can feasibly be syringed, and addresses the Agency's recommendation to explore conditions required to produce an injectable solution.

- *Teva designed its simulated IV studies to employ a functional definition of low viscosity, that is, a volume of solution can be passed through a syringe, filter and needle (either 22 G or 27 G). When no suitable low viscosity solution could be obtained extracting a single tablet with the lowest (5 mL) extraction volume, then 10 mL were employed. 10 mL extraction solution was required for many experiments, as expected for a formulation that includes (b) (4). The majority of the experimental permutations performed yielded syringeable solutions (by this definition) at either 5 mL or 10 mL extraction volumes.*
- *Many of the extracts contained relatively low concentrations of hydrocodone bitartrate, due in part to the greater extraction volume required to provide a syringeable solution. However, Teva found some manipulation and extraction conditions that yielded relatively higher concentrations of drug in extracts that were syringeable. That an ideal solution for IV administration was not obtained illustrates the formulation's resistance to such extractions, and the fact that usable samples were obtained demonstrates that the experiments were of sufficient rigor to explore the abuse condition.*

Teva believes that the extraction of multiple tablets in higher volumes (3–5 tablets in 30–50 mL, for example) would not be expected to yield significantly different extracts (concentrations or viscosity) than the experiments already performed, since the ratio of excipients-to-volume and drug-to-volume vary proportionally. Does the Agency concur? If not, please clarify how the multiple tablet extraction experiments and end points are intended to provide additional clarification of the product's resistance to extraction.

Discussion

Discussion on this portion of the firm's response to Question 5 was tabled until the firm provides the comprehensive summary suggested above.

Nonclinical Question

Question 6

Nonclinical safety studies with CEP-33237 have evaluated reproductive performance, embryofetal, perinatal, and postnatal development, and genotoxicity. Also included in the nonclinical safety program were studies to evaluate the potential safety of degraded hydrocodone, excipients used in the CEP-33237 formulation, process impurities, and the major degradation product, (b) (4). Does the Division agree that this nonclinical safety program is sufficient to support the NDA?

FDA Response

No, we do not agree. Your proposed nonclinical studies to support the safety of hydrocodone drug substance, including having your carcinogenicity studies underway at the time of the NDA submission, appear adequate to support filing the NDA. However,

you do not appear to have completed the minimal genetic toxicology studies for any impurity or degradation product that exceeds the ICH Q3A(R2) or ICHQ3B(R2) qualification thresholds, respectively. Unless you tighten the specifications, these genetic toxicology studies with the isolated impurity will be required in order to file the NDA.

Likewise, your NDA must include adequate safety justification for all of the excipients in the drug product up to the maximum theoretical daily dose of 3 grams per day. The completed 90-day toxicology study in the dog with the drug product formulation is not adequate to support all of the toxicology endpoints as noted in the FDA guidance to industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.

Sponsor Response to FDA Comments on Question 6 (via July 22, 2014 email)

1. *Teva previously provided the qualification plan for the 4 process impurities* (b) (4)

(b) (4) present in the hydrocodone drug substance and one degradation product (b) (4) in the drug product that exceeded the ICH qualification threshold in our previous preNDA briefing package from September 15, 2011.

A structural alert for (b) (4) was identified by (b) (4), the API manufacturer. They conducted in vitro genetic toxicology assays, which were negative for the induction of mutations and structural and numerical chromosome aberrations, as previously discussed at the 20 Oct 2010 CMC End of Phase 2 meeting.

Teva has subsequently conducted in silico SAR studies utilizing DEREK on the remaining impurities and degradation product and the results are provided in Table 3. The results of the DEREK analysis did not show any evidence of structural alerts for genetic toxicology.

Table 3: QUALIFICATION SPECIFICATIONS FOR THE HYDROCODONE DRUG SUBSTANCE/DRUG PRODUCT

Impurity/ Degradation Product	Structure	Drug Sub Source	DEREK NEXUS Result	Impurity Qualification Study (Doses mg/kg/day)	NOAEL	HED	Qualification Specification	Study #
		(b) (4)	No Structural alerts for genetic toxicity	13-Week oral (daily dosing) toxicology study in beagle dogs (b) (4) mg/kg/day)	(b) (4) mg/kg/day (b) (4) mg/m ² / day	(b) (4) mg/day	(b) (4) %	DS- 2011- 036
			No Structural alerts for genetic toxicity	13-Week oral (daily dosing) toxicology study in Sprague Dawley rats (b) (4) mg/kg/day)	(b) (4) mg/kg/day (b) (4) mg/m ² /day)	(b) (4) mg/day	(b) (4) %	DS- 2011- 038
			No Structural alerts for genetic toxicity	13-Week oral (daily dosing) toxicology study in Sprague Dawley rats (b) (4) mg/kg/day)	(b) (4) mg/kg/day (b) (4) mg/m ² /day)	(b) (4) mg/day	(b) (4) %	DS- 2011- 038

(b) (4)	No Structural alerts for genetic toxicity	13-Week oral (daily dosing) toxicology study in Sprague Dawley rats (b) (4) mg/kg/day)	(b) (4) mg/kg/day (b) (4) mg/m ² /day)	(b) (4) mg/day	(b) (4) %	DS-2011-038
	Structural Alert for genetic toxicology	In vitro bacterial mutation assay (b) (4) µg/plate +/- S9) In vitro mammalian chromosome aberration assay (HPBL) (b) (4) µg/mL +/-S9)	(b) (4) µg/mL (b) (4) µg/mL (4-hour incubation -S9) ^a (b) (4) µg/mL (20-hour incubation -S9) ^a (b) (4) µg/mL (4-hour incubation +S9) ^a	N/A	(b) (4) %	

HPBL = human peripheral blood lymphocytes; (b) (4)

^a Selection of does for cytogenetic analysis was based on mitotic inhibition, with the lowest dose with at least a 50% reduction in mitotic index and two lower doses being evaluated

According to the new ICH guidance M7 “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (February 6, 2013), a computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert-rule based and the second methodology should be statistical-based.-The guidance indicates that the outcome of any computer system-based analysis should be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive or negative prediction and to elucidate underlying reasons in case of conflicting results.

The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no concern, and no further testing is required.

To follow up on a structural alert, a bacterial mutagenicity assay can be applied. An appropriately conducted negative bacterial mutagenicity assay would overrule any structural based concern, and no further genotoxicity assessments would be required. These impurities should be considered as a non-mutagenic impurity. A positive bacterial mutagenicity result would warrant further hazard assessment and/or control measures. Alternatively adequate control measures in the case of a positive structural alert alone could be applied in place of bacterial mutagenicity testing.

The Sponsor has performed Q(SAR) expert-rule methodology (ie DEREK) for the evaluation of the three in process impurities that exceed the ICH qualification threshold and the one degradation product that exceeds the ICH qualification threshold. All four structures are predicted to be inactive for mutagenicity.

Based on the M7 guideline, the Sponsor agrees to conduct a second A(SAR) evaluation (statistical based methodology) to provide a complementary prediction as to the potential mutagenicity of these impurities/degradation product.

If both the expert-rule based and statistical (Q)SAR methodologies are negative for the prediction of mutagenicity, the Sponsor believes that these (Q)SAR evaluations are sufficient to conclude that these impurities/degradation product are of no concern, and that no further testing will be required.

If the statistical based (Q)SAR methodology predicts that these impurities/degradation product are potentially mutagenic, the Sponsor will conduct a follow-on in vitro bacterial mutagenicity (AMES) assay for the applicable product. If the Ames assay is negative for mutagenic potential, no further genetic toxicology testing will be performed, as per ICH M7.

Additionally, the in silico SAR evaluation for identified impurities that did not exceed the qualification threshold will be evaluated by the (Q)SAR methodologies

Does the Division agree with this testing strategy?

Discussion

The Division clarified that the ICH M7 approach to accept negative QSAR predictions as an alternative to conducting the Ames assay is only applicable to compounds with structural alerts for mutagenicity. The ICH M7 approach does not supersede the ICH Q3A and Q3B recommendation that once an impurity exceeds the qualification threshold, it should be qualified via the appropriate minimal genetic toxicology screen (one in vitro assay to detect point mutations and one in vitro assay to detect chromosomal aberrations) and an appropriate duration toxicology study. Any impurity, regardless of structural alert,

that exceeds the qualification threshold should be adequately qualified via the recommended studies.

The Sponsor acknowledged that genotoxic impurities with structural alerts should be addressed as per the new ICH M7 guidance document and noted that, in the guidance there is an 18-month implementation period and the Agency will not yet require that both an expert-based and statistical-based QSAR assessment be conducted. The Agency plans to complete both assessments independently for any impurity with a structural alert and act accordingly and recommended that the Sponsor do the same.

2. *In the End of Phase 2 meeting minutes of August 27, 2010, the Agency recommended that 3 month studies in a single species would qualify the drug product if tested up to the equivalent of 3 grams human dose. Testing of the clinical formulation would serve to qualify any impurities and degradants, as well as excipients. The Agency went on to note that this study would most likely need to be conducted in dogs due to the tablet formulation. Although the excipients used in the clinical formulation of hydrocodone ER tablets are compendial, GRAS, and are listed on the CDER Inactive Ingredient database, the Division also noted that the excipients might need qualification if the "GRAS dose" or levels found in previously approved products is exceeded, based on the 3 gram maximum daily dose. The Agency proposed that a single 3-month study with the clinical formulation could be designed to provide support for the safety of an excipient, particularly if an adequate placebo was administered. The Division also stated that the sponsor could submit a rationale as to why they believe that the study should be conducted with the API rather than the clinical formulation.*

Teva conducted the recommended 3-month dog study with degraded and nondegraded 45 mg tablets (DS-2011-025), and was able to achieve a top dose of 180 mg of hydrocodone bitartrate (equivalent to approximately a 584 mg human dose). However, due to the effects of the opioid, the dogs could not tolerate the equivalent of a 3 g hydrocodone bitartrate dose of the clinical formulation. Therefore, separate 3 month repeat-dose impurity qualification studies were conducted with the API in-process impurities, the degradation product that exceeded the ICH qualification threshold, and excipients (DS-2011-037 & DS-2011-037).

The 3-month oral toxicity study in the dog (DS-2011-037) was conducted with a blend of the formulation excipients, with the high dose of these excipients equivalent to the amount of excipients in the clinical formulation that would be ingested if a human took sixty-seven 45 mg tablets (3 grams hydrocodone bitartrate). Dogs were dosed with a mixture of the clinical formulation excipients at a high dose of (b) (4) mg/kg/day (b) (4) mg/m2/day.) Dogs treated with the excipients were compared to dogs that were untreated, in order to ascertain any safety issues associated with the excipients.

Parameters evaluated in the 3-month dog study included clinical observations, body weight measurements, food consumption, electrocardiographic evaluations, ophthalmoscopic

examinations, clinical pathology evaluations (serum chemistry, hematology, coagulation and urinalysis), and gross postmortem examination, organ weight measurements and full complement of tissues was evaluated microscopically.

There were no mortalities, or treatment-related effects on clinical signs, body weight, food consumption, clinical pathology parameters, ECG examinations, ophthalmology examinations, gross post mortem observations, organ weight measurements and histopathology in dogs that were administered oral doses up to (b) (4) mg/kg/day ((b) (4) mg/m2/day) for 90 a minimum of consecutive days.

Based on the meeting minutes from the July 14, 2010 meeting, the Sponsor believes that the excipient study conducted meets the requirements listed by the Division for qualification of the clinical formulation excipients.

Teva requests that the Agency provide clarification on which toxicology endpoints in the referenced FDA guidance to industry were not supported by the 3-month dog study to support safety qualification.

Discussion

The Division stated that the 90-day dog study alone is not sufficient to qualify the excipients to the maximum theoretical daily dose of 3 grams per day. The Division referred to the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>, which states that a 6-month rodent and 9-month nonrodent repeat-dose toxicology study may be required, as well as other standard toxicology assessments (genotoxicity, carcinogenicity and reproduction and developmental toxicology).

In addition to data from the 90-day dog study, a full risk analysis, including a literature review regarding chronic toxicity, reproductive, genetic, and carcinogenicity data, is required to support the safety of the excipients. If the Sponsor identifies any gaps in justifying the safety of any of the novel excipients, they may need to conduct additional toxicology studies. The risk assessment must take into consideration the MTDD of hydrocodone and justify the safety of the excipient up to the level that would be consumed up to the MTDD of hydrocodone.

Clinical Questions

Question 7

No integration of efficacy data from the two Phase 3, double-blind studies with CEP-33237 (C33237/3079 [hereafter referred to as study 3079] and C33237/3103 [hereafter referred to as study 3103]) is planned for the analyses that will be presented in the Integrated Summary of Efficacy (ISE). The design of study 3103 was changed from that of study 3079, with notable differences between the 2 studies including primary efficacy measure, disease

population, permitted rescue medication, and dosing regimen. Does the Division agree with this approach and have any additional comments concerning the ISE shell (see Appendix C)?

FDA Response

Yes, we agree. Although, no integrated efficacy analysis is required for Studies 3079 and 3103, the ISE should contain a discussion of the differences in efficacy findings between the two studies.

Discussion

There was no further discussion on this point.

Safety Questions

Question 8

Study 3104, the open-label, long-term safety study, will not be completed before the planned NDA submission date. A cut-off date of 28 March 2014 will be used for inclusion of data in the ISS and an interim clinical study report will be included in the NDA submission. The final clinical study report for study 3104 will be included with the 4-month safety update, along with updated Integrated Summary of Safety (ISS) and Summary of Clinical Safety (SCS) documents. Does the Division agree with this approach?

FDA Response

Yes, we agree.

Discussion

There was no further discussion on this point.

Question 9

Although a range of doses was used in each of the Phase 3 studies with hydrocodone, Teva does not plan to perform an analysis of adverse events by study drug dose because the complexities of titration and concomitant use of rescue medications would confound interpretation of “dose response.” Does the Division agree with this approach?

FDA Response

No, we do not agree. Include an analysis of adverse events by study-drug dose in the NDA submission. If multiple factors potentially confound this analysis, subgroup analyses may be helpful (e.g., the influence of opioid-experienced versus opioid-naïve, age, and rescue medication use on dose-related adverse events).

Sponsor Response to FDA Comments on Question 9 (via July 22, 2014 email)

Summaries of adverse events by optimal dose will be provided for AEs occurring during titration period and post-titration period for randomized double-blind studies (studies 3079 and 3103) and for hydrocodone treated patients from all 4 studies (3079, 3080, 3103, and 3104), respectively.

As defined in the ISS SAP, an optimal dose of CEP-33237 is the dose strength found to be both effective and tolerable during the titration treatment period and designated as such on the CRF. For patients entering study 3080/3104 who were treated with CEP-33237 in the double blind treatment period in 3079/3103, the optimal dose is the optimal dose from study 3079/3103. For patients entering study 3080/3104 who were treated with placebo in the double blind treatment period in 3079/3103, the optimal dose is the optimal dose from study 3080/3104.

To further explore other confounding factors with optimal dose in the adverse event summaries, summaries of adverse events by optimal dose stratified by opioid status (opioid – naïve vs. opioid experienced), age (≤ 65 years vs. > 65 years), and rescue medication usage. Rescue medication usage will be cut off at median usage level in each of the study periods for the summaries.

Does the Division agree with this strategy?

Discussion

The Sponsor's proposal is acceptable to the Agency. The Sponsor indicated they would include it in the ISS.

Question 10

Recommendations regarding the ISS made by the Division at the Type B meeting on 15 September 2011 have been incorporated into the proposed ISS shell. This has also been updated to include data from clinical studies 3103 and 3104. Does the Division have any additional guidance on the proposed presentation of data in the ISS?

FDA Response

We do not have any additional comments beyond what is presented in the guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

and the *Study Data Standards for Submission to CDER*, available at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Discussion

There was no further discussion on this point.

Statistical Questions

Question 11

The following describes the planned submission format, datasets and CRF format to be included in the NDA. Does the Division agree or have any advice on the plan or the ISS Statistical Analysis Plan (SAP) that has been provided?

FDA Response

We agree with the planned submission format, datasets, and case report forms to be included in the NDA.

Discussion

There was no further discussion on this point.

Additional Clinical Pharmacology Comments

- 1. Indicate if the to-be-marketed product was used in the clinical pharmacology, abuse liability (in vitro and in vivo), and clinical studies.**
- 2. Using in-house data or publications, address drug interactions of hydrocodone with regard to concomitant medications and herbal/food supplements.**
- 3. Provide studies or publications characterizing in vitro metabolism of hydrocodone.**
- 4. Based on in vitro studies or publications, address the potential for clinical drug interaction.**
- 5. Based on the comments provided above regarding alcohol interaction evaluation in vitro (see our response to Question 3), if dose dumping is observed with the 90 mg strength, an in vivo alcohol interaction study may be necessary.**

Discussion

There was no further discussion on this point.

OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness

for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Sponsor Response to FDA Comments on Nonclinical Comment 8 of Attachment 1 (via July 22, 2014 email)

The “Other Important Information” section of the Preliminary Comments (Attachment 1: Nonclinical Comments, #8, p.17) states:

“The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the

FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.”

In Teva’s experience this information is not typically submitted for solid oral dosage forms. Does the Agency agree that this information is not needed to support the NDA filing?

Discussion

The Division clarified that the comments provided are general in nature and not applicable to all drug products. The Division agreed that these comments were not applicable to solid oral dosage forms.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

SPONSOR SUMMARY OF DISCUSSION (Includes Action Items)

1. The Sponsor understands that any impurity or degradant that exceeds ICH Q3A(R2) and Q3B(R2) qualification thresholds, respectively, must be adequately qualified for safety via both a repeat-dose toxicology study of appropriate duration and the minimal genetic toxicology screen (one in vitro point mutation study and one in vitro chromosomal aberration assay). QSAR evaluations alone are not appropriate if the Q3A(R2) or the Q3B(R2) qualification thresholds are exceeded.
2. Regarding safety justification for new or novel excipients when the product is dosed up to the MTDD, the Sponsor understands that the 90-day dog study with the drug product formulation alone is not adequate.

The toxicological risk assessment must address all endpoints discussed in the CDER guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*. The Division recommends that the Sponsor conduct a literature search, and if they find areas that cannot be adequately addressed by referencing the literature, the Sponsor may need to conduct additional studies to address these deficiencies.

3. Regarding Question 3, surrounding dissolution information, the eight batch approach that the firm proposes is acceptable to the Agency. The (b) (4) % criterion is acceptable, however the Sponsor should (b) (4) they reach either 85% dissolution or a plateau, whichever comes first.
4. Regarding dissolution with 40% alcohol, the 90 mg data may be acceptable. However, the Division would like to see it as soon as possible in all strengths in order to confirm the conclusion. The Division clarified that the actual data, including the individual profiles, raw data profiles, should be submitted to the IND. The Sponsor stated that they would submit these data as soon as possible.

5. Regarding Question 5, the Sponsor understands that this issue will be tabled until they provide a summary of what has been done to date and the Agency provides feedback on that. The Agency clarified that the Sponsor should attempt to consolidate their findings as much as possible in a table. The Sponsor stated that they will still plan to provide data in 30 mL at 20% ethanol in order to match previously submitted data.
6. Regarding Question 9, the responses provided by the Sponsor in their reply to the Agency's preliminary comments are acceptable.
7. Regarding Question 1, the Sponsor understands that it is acceptable to provide the information as it becomes available, with the understanding that it may not be possible to review right away.
8. Regarding Question 2, the Sponsor understands that PMRs are issued only if data are still needed, and that carcinogenicity studies need to be underway at the time of application submission. The Division clarified that the carcinogenicity studies need to have at least been reviewed by the Carcinogenicity Assessment Committee (CAC) and a study start date placed on the calendar. The Sponsor stated that they expect to submit their protocol for CAC review by the end of the month, hoping for a decision around the beginning of December. The Division stated that if the carcinogenicity studies are not underway by the submission of the final component of the NDA, the Sponsor should include the dosing start date confirmed with the contract laboratory.
9. The Division stated that it would be acceptable for the Sponsor to submit Module 2.6 and 2.7 without the excipient safety assessment and the minimal genetic toxicology screen studies and then update those sections in a later submission when they submit the completed study reports and safety assessments. However, the Division noted that the Sponsor must submit these studies and updated Module 2.6 and 2.7 in order for the NDA submission to be deemed complete in order to start of the user fee goal date "clock". The Sponsor understands that, when they submit any incomplete modules, they will need to clearly delineate what they expect to update later and specify when they expect to submit it.

ATTACHMENTS AND HANDOUTS

The Preliminary Responses issued to the firm on July 18, 2014 included a list of guidance documents that may be relevant in the drug development process as well as a listing of items possibly useful at pre-NDA preparation stage. Please refer to that document for a complete copy, as it is not reproduced here.

There were no separate slides or other documents used for the meeting.

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

/s/

KIMBERLY A COMPTON
08/21/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 105587

MEETING MINUTES

Teva Branded Pharmaceutical Products R & D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Douglas C. Harnish, Ph.D.
Director, Regulatory Affairs

Dear Dr. Harnish:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hydrocodone bitartrate extended-release tablets.

We also refer to the teleconference between representatives of your firm and the FDA on September 6, 2012. The purpose of the meeting was to discuss how to move forward with your development program after the failure of one of your pivotal Phase 3 studies.

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

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Anesthesia, Analgesia, and
Addiction 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: Type A,
Meeting Category: Guidance on stalled development program
Meeting Date and Time: September 6, 2012, at 3:30 PM
Meeting Location: Teleconference
Application Number: IND 105587
Product Name: Hydrocodone bitartrate extended-release tablets
Regulatory Status: Active IND
Proposed Indication: [REDACTED] (b) (4)
Sponsor Name: Teva Branded Pharmaceutical Products R & D, Inc.
Meeting Chair: Frank Pucino, Pharm.D., M.P.H., Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Industry Representatives	Title
Douglas Harnish, Ph.D.	Director Internal Medicine Regulatory Affairs
Susan Franks, M.S.	Sr. Director Internal Medicine Regulatory Affairs
James Ottinger, R.Ph.	Vice President, Regulatory Affairs
Esther Lukasiewicz-Hagai, M.D., Ph.D.	Director, Clinical Program Leader
Charles Laudadio, M.D., MBA	Medical Director of Hydrocodone Study
Serge Stankovic, M.D.	Vice President, Clinical Development
Eli Eyal, M.Sc.	Associate Director, Global Biostatistics Unit
FDA Attendees	Title
Bob A. Rappaport, M.D.	Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Neville Gibbs, M.D., MPH	Medical Officer, DAAAP
Frank Pucino, Pharm.D., M.P.H.	Clinical Team Leader, DAAAP
Dionne Price, Ph.D.	Biostatistics Team Leader, Division of Biometrics II (DBII)
David Petullo, M.S.	Biostatistics Reviewer, DBII
Kim Compton	Sr. Regulatory Project Manager, DAAAP

BACKGROUND

The Sponsor stated that the purpose of this meeting was to discuss the failure of their pivotal Phase 3 study (Protocol 3079) to meet its primary endpoint on average pain intensity. The Sponsor stated that the design of Study 3079 contained several deficiencies which reduced assay sensitivity, not enabling the drug product to show a significant analgesic effect. A pre-NDA meeting was held with the firm on October 7, 2011.

In the background material for this meeting, the Sponsor provided a new Phase 3 study synopsis (Protocol 3103). They seek agreement that changes to the protocol to improve assay sensitivity are scientifically sound, and that, if this study is positive, no additional clinical studies would be required to support approval of their product via the 505(b)(2) pathway.

The Agency's preliminary responses were sent via email on August 28, 2012. On September 4, 2012, via email, the firm provided their responses. The firm indicated that they would like to change the format of the meeting to a teleconference and discuss the Additional Clinical Comments and Statistical Comments from the preliminary responses.

The Sponsor's responses are incorporated below in *italics* following the FDA Response or Comment to which they pertain. The Figures and Tables included with their response are appended at the end of this document for reference. Discussion that took place at the teleconference is captured following the question to which it pertains in normal text.

DISCUSSION

Clinical

Clinical Question 1

Teva is proposing to conduct a new confirmatory Phase 3 study (study C33237/3103). This study will include a number of study design changes intended to improve assay sensitivity and allow reliable assessment of hydrocodone bitartrate extended-release tablets in patients with moderate to severe chronic pain. Does the Agency agree with the proposed design of the new study (study C33237/3103) and consider it sufficient for a confirmation of efficacy for the intended indication?

FDA Response

We note that the proposed clinical trial, Study C33237/3103, is a 12-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of your product for relief of moderate to severe pain in opioid-experienced patients with chronic low back pain.

Based on the information provided in your briefing packet, the patient population, endpoints, study design, and treatment duration for your proposed study appear suitable for a Phase 3 clinical trial intended to support efficacy for a chronic pain

indication. Whether the data from the proposed study will provide substantial evidence of efficacy for the intended indication would be assessed during the NDA review cycle.

Additionally, the proposed indication for your product is for (b) (4)

Since the patient population you intend to study must have chronic pain (i.e., low back pain for at least six months) and be opioid-experienced (i.e., receiving ≥ 40 mg/day oxycodone equivalent dose), the indication and product labeling may need to reflect the population studied.

Discussion

There was no further discussion of this point.

Additional Clinical Comments

- 1. We have concerns related to the rationale for your proposed Phase 3 study, Study C33237/3103, and whether the results would be generalizable to a broad chronic pain population. The study design could result in restricting the labeling of your product to opioid-tolerant patients, imply the lowest effective dose is 30 mg twice daily, and result in the inclusion of a statement suggesting a lack of efficacy for osteoarthritis patients.**
 - a. For eligibility to participate in the Study C33237/3103, patients must have been receiving a stable around-the-clock opioid pain medication equivalent to a minimum total daily dose of 40 mg of oxycodone for at least two weeks. Therefore, enrollment into this study would require patients to be opioid-tolerant and the indication for your product may need to be restricted to an opioid-experienced population. This type of restriction is generally reserved for products that require patients to be opioid-tolerant for safety reasons.**

Teva's Response (received via email, September 4, 2012)

Teva acknowledges that the patient population for Study C33237/3103 would be opioid-experienced patients. However, the decision to limit this study to opioid-experienced and not to include opioid naïve was to reduce the heterogeneity of the study population.

Teva has no data supporting a different safety profile or a different effect on pain of hydrocodone ER according to the opioid status of the patient. In study 3079, both populations had a similar response to hydrocodone ER. As shown in Figures 1 & 2 (showing observed mean change from baseline), both opioid-experienced and opioid-naïve patients presented a slight decrease as compared to baseline in API scores during the double-blind period. As stated in the briefing package, the lack of demonstrated analgesic activity of hydrocodone ER tablets in study 3079 appears to be due to the overall lack of worsening in the placebo treated patients and does not seem to depend on opioid status.

Discussion

There was no further discussion of this point.

- b. Other than the post hoc analysis of the results of Study C332373/3079, you have not provided a rationale for why your product would not work in osteoarthritis or in opioid-naïve patients.**

Teva's Response (received via email, September 4, 2012)

As stated in answer to 1.a, Teva does not have data supporting a differential effect of hydrocodone ER in opioid naïve as compared to opioid experienced patients. Teva does not have either data supporting that hydrocodone ER is not efficacious in osteoarthritis (OA) patients. As shown in Figures 3 & 4 (showing observed mean change from baseline), both OA and LBP presented a slight decrease as compared to baseline in API scores during the double-blind period.

In addition, when considering the effect size on API estimated using the same method as the one used for the primary analysis (see tables 1 and 2), OA patients and LBP patients were very similar (0.43 vs.0.32) in study 3079. When considering WPI (the proposed primary endpoint for the new study), OA patients even shows a larger effect size than LBP (0.84 vs. 0.48).

Thus, Teva does not believe that hydrocodone ER effect depends on the etiology of pain. The decision to remove the OA patients from the current Study C332373/3103 was again based on reducing patient heterogeneity as well as simplifying certain clinical operation aspects (reduce need for OA specific secondary disability endpoint; different investigators to be involved for OA vs LBP patients).

Discussion

There was no further discussion of this point.

- c. We note that for patients to be randomized into the double-blind treatment phase of the study, they achieve “stable pain relief” (i.e., tolerate the dose and experience a reduction in the Average Pain Intensity [API] score to 4 or less and the Worst Pain Intensity [WPI] score to 6 or less on an 11-point numerical rating scale for 7 consecutive days) on a daily hydrocodone bitartrate extended-release dose of 30 mg every 12 hours during the open-label titration period. However, in Study C332373/3079, only 25% of patients were able to achieve “stable pain relief.”**

Teva's Response (received via email, September 4, 2012)

For clarification, stable pain relief using the above criteria (tolerates the dose and experiences a reduction in the Average Pain Intensity [API] score to 4 or less and the Worst Pain Intensity [WPI] score to 6 or less on an 11-point numerical rating scale for 7 consecutive days) was achieved at the time of randomization to the double-blind period by 28% (32 out of 113) of LBP opioid-experienced patients in study C332373/3079 (and by around 30% of all patients) . It is important to note that this percentage cannot be totally

extrapolated to what will be observed in the new study since the criteria used to define stable pain relief was less stringent in study 3079 and thus patients were not given the opportunity to see the influence on a possible higher dose of hydrocodone ER on their daily pain scores. It is expected that the percentage of patients reaching stable pain relief would be higher than 28% in study 3103 since patients will be provided the opportunity to titrate to a higher dose of hydrocodone ER based upon this new criterion. Teva believes that the criteria proposed for definition of stable pain relief in study 3103 will ensure the enrollment in the double-blind period of patients who achieve a true successful dose of hydrocodone ER. Teva plans to monitor the enrollment rate to the double-blind period of 3103 very closely at the beginning of the study in order to detect a negative impact of these criteria on the number of patients needed to be screened. Teva will consider modifying the criteria if it is deemed too restrictive.

Discussion

The Sponsor stated that they intend to obtain a pain score prior to the administration of rescue medication and use the 24-hour worst pain intensity (WPI) as the primary measure. The Division acknowledged that the 24-hour WPI would be acceptable.

2. **You have identified the following factors that may have contributed to your failed clinical trial (i.e., Study C332373/3079): heterogeneity of the patient population studied; choice of primary outcome measures; choice of dose; and allowed rescue medication. To address these potential limitations, you plan to implement several changes in the design of Study C33237/3103 to improve assay sensitivity and allow for a “reliable demonstration of the therapeutic effect” of your product. However, it is unclear whether the limitations you have identified are relevant factors that contributed to your study failing and, therefore, whether the changes you propose in the study design based on these factors will improve the outcome of the proposed study or demonstrate efficacy in a relevant population. For instance:**
 - a. **According to Table 6-1 (Patient Disposition by Treatment Group) in your briefing packet, approximately 27% of patients in the active treatment arm withdrew due to noncompliance and protocol violations, which was more than the withdrawals due to adverse events (7%) and lack of efficacy (3%). This finding is extremely unusual for a clinical trial evaluating the use of an opioid analgesic for moderate to severe pain and suggests problems with the conduct of the study. We recommend that you explore the nature of these reports of noncompliance and protocol violations and correct the protocol so that this pattern of patient outcomes is not repeated.**

Teva's Response (received via email, September 4, 2012)

Teva acknowledges that there were an usually large percentage of patients (19%) in the active treatment arm that withdrew due to either noncompliance or protocol violations as the Division has noted and has plans to monitor and address these issues in Study C332373/3103.

Discussion

There was no further discussion of this point.

- b. To reduce the likelihood of spontaneous pain resolution for Study C33237/3103, you intend to enroll patients who have had moderate to severe chronic low back pain for at least six months (vs. three months in the previous trial) prior to screening. However, we note that for Study C332373/3079, patients were diagnosed with their pain condition on average 12 years prior to participation.**

Teva's Response (received via email, September 4, 2012)

Teva agrees with the Division but this change is simply meant to ensure that only patients with chronic pain will be enrolled into Study C332373/3103 to avoid the possibility of encountering cases of spontaneous resolution.

Discussion

There was no further discussion of this point.

- c. During the double-blind treatment period, the placebo treatment arm showed minimal worsening in the API as compared to baseline, and the withdrawal rate due to lack of efficacy was relatively low (i.e., 11%). However, the submission did not include adequate information to ascertain differences in rescue medication use between the active and placebo treatment arms. Further, the timing of rescue medication use and the assessment of pain was not provided. Rather than relying on restricting the use of rescue, you may want to consider asking patients to assess their pain prior to the use of rescue so that there is less influence of rescue on the pain assessments. Restricting the use of rescue could result in a larger number of dropouts due resulting in more missing data.**

Teva's Response (received via email, September 4, 2012)

As one can see in Figure 5, placebo patients used slightly more rescue medications especially during the first weeks of tapering as expected. However, overall the mean use of rescue medication was low in both hydrocodone ER and placebo groups. The maximal mean use in placebo was 5.4 mg hydrocodone equivalent daily dose (HED) and occurred during week 2 at the end of the tapering indicating that patients may not have been experiencing higher end of pain intensity spectrum (for the same week, the mean daily use in active arm was of 3.5 mg (HED)).

Similarly, the mean use of NSAIDs overall was low in both hydrocodone ER and placebo groups, indicating, again, that the patients' pain may have been on the lower end of the intensity spectrum. (Figure 6).

Overall, based upon the reported use of rescue medication and NSAIDs, it would appear that the usage of rescue medications was limited and well below the protocol defined limits. Therefore, it does not seem that the slightly higher usage of rescue medication in placebo as compared to active group can totally account for the absence of worsening of pain in placebo.

In Study C33237/3709, Teva did not collect the timing of rescue medication use versus when the pain assessment was conducted. Teva recognizes the importance of recording the timing of pain rescue medication and this monitoring has been incorporated into Study C33237/3103. Teva plans to implement the primary analysis as proposed in the submitted synopsis and to take into account data on pain recorded prior to first rescue medication in a sensitivity analysis. Does the Agency agree?

In terms of our restricted use of rescue, based upon our stable pain relief criteria, Teva believes that this will help patients to find a reliable stable pain relief dose of hydrocodone ER that is not reliant on rescue medication. We believe that this will ultimately reduce the number of drop-outs in Study C33237/3103 of patients on active drug. Additionally, as indicated elsewhere, Teva will implement careful monitoring to ascertain reason for drop out of study.

Discussion

There was no further discussion of this point.

- d. Although the difference between treatment arms for the secondary endpoint, WPI, was statistically significant, the mean change from baseline in API (i.e., +0.14) and WPI (+0.20) scores for the placebo arm were similar, and differences did not appear to be clinically meaningful. While we believe that a pain intensity score based on worst pain for the past 24 hours more accurately reflects the patients experience than a pain intensity score based on average pain, it is not clear that this change will contribute much to improve the outcome.**

Teva's Response (received via email, September 4, 2012)

Teva acknowledges that the WPI scores generated in Study C33237/3079 while statistically significant were not clinically meaningful. We are planning in Study C33237/ 3103 to demonstrate both statistical and clinically meaningful differences between the groups.

Discussion

There was no further discussion of this point.

- e. Based on the information provided in your briefing packet, it is not possible to determine what contribution the inclusion of opioid-naïve and osteoarthritis patients may have had to the failed efficacy findings. It would be informative to know whether these patients used more rescue, had less pain at baseline, or whether there were other factors that differentiated these patients from patients with low back pain and who were opioid experienced that could explain the difference in response to study drug.**

Teva's Response (received via email, September 4, 2012)

The failure to meet the primary endpoint API appears to be due to a large extent on the lack of expected worsening in the placebo group over time and not necessarily due to the etiology of the pain or the opioid status. The explanation for the lack of placebo worsening is uncertain since no one issue was identified by our subgroup analysis and was likely due to a combination of various assay sensitivity issues that has plagued other opioid analgesic studies. One factor that may have contributed to the failure of the study may be the significant percentage of patients (27%) who achieved stable pain relief at the end of the open-label titration with a dose of only 15 mg of hydrocodone ER bid. Post-hoc analyses performed on the patients who were titrated to more than 15 mg hydrocodone ER bid show that there is an important increase in effect size on both API and WPI as compared to those who were titrated to 15 mg bid only. As shown in Tables 1 and 2 (in section 1.b), this is true for the whole population and also when looking at the subgroups of patients based on their opioid status (naïve vs. experienced) or the origin of their pain (LBP vs. OA).

Please see also response to Comments 1a, 1b and 2c.

Discussion

The Sponsor stated that they were unclear what the appropriate follow-up should be for patients who discontinue study medication early. The Division stated that the Sponsor should continue to collect safety as well as efficacy information for these patients. Using efficacy data collected after withdrawal from study medication is novel, but would avoid excessive amounts of missing data. Including this data in the primary efficacy analysis will depend on the choice of causal estimand. The Division referred the Sponsor to the National Academy of Science (NAS) report on the prevention and treatment of missing data for examples of casual estimands. The report is available online at <http://www.nap.edu/catalog/12955.html>.

The Division stated that, for a Phase 3 clinical trial, it is essential to work to keep the number of patients who withdraw from the study early as low as possible. Since limiting the amount of rescue may increase the number of withdrawals, the Division disagreed with restricting its use. Patients should only be discontinued if the amount of rescue administration is aberrant or unusual. To avoid inflation of the treatment effect based on the use of rescue, pain could be assessed prior to use of rescue medication.

The Division noted that there appeared to have been inherent problems with the conduct of the failed study, while the basic study design was one which often has been successful. The Division cautioned the Sponsor not to over-interpret the failure of the trial and make too many changes in the study design for the proposed Phase 3 study. The Division expressed concern that a restrictive patient population excluding opioid-naïve patients, in an attempt to increase the likelihood of positive efficacy results, would limit the inferences allowed in product labeling. This would not be appropriate for a product such as an extended-release hydrocodone. Therefore, the study should include an appropriate patient population.

The Division further questions rolling over patients who drop out due to lack of efficacy into an open-label safety study. Patients who failed to respond to the study drug would not provide meaningful safety data if they were undertreated. The Sponsor stated that they believe there may be sufficient safety data from the previous completed study, but the Division noted that relying on safety data from a failed study would not be acceptable.

The Division stated that there are several concerns the Sponsor must address in a revised protocol.

1. Avoid restricting the population for the proposed study such that it no longer reflects the population intended for use once approved.
2. Keep patients who require rescue medication in the study.
3. Rolling over patients who drop out early due to lack of efficacy into the safety study is not acceptable.

The Division stated that a single diagnosis (e.g., low back pain) in the study population is acceptable.

3. **We note that you are planning to conduct a six-month open-label safety clinical trial (Study C33237/3104) to provide additional long-term safety information on hydrocodone bitartrate extended-release tablets.** (b) (4)

Teva's Response (received via email, September 4, 2012)

For clarification; (b) (4)

Discussion (b) (4)

patients completing the double-blind portion of the study should be enrolled into the open-label safety study.

4. According to the protocol synopsis for Study C33237/3103, it appears that you intend to perform pure tone audiometry within two weeks of the start of the open-label titration period and within 4 weeks of the final visit (week 12 or last post-baseline observation). It is unclear if the first assessment will be conducted prior to receiving study medication or during the titration phase, and whether the second assessment will be conducted within 4 weeks prior to or following the final visit. To adequately detect a safety signal, conduct audiology assessments before, during and after the treatment period.

Teva's Response (received via email, September 4, 2012)

The wording is correct. The first audiometry will be performed within 2 weeks of starting OLT prior to receiving drug. The final audiometry will be obtained as close as possible to the final visit (week 12) but in no case more than 4 weeks prior to that visit. This scheduling flexibility is allowed to accommodate for the utilization of local audiologist (as the test will not be performed at the study site) and is considered methodologically acceptable.

Discussion

There was no further discussion of this point.

Regulatory

Regulatory Question 1

In order to reduce the heterogeneity of the patient population in the proposed study, Teva has limited the patients to be evaluated to those with moderate to severe chronic low back pain who are opioid-experienced. Does the Agency agree that positive efficacy results obtained from this study will support the indication (b) (4)

?

FDA Response

Refer to our response to Clinical Question 1.

Discussion

There was no further discussion of this point.

Regulatory Question 2

Does the Agency agree that, if the proposed Phase 3 study is positive, no additional efficacy studies will be required to support registration of hydrocodone bitartrate extended-release tablets (b) (4)

by the 505(b)(2) pathway?

FDA Response

Should you be able to demonstrate efficacy for your product based on the proposed Phase 3 clinical trial (i.e., Study C33237/3103), it may be possible to use this single clinical trial to support submission of an NDA application for a chronic pain indication

through the 505(b)(2) regulatory pathway. However, all available data, including the results of your failed clinical trial (i.e., Study C332373/3079), will need to be reviewed during the NDA review cycle, and product labeling may need to reflect the results of the failed study and limitations to the intended population based on the successful study.

*Teva's Response (received via email, September 4, 2012)
Teva acknowledges the Division comments.*

Discussion

There was no further discussion of this point.

Statistical

Statistical Comments regarding Study C33237/3103

We will evaluate the appropriateness of your statistical analyses including the approach to handling missing data once you submit a full protocol. In the protocol, clarify how intermittent missing data will be handled in the primary analysis. Also, you indicate that patients using excessive amounts of rescue medication will be withdrawn from the study. These patients may be considered treatment failures and withdrawn from study drug, but they should generally not be withdrawn from the study. The protocol should include how the efficacy data from these patients will be handled in the primary analysis.

We further emphasize that the National Academy of Sciences report recommends explicit specification of the causal estimand. The choice of a causal estimand may have important implications for trial design, conduct and statistical inference. For example, whether to collect outcome data after a subject discontinues assigned treatment depends on the choice of causal estimand.

Teva's Response (received via email, September 4, 2012)

The reason for withdrawing patients from the study in case they use excessive amounts of rescue medication is to avoid a confounding effect on the estimate of pain.

Teva would like to discuss further during the meeting the recommendations of the FDA to withdraw patients who used excessive amount of rescue medications from the study drug (and consider them as treatment failure) but keep them in the study and continue collection of pain data when they are off study drug.

Teva would like to clarify during the meeting the most appropriate way to handle efficacy data from these patients. Teva intends to consider these data as part of a sensitivity analysis but not as part of the primary analysis.

In respect to sensitivity analysis to assess the impact of missing data on the primary analysis treatment effect estimate, Teva believes that the following method addresses the

recommendations published in the National Academy of Sciences report and would like to discuss this further during the meeting.

- (1) Before revealing of the blind, missing observations will be classified according to type of missingness mechanism: MCAR, MAR or MNAR.*
- (2) Sensitivity analysis to assess the impact of missing data assuming MNAR*

In order to explore the possible impact of MNAR missing values on study results, the multiple imputation analysis will be modified so that the results will be examined under a range of assumptions about the effect of treatment in the MNAR unobserved data.

This analysis will combine MAR (and MCAR) as well as MNAR imputation, according to the following steps:

- 1. If the missing data pattern is not monotonic, a Markov Chain Monte Carlo (MCMC) method with 5 imputations will be used to achieve a monotone missing pattern. Then, the regression method of multiple imputation will be performed on the data with monotone missing pattern with 1 imputation.*
- 2. If the missing data pattern is monotone, then a regression method for imputing missing data with 5 imputations will be performed.*
- 3. MNAR Missing observations (that cannot be deemed as MAR or MCAR) that belong to active treated subjects will be removed.*
- 4. The Mixed repeated measures model with categorical time effect will be applied for each of the datasets created in step 1-3 to derive treatment effect at each scheduled week (1 through 12).*
- 5. Assuming that the treatment effect for MNAR missing data at certain time is only $(1-\delta)*100\%$ (δ ranging from 0 to 1) of the estimated treatment effect for that time, MNAR imputation for MNAR missing observation that belong to active treated subjects will be calculated as the MI imputed value minus $(1-\delta) * \text{treatment effect}$.*
- 6. The imputed data will be analyzed at week 12 using an analysis of covariance (ANCOVA) model (SAS MIXED procedure). The model will include treatment, center, and baseline WPI score. The least squares means at week 12 of the change from baseline in WPI will be compared between the active-drug and placebo treatment groups. Treatment effect, 95% confidence interval, and p-value will be calculated using the SAS MIANALYZE procedure.*
- 7. Steps 4-6 will be repeated for a grid of values for δ , the portion of preserved treatment effect, among MNAR missing observation that belong to treated subjects, where $\delta=1$ correspond to full observed effect and $\delta=0$ to no effect at all.*
- 8. The treatment effect p-values for the grid of δ will be presented.*

Discussion

The Sponsor stated that the reason for withdrawing patients from the study if they use excessive amounts of rescue medication was to avoid the potential for confounding the estimate of pain.

The Division recommended that the Sponsor collect both efficacy and safety data from all patients who discontinue the assigned study medication early. The Division reiterated that the

choice of estimand will affect whether the data collected after discontinuation from study medication are included in the primary analysis.

ISSUES REQUIRING FURTHER DISCUSSION

The Sponsor contacted the Division via email following the meeting asking for clarification regarding whether the safety database requirements of at least 500 patients total and with 100 patients for six months and 50 patients for one year is still acceptable, barring any unforeseen safety finding, as stated in the July 14, 2010, EOP2 meeting

Division Response

In your email of September 7, 2012, you state the following:

To date, we have a total of 329 patients treated in Study 3080 with 185 completing at least 12 months (98 rollover patients from Study 3079 and 87 new patients). If we exclude those patients who took 15 mg hydrocodone ER as their stable dose since that dose is no longer being offered in the new study 3103, there were 224 patients treated with stable doses ≥ 30 mg (115 rollover and 112 new patients). From these, 139 out of 224 completed 12 months of treatment (71 rollover and 68 new patients).

As we discussed during the September 6, 2012, meeting, it is important that the safety database reflect safety from subjects treated with a dose high enough to provide efficacy. As long as the majority of the safety data are collected from patients, in past or future studies, with dosing appropriate for the management of their pain, your proposal to include those data in combination with the additional patients you plan to enroll in the next efficacy trial, appears to be adequate to produce an acceptable safety database.

ACTION ITEMS (Includes Sponsor Summary of Issues)

1. The Sponsor will amend the protocol to include opioid-naïve patients.
2. The Sponsor will not enroll patients who drop out of the double-blind portion of the study due to lack of efficacy into the open-label safety study.
3. The Sponsor noted that the Division recommends that they not discontinue patients from the study due to use of rescue. The Sponsor can limit rescue to a safe amount, so that only patients who require more than a safe amount will discontinue early. The collection of pain scores prior to use of rescue can minimize the effect of rescue medications on the outcome.
4. The Sponsor understands that enrolling patients with only one chronic pain diagnosis may be acceptable for a broader chronic pain indication because hydrocodone is already approved in combination with other analgesics for broad pain indications (i.e., acute pain, or moderate to moderately severe pain).

5. The Sponsor plans to revise their protocol and submit it with details of the statistical analysis plan for review.

ATTACHMENTS AND HANDOUTS

Copies of the responses provided by the Sponsor via email on September 4, 2012, have been included above following the item to which they pertain. Copies of the Tables and Figures in that material are appended at the end of this document.

Appendix 1: Figures and Tables from Sponsor's September 4, 2012 emailed responses

Figure 1: Change from baseline in observed weekly average API Scores in Opioid Experienced Patients

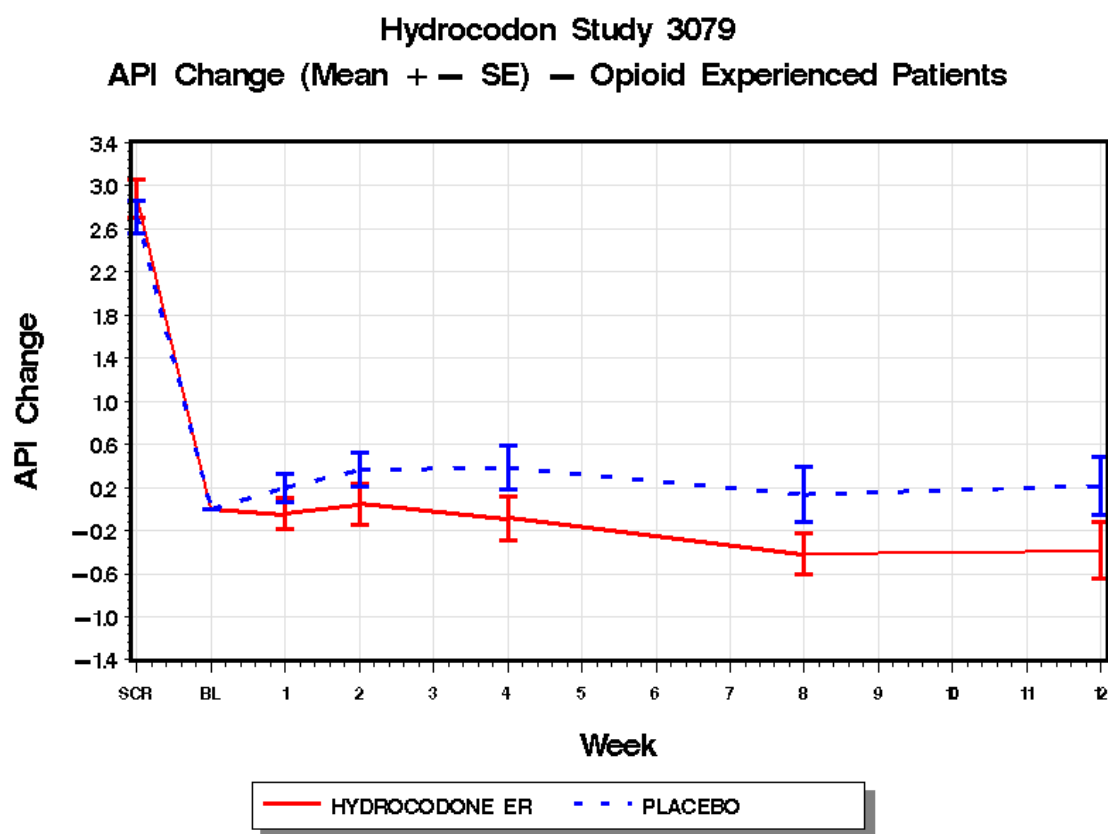


Figure 2: Change from baseline in observed weekly average API Scores in Opioid Naïve Patients

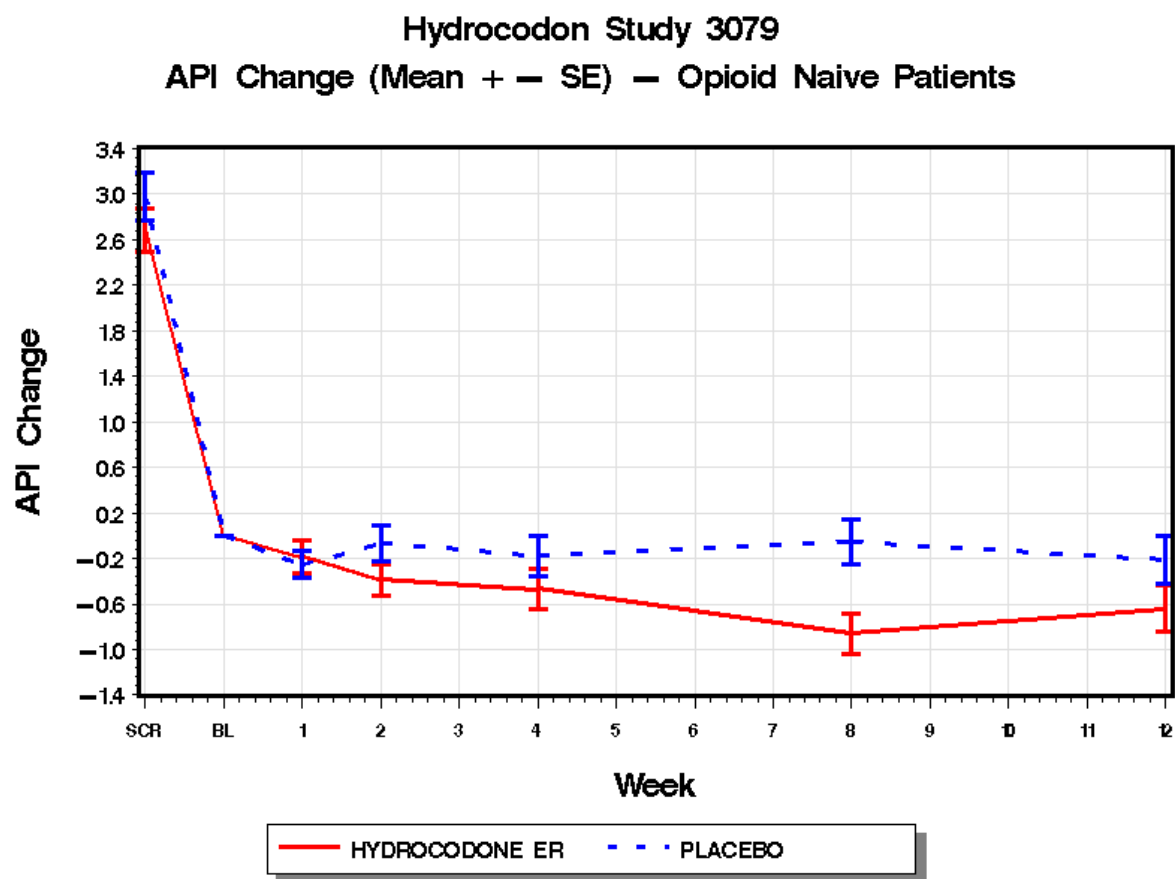


Figure 3: Change from baseline in observed weekly average API Scores in LBP Patients

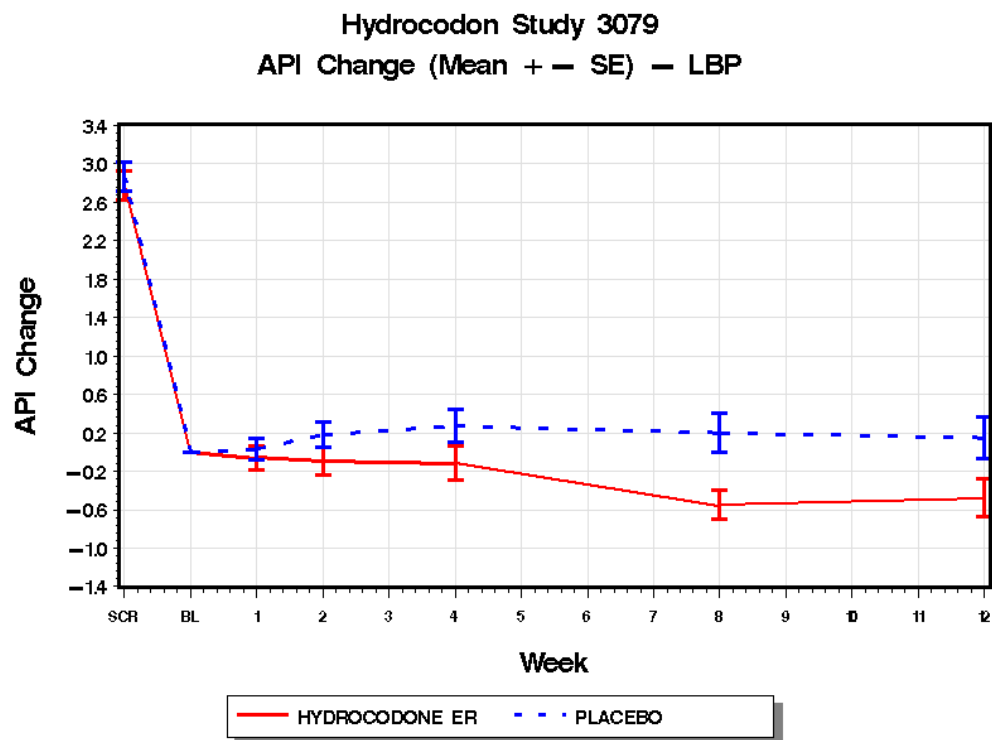


Figure 4: Change from baseline in observed weekly average API Scores in OA Patients

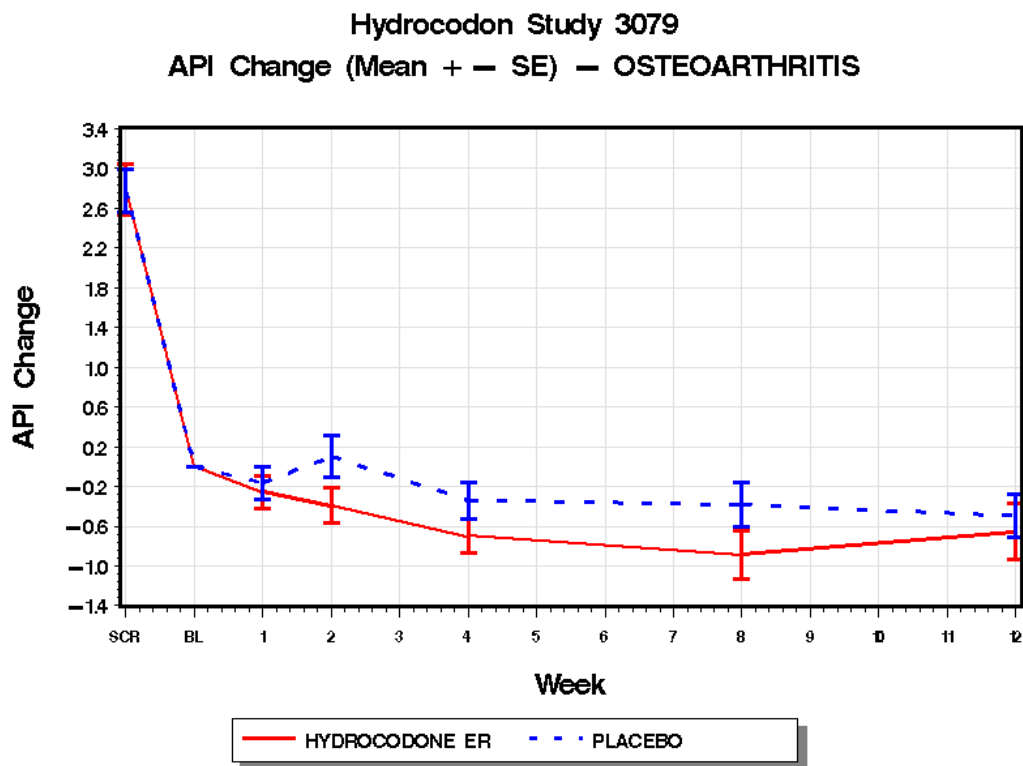


Table 1. Imputed Data Analysis Set after using Multiple Imputation Method for Missing Values
API Treatment Effect Estimates

	ESTIMATE	SE	P-Value	Lower 95% CI Limit	Upper 95% CI Limit
Population					
All *	0.353	0.231	0.1336	-0.112	0.818
Opioid Experienced Patients**	0.523	0.324	0.1102	-0.121	1.166
Opioid Experienced Patients and Dose $\geq$ 30mg**	0.618	0.354	0.0829	-0.081	1.317
Opioid Naive Patients**	0.208	0.284	0.4648	-0.351	0.768
Opioid Naive Patients and Dose $\geq$ 30mg**	0.513	0.346	0.1398	-0.170	1.196
Patients with LBP**	0.315	0.260	0.2261	-0.197	0.828
Patients with LBP and Dose $\geq$ 30mg**	0.485	0.308	0.1182	-0.125	1.095
Patients with OSTEOARTHRITIS**	0.427	0.387	0.2748	-0.350	1.204
Patients with OSTEOARTHRITIS and Dose $\geq$ 30mg**	0.809	0.462	0.0877	-0.125	1.743
All with Successful Dose $\geq$ 30mg**	0.562	0.269	0.0415	0.023	1.102

*Primary analysis

** Post-hoc analyses. No adjustment for multiple tests was done.

**Table 2. Imputed Data Analysis Set after using Multiple Imputation Method for Missing Values
WPI Adjusted means Estimates**

	ESTIMATE	SE	P-Value	Lower 95% CI Limit	Upper 95% CI Limit
Population					
All*	0.543	0.240	0.0261	0.066	1.019
Opioid Experienced Patients**	0.588	0.351	0.0971	-0.108	1.284
Opioid Experienced Patients and Dose $\geq$ 30mg**	0.659	0.385	0.0911	-0.108	1.426
Opioid Naive Patients**	0.457	0.310	0.1419	-0.154	1.069
Opioid Naive Patients and Dose $\geq$ 30mg**	0.692	0.392	0.0800	-0.084	1.467
Patients with LBP**	0.479	0.282	0.0911	-0.077	1.036
Patients with LBP and Dose $\geq$ 30mg**	0.649	0.321	0.0454	0.013	1.284
Patients with OSTEOARTHRITIS**	0.842	0.416	0.0515	-0.006	1.691
Patients with OSTEOARTHRITIS and Dose $\geq$ 30mg**	1.077	0.570	0.0732	-0.111	2.265
All with Successful Dose $\geq$ 30mg**	0.722	0.293	0.0178	0.131	1.312

*Secondary analysis

** Post-hoc analyses. No adjustment for multiple tests was done.

Figure 5: Mean Rescue Medication Usage in Hydrocodone ER Treated Patients vs Placebo

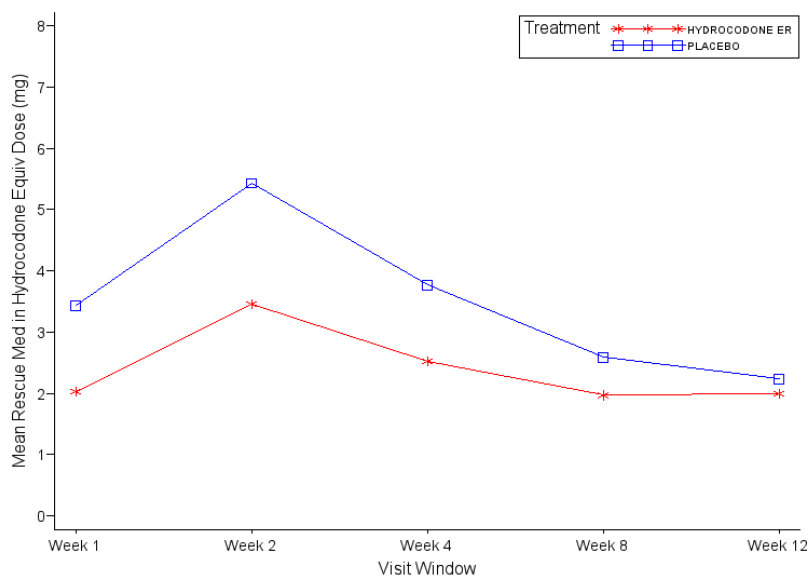
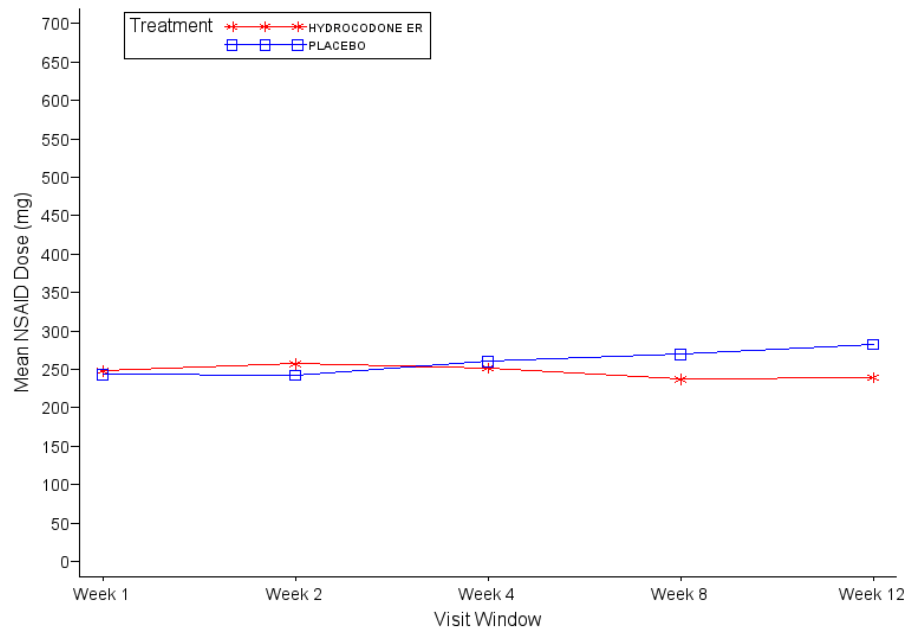


Figure 6: Mean NSAID Medication Usage in Hydrocodone ER Treated Patients vs Placebo



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

/s/

KIMBERLY A COMPTON
10/10/2012



IND 105587

MEETING MINUTES

Cephalon, Inc
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Susan Franks, M.S.
Director, Regulatory Affairs

Dear Ms. Franks:

Please refer to your Investigational New Drug Application (IND) submitted under section 595(i) of the Federal Food, Drug and Cosmetic Act for CEP-33237 (hydrocodone bitartrate extended-release tablets).

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2011. The purpose of the meeting was to discuss your plans and preparations for submission of a new drug application (NDA) for your product.

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

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

If you have any questions, call me at (301) 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly A. Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

INDUSTRY MEETING MINUTES

Deleted: <sp>

Meeting Date: September 15, 2011

Time: 12:00 PM EST

Location: White Oak Conference Room 1311

Application: IND 105587

Regulatory Status: Active IND

Investigational Product: CEP-33237 (Hydrocodone extended-release tablets)

Proposed Indication:

(b) (4)

Sponsor: Cephalon, Inc.

Type of Meeting: Type B

Meeting Chair: Frank Pucino, Pharm.D., M.P.H., Acting Clinical Team Leader

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Industry Representatives	Title
Brad Barnes, Ph.D.	Sr. Director, Drug Safety
Mona Darwish, Ph.D.	Sr. Director and Group Leader, Clinical Pharmacology
Susan Franks, M.S.	Director, Regulatory Affairs
Christine Kampf	Regulatory Associate
Derek Moe, Ph.D.	VP, CIMA Drug Delivery Technologies
Gwendolyn Niebler, D.O.	VP, Clinical R&D
James Ottinger, R.Ph.	VP Worldwide Regulatory Affairs
Jennifer Pansch, D.V.M.	Senior Manager, CIMA Regulatory Affairs
Randal Seburg, Ph.D.	Director, CIMA Analytical Development
Srdjan Stankovic, M.D., MSPH	Sr. VP Worldwide Clinical Research
Renee Yancey	Director, CMC, Regulatory Affairs
Ronghua Yang, Ph.D.	Sr. Director, Biostatistics
Philip G Simonson, Ph.D.	Sr. Director, CIMA Regulatory Affairs
Denise D'Andrea, M.D.	Sr. Director and Group Leader, Clinical Research, Cephalon
FDA	Title
Bob A. Rappaport, M.D.	Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Frank Pucino, Pharm.D., M.P.H.	Medical Team Leader, DAAAP
Neville Gibbs, M.D., M.P.H.	Medical Officer, DAAAP
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAAP
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
David Petullo, M.S.	Biostatistics Reviewer, Division of Biostatistics II (DBII)
Dionne Price, Ph.D.	Biostatistics Team Leader, DBII
Danae Christodoulou, Ph.D.	CMC Lead, Office of New Drug Quality Assurance (ONDQA)
Lori Love, M.D., Ph.D.	Team Leader, Controlled Substance Staff (CSS)
Silvia Calderon, Ph.D.	Team Leader, CSS
Sandra Suarez-Sharp	ONDQA/Biopharmaceutics Reviewer
Kim Compton	Senior Regulatory Project Manager, DAAAP
Thanh-Van (Vicky) Nguyen	Pharm.D. Candidate, Medical College of Virginia, School of Pharmacy
Carmen Gay	Pharm.D. Candidate, Florida A&M University, College of Pharmacy and Pharmaceutical Sciences

BACKGROUND

The purpose for this meeting was to provide the Sponsor with feedback on the questions in their August 4, 2011, meeting package, which were related to plans and preparations for submission of a new drug application (NDA) for this product.

On September 14, 2011 (prior to the September 15, 2011, meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the Sponsor in their August 4, 2011, meeting package.

The meeting entailed further discussion of Questions 6.1, 8, 11, and 14.

Presented below are the Agency's September 14, 2011, comments and responses to questions in the background meeting package, followed by a summary of relevant discussion that took place at the meeting itself. The Sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

DISCUSSION

Chemistry Questions

Question 11

At the End of Phase 2 Meetings held on July 14th (Clinical) and Oct 20th 2010 (CMC), the Agency advised that physicians may prescribe much higher doses of a single ingredient hydrocodone product to opioid tolerant patients than what is traditionally given in combination hydrocodone products. Specifically, FDA advised that a maximum daily dose would be 3 gram per day, and that this dose should be used to determine qualification thresholds and toxicology testing plans. Considering that the Sponsor's highest proposed dosage strength is a (b) (4) tablet, dosing patients with 3 grams of hydrocodone per day would require no fewer than (b) (4) tablets weighing (b) (4) mg each, split between two daily doses.

Cephalon has reviewed the published literature and analyzed IMS market research data and has summarized this information in the document entitled "Justification for Maximum Expected Human Daily Dose" in the Background Materials. Based on the literature and opioid prescribing practices, the Sponsor proposes (b) (4)

Based on the information summarized in this review document, would the Agency agree that the anticipated maximum permitted daily exposure of hydrocodone bitartrate for humans (b) (4) gram/day is justified?

FDA Response

We note that there are no clinical usage data for single-entity hydrocodone products, therefore, a Maximum Theoretical Human Daily Dose (MTDD) can only be estimated. Currently, the MTDD for controlled-release morphine products has been set at 2 grams/day and for oxycodone controlled-release products at 1.5 grams/day based on clinical usage data. Although the relative potency of hydrocodone compared to oxycodone and morphine reported in the literature is variable, your proposal for a MTDD (b) (4)



We recommend that you continue to evaluate the safety of impurities and excipients based on a 3 gram/day MTDD which will provide coverage for a broad range of dosage strengths.

Discussion

The Sponsor stated that they were only able to reach a top dose of 180 mg in their 3-month dog study because of dosage formulation feasibility limitations and that they would not be able to qualify the 3 g/day clinical dose. The Sponsor stated that they could probably qualify the degradants at the 3 g/day level, but were doubtful about being able to do so with the excipients. The Division stated that the Sponsor should dose to a maximum feasible dose and then provide additional information such as literature references or information on similar compounds to build a weight-of-evidence approach in order to justify the levels of the excipients.

The Sponsor stated that the (b) (4) impurity is the main degradant in their product and that it forms rapidly and then levels off. They have synthesized the (b) (4) impurity and will use it in an independent qualification study.

The Division stated that, while the *FDA Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)* does not specify that the excipients need to be qualified separately, the excipients may be tested in combination via the use of a placebo formulation. However, testing the placebo formulation may result in dose-limiting toxicity which could limit the ability to determine which excipient in the placebo was contributing to the toxicity. The Division also noted that, in general, testing of a placebo formulation is recommended if there is any reason to believe that the excipients could interact and result in a differential toxicological profile.

The Division clarified that the limit on dosing in the labeling for the Nucynta ER product, which is not a pure opioid and which exhibits a ceiling effect, cannot be generalized to other opioid analgesic products for which tolerance develops and which do not have a similar ceiling. If there is a known toxicity for one of the excipients at a specific level, it may be necessary to consider a limit on dosing of the product in the product labeling.

The Division acknowledged that the maximum daily dose of 3 g/day of hydrocodone would require consumption of a large number of pills. However, clinical use data for oxycodone drug products indicates that there are some individuals who take up to 1.5 grams per day of that product. Therefore, there is evidence that at least some patients are consuming a large number of pills per day, so while perhaps uncommon, this level of dosing does occur.

Question 12

A registration stability plan was previously discussed at the End of Phase 2 CMC meeting and was considered acceptable with the addition of bioequivalence studies to bridge the Phase 3 and commercial manufacturing sites. The current stability plan (Drug Product Overview- Section 1.6) is similar with the exception of the potential for two commercial sites and the (b) (4) *.*

At time of the NDA submission, the following stability database will be available for three tablet strengths: (15 mg, 30 mg and 45 mg)

- *24 months of supportive stability data from seven prototype formulation batches manufactured at the laboratory scale at Cephalon's CIMA LABS INC Brooklyn Park, MN facility;*
- *12-18 months of supportive stability data from six Phase 3 formulation batches (2 batches per strength) manufactured at the pilot scale in Cephalon's CIMA LABS INC Eden Prairie (EP), MN facility using the same* (b) (4) *formulation as used for primary stability batches;*
- *A minimum of 12 months primary stability data for six Phase 3 formulation batches (2 batches per strength) manufactured at the pilot scale in EP using a* (b) (4) *formulation.*

Two manufacturing sites are under consideration for commercial production, Cephalon Inc, Salt Lake City (SLC), UT and the aforementioned CIMA EP site. The proposed commercial batch sizes are approximately (b) (4) *times the size of pilot scale batches. Scale up optimization is underway and the proposed commercial scale formulation is yet to be finalized. If any changes to the Phase 3/pilot scale formulation are required, these are expected to be Level 1 changes permitted by SUPAC-MR guidance, as described in section Drug Product Overview, Section 1.2.4.*

- *If the Phase 3/pilot scale manufacturing site (EP) is selected as a commercial site, the Sponsor would propose, at a minimum, to study stability of the commercial scale validation batches manufactured in EP, and file the stability documentation in annual reports.*
- *If the SLC site is selected as a commercial site, the Sponsor will include 3 months of long-term and accelerated stability data in the NDA from at least one batch of each strength of the commercial formulation manufactured at the SLC site. Bioequivalence of the SLC materials to Phase 3 materials will be established as previously agreed in the bioequivalence site bridging plan submitted to IND 105587 Sequence 0026 on 18 Feb 2011.*

Does the Agency agree that the registration and supportive stability database proposed is sufficient to support an NDA for this extended release dosage form with a proposed shelf life of (b) (4) *months?*

FDA Response

Your proposal for the EP manufacturing site appears reasonable, provided that you submit batch release data for the commercial formulation of the three strengths in the NDA.

Should you decide to modify your commercial formulation as described in your pre-NDA meeting package, include batch release data for the commercial formulation of each of the proposed (b) (4) strengths in the NDA. In addition, provide a side-by-side comparison to show any changes in formulation components and composition, batch size, manufacturing process, and equipment, from Phase 3 to commercial product manufacturing. Provide adequate justification in the NDA for the proposed level of change(s).

We remind you that, if the SLC site is selected, you must submit three months of stability data for a full-scale batch of each strength manufactured at the SLC site with your initial NDA package according to the EOP2 meeting minutes of Nov. 18, 2010.

Discussion

There was no further discussion on this point.

Question 13

In a General Advice letter dated 5 May 2011 that was issued in response to IND 105587 sequence 0026, the Agency noted "The in vivo alcohol dose dumping study was conducted with a prototype formulation for the hydrocodone bitartrate extended-release 15 mg tablets containing (b) (4). Given that the formulation intended for marketing contains a different amount of (b) (4) (%), we recommend that you conduct an additional in vitro alcohol interaction study using different alcohol concentrations (0%, 5%, 10%, 20%, and 40%) in an additional medium (0.1N HCl)."

The (b) (4) contained in the prototype tablets used in the alcohol in vivo study was (b) (4) compared to the (b) (4) used on (b) (4) for the Phase 3 batches and an estimated (b) (4) for the commercial formulation as further described in Drug Product Overview, Section 1.2.5.1. Though there are differences between the formulations of the clinical prototype dosed in the in vivo alcohol interaction study C33237/1076 and the potential commercial scale product, the levels of (b) (4) are essentially the same. While the commercial scale formulation has yet to be finalized, no changes to (b) (4) levels are anticipated, and the overall differences in release controlling excipients between the prototype PK batch and the final commercial formulation will be classified as a SUPAC-MR level 1 change.

In vitro alcohol interaction studies at the 40% alcohol concentration in 0.1 N HCl medium have been routinely performed on tablet batches during development, with example profiles also provided in Drug Product Overview, Section 1.2.5.1. Additional profiles generated on a batch at five alcohol concentrations ranging from 0-40% are also provided, which demonstrate that the 40% ethanol concentration is the most aggressive condition. The Sponsor proposes conducting the in vitro alcohol interaction study on the commercial formulation at the extreme 0 and 40% ethanol conditions in 0.1N HCl, and will report the results in the NDA in section 3.2.P.2.2.3.

Does the Agency concur that the data provided support that the 0 and 40% alcohol concentrations in 0.1 N HCl medium adequately bracket intermediate alcohol concentrations (5-20%), and that the 0 and 40% alcohol concentrations are sufficient for the in vitro alcohol

FDA Response

Yes, we concur with your proposal.

Discussion

There was no further discussion on this point.

Question 14

The optimization of the dissolution method (b) (4)
, and the rationale for setting the dissolution specifications are described in Drug Product Overview- Section 1.4.

Does the Agency agree with the proposed dissolution method and rationale for setting specifications for finished product?

FDA Response

No, we do not agree. We strongly recommend that you follow the approach below:

- 1. conduct additional studies to further optimize the dissolution method to achieve at least 80% dissolution at the proposed 12-hour specification time point, or,**
- 2. to ensure that at least 80% of the drug has been released, set the last specification-time point at a later time (i.e., 18 hrs).**

Discussion

The Division clarified that the 18 hours cited in response point #2 above was merely an example and that the actual time point should be data driven based on the Sponsor's actual testing.

Question 15

The Sponsor revised the In Vitro Tampering Protocol in response to the Agency's recommendations at the 20 October 2010 End of Phase 2 Meeting. The revised protocol explores a range of conditions relevant to potential abusers that could alter extractability or release of hydrocodone from the matrix, including particle size effects, solvent effects, and various extraction conditions, and includes justification for the experimental conditions proposed. The experiments will be conducted on the commercial formulation. The Sponsor proposes to include a summary of the in vitro tampering study results together with the data from the comparative human PK study (crushing versus intact tablets) in Module 2.7.1, within section 2.7.1.3 - Comparison and Analyses of Results Across Studies. The detailed methodologies and complete reports for the in vitro tampering will reside in 3.2.P.2.2.3 and the comparative PK study report would reside in Module 5.

Does the Division agree the revised protocol adequately explores a range of tampering conditions relevant to potential abusers and to the Sponsor's plan for reporting the data?

FDA Response

Based on your background studies, the proposed in vitro tampering protocol for the to-be-marketed product appears adequate.

Your proposal to place the results in the above mentioned sections is acceptable.

Discussion

There was no further discussion on this point.

Nonclinical Questions

Question 8

Table 1 in the Nonclinical Background information outlines the process impurities for hydrocodone drug substance and drug product, the estimated/proposed specification, the anticipated exposure using a maximum daily dose of 3 gram/day, and the qualification plan for these impurities. A maximum daily dose of 3 gram/day was used for this Plan as this was the advice given during the End of Phase 2 meeting; if the Division agrees to the proposed (b) (4) maximum daily dose as presented in the Justification for Maximum Expected Human Daily Dose the Qualification plan may be revised. Does the Division agree that this is an acceptable approach for qualification of degradation products/impurities in the hydrocodone drug product?

FDA Response

Your plan to qualify the impurities based on a maximum daily dose of 3 grams/day is appropriate. We note that the exposure margins used to qualify an impurity must be based on a body surface area comparison. Comparisons using mg/kg are not acceptable. If the studies do not provide adequate coverage based on the No Observed Adverse Effect Level (NOAEL), the Lowest Observed Adverse Effect Level (LOAEL) may be used to define the exposure margin if it is based on typical exaggerated pharmacodynamic effects characteristic of an opioid. An exposure margin of > 1 at the NOAEL or acceptable LOAEL is necessary to adequately qualify an impurity. The adequacy of the toxicology studies used to define the NOAEL or LOAEL can only be determined upon formal review of the studies.

Discussion

The Sponsor inquired as to whether they should test the impurities individually or use a cocktail. The Division stated that either approach is acceptable with the caveat being that, if a cocktail is tested and toxicity is observed, it would not be possible to determine which impurity was responsible for the observed effect. The Division also stated that the stability of the individual impurities in the cocktail must be demonstrated.

The Sponsor asked whether *in silico* models (i.e., DEREK) would be adequate to determine the presence of a structural alert. The Division stated that, according to the current draft guidance (December 2008 Draft *FDA Guidance to Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*), the Sponsor's approach would be acceptable. However, the Division noted that compounds with an (b) (4) would require both mutagenicity and clastogenicity qualification studies because there are data to show that compounds with this particular structural alert can be positive for clastogenicity as well as mutagenicity. If no structural alert is predicted, no further qualification would be needed as long as the levels of impurities or degradants are below qualification thresholds set by ICH Q3A(R2) and ICH Q3B(R2). Any impurity or degradation product that exceeds ICH Q3A(R2) and ICH Q3B(R2) thresholds must be adequately qualified for safety. Adequate qualification would include a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) and a repeat dose toxicology study of appropriate duration to support the proposed indication.

The Division also stated that they will conduct an internal QSAR analysis using four different modules to identify any structural alerts and would contact the Sponsor if the results of the internal analysis differ from those submitted by the Sponsor.

Question 9

Does the Division agree that the described tox/qualification plan in Table 1 is an acceptable approach for qualification of degradation product/impurities in the hydrocodone drug substance?

FDA Response

See response to Question 8.

Discussion

There was no further discussion on this point.

Question 10

Given that the levels of the (b) (4) impurity found in the degraded tablets used in the 3 month dog toxicity study did not reach a sufficient level for qualification purposes, Cephalon will conduct a separate 3 month dog tox study to qualify this impurity.

Cephalon proposes submitting an interim (4 week) report on the qualification of the (b) (4) impurity in the NDA, with the full report to be submitted within three months of the NDA filing date. Does FDA agree?

FDA Response

Your proposal to qualify (b) (4) with a 3-month dog toxicology study is acceptable; however, final study reports must be submitted at the time of NDA submission. Note that the study may be conducted in either dog or rat.

Discussion

There was no further discussion on this point.

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. We recommend that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the NDA in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May

2005) which is available on the CDER web page at the following address:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*” (emphasis added).

5. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in the ICH Q3A(R2) and ICH Q3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT ^(b)₍₄₎ mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICH S2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT ^(b)₍₄₎ mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 7. ^(b)₍₄₎ opioid drug products may contain impurities containing an ^(b)₍₄₎, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to NMT ^(b)₍₄₎ mcg/day or adequate safety qualification must be provided. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.
 8. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the

product, and how these levels compare to ICH Q3A and ICH Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.

9. Failure to submit adequate impurity qualification or justification for the safety of new excipient use may result in a Refusal-to-File or other adverse action.

Discussion

There was no further discussion on this point.

Clinical Questions

Question 4

Since we anticipate that our ISS will be small (including incorporated tables and figures), and based on the Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, April 2009, Cephalon would propose that the narrative portion of the ISS would reside in Module 2.7.4 (Summary of Clinical Safety) with a cross reference (for additional tables, figures and/or datasets) to Module 5.3.5.3. Section 5.3.5.3 would then refer the reader to Section 2.7.4 for the text portion of the ISS. Does the Division agree with this proposal?

FDA Response

No. Module 2 is intended for summary information. To facilitate the review of your NDA submission, we strongly recommend that the ISS, which is actually an analysis across studies and not a summary, and associated documents and data be placed in Module 5 in conformance with the Guidance for Industry Common Technical Document located at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

You are also directed to the following document that communicates general CDER preferences and experiences regarding the submission of standardized data to aid Sponsors in the creation of standardized datasets:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>

Additionally, the following link provides study specifications for submitting animal and human study datasets in electronic format:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

Discussion

There was no further discussion on this point.

Question 5

Given that the basis for the determination of efficacy for this NDA will rely on one pivotal Phase 3 clinical trial, Cephalon would propose the same strategy for the ISE as described above for the ISS. That is, the narrative portion of the ISE would reside in Module 2.7.3 with cross reference to additional tables, figures and/or datasets which would reside in Module 5.3.5.3. Does the Division agree with this proposal?

FDA Response

No. Refer to the response to Question 4.

Discussion

There was no further discussion on this point.

Question 6.1

Can the Division provide feedback on the following questions relative to the ISS/SCS Shell, ISE/SCE Shell and the SAP for the ISS/SCS:

Given that naltrexone was concurrently administered in most Clinical Pharmacology studies, summaries of the safety data from each Clinical Pharmacology study will be presented in section 2.7.2 (Summary of Clinical Pharmacology) and an overall brief summary of safety data across studies in healthy volunteers (naltrexone-blocked) as well as summaries of the safety data in subjects with varying degrees of renal function (naltrexone-blocked) and varying degrees of hepatic function will be presented in section 5.1.5 (Safety in Special Groups and Situations, Healthy Subjects) of the ISS/SCS. Is this acceptable?

FDA Response

Your proposal to place a brief summary overview of safety data of the naltrexone-blocked healthy subjects in clinical pharmacology studies in section 2.7.2 (Summary of Clinical Pharmacology) and the naltrexone-blocked renally and hepatically impaired study subjects in Section 5.1.5 of the ISS is not acceptable. Include the safety data and assessment of the naltrexone-blocked subjects in the full ISS.

Discussion

The Division clarified that it was not expecting to see the data from the Phase 1 studies of naltrexone-blocked patients integrated into the ISS pool, but rather, that the information should simply be discussed there. The Sponsor should submit a complete ISS with text and tables to help facilitate the safety review.

Question 6.2

Does the Division have any additional guidance on the proposed presentation for data in the ISS/SCS?

FDA Response

Although the overall presentation of the content of the ISS and SCS appear adequate, refer to our response to Question 4 regarding placement in the appropriate Modules.

Discussion

There was no further discussion on this point.

Question 6.3

Does the Division have any additional guidance on the proposed presentation of data in the ISE/SCE?

FDA Response

Although the overall presentation of the content of the ISE and SCE appear adequate, refer to our response to Question 4 regarding placement in the appropriate Modules.

Discussion

There was no further discussion on this point.

Question 6.4

Does the Division have any feedback or advice on the proposed SAP for the ISS/SCS?

FDA Response

It appears that the proposed SAP for the ISS/SCS may be adequate.

Discussion

There was no further discussion on this point.

Question 7

The following describes the planned submission format and datasets to be included in the NDA. Does the Division agree or have any advice on the plan?

Submission Format Summary/Datasets:

The application will be prepared according to eCTD format and the data will follow the CDISC Study Data Tabulation Model (SDTM). All study datasets from studies conducted in patients will be submitted. Cephalon will provide SAS datasets in lieu of classic case report tabulations. Patient profiles will not be submitted. Each dataset will be provided as a SAS transport file and a Data Definition Table in accordance with the FDA Guidance for Industry. Both raw and derived data will be provided

Clinical/Statistical Data

Patient data listings and summaries will be included with the individual clinical study reports. Integrated Datasets for the Summary of Clinical Safety (SCS) will be provided as a statistical review aid. The Summary of Clinical Efficacy (SCE) analyses will be included with the Study 3079 report.

Phase I Studies Data

Data listings and summary tables for each Phase 1 study will be included with the individual clinical study reports. Integrated datasets for pharmacokinetic summaries will be provided as a statistical review aid.

Case Report Forms (CRFs)

In accordance with 21 CFR 314.50, CRFs will be provided for any patient who: 1) Experienced serious adverse events during a clinical study 2) Discontinued from a clinical study due to adverse events, whether believed to be drug-related or not, including subjects receiving placebo 3) Died during a clinical study. All CRFs will be provided as PDF files, organized by study, site, and patient.

FDA Response

Your proposed specifications for submitting electronic datasets appear to be adequate. However upon review of the submitted data, additional requests may be warranted.

Discussion

The Division stated that it was planning to issue comments on the statistical analysis plan (SAP) proposed for the primary efficacy study (3079) to the firm the week following this meeting.

*****Post-Meeting Note**

An advice letter was issued on September 20, 2011.

Clinical Pharmacology Comments

Ensure adequate bridging bioequivalence data are provided between the to-be-marketed formulation and all strengths of the proposed product used in your clinical program.

In the future, consider submitting a brief synopsis or investigational plan explaining the fundamental approach to the clinical pharmacology program. Additional details describing the purpose and preliminary results (if available) of each study or a group of studies would be appropriate for a Pre-NDA setting.

Discussion

There was no further discussion on this point.

Regulatory Questions

Question 1

Since the formulation for this long-acting hydrocodone product has inherent features that provide tamper deterrence and will also be APAP-free, Cephalon will request a Priority Review for this NDA based on the data that will be included in the submission. Does the Division have any advice or recommendations for our planned request for Priority Review?

FDA Response

Priority review designation may be granted for opioid products that demonstrate tamper-deterrent properties in in vitro, pharmacokinetic and clinical liking studies. The request for priority review is made at the time of the NDA submission. We will inform you in writing of a priority designation by Day 60 of the review. A determination regarding whether a

Priority or Standard Review will be assigned will be based on the acceptability of the design, conduct and results of the studies submitted to support the tamper-deterrent properties of your product.

Discussion

There was no further discussion on this point.

Question 2

Hydrocodone Extended-Release Tablets share similar tamper deterrent strategies and studies to other long acting opioids which have been reviewed by the Joint ALSDAC and DSaRM Committees. Does the Division anticipate that this NDA would be presented to an Advisory Committee prior to an Action being taken?

FDA Response

A decision regarding whether your NDA will need to be presented to an advisory committee to obtain guidance will be made at the time of the NDA review. This decision depends on the safety and efficacy findings of your formulation from the studies included in your NDA submission and the implications for public health should your product be approved.

Discussion

There was no further discussion on this point.

Question 3

Cephalon will include a proposed REMS in the NDA in line with the requirements for all long acting opioids presented by FDA in April 2011. Based on the current implementation timelines released by FDA, the LAO REMS should be approved by the time of the submission of the hydrocodone extended-release tablets NDA. Cephalon proposes to submit an identical copy of the LAO REMS with the addition of educational material specific to extended-release hydrocodone. Does the Division agree with this approach?

FDA Response

Your proposal to submit a REMS that is identical to the long-acting opioid class REMS that the Agency approves, with the exception of including additional educational material specific to extended-release hydrocodone, will be acceptable. We recommend that you work closely with the Industry Working Group (IWG) to develop the class-wide REMS. Your REMS program must be in conformance with the class-wide REMS under development at this time.

Discussion

There was no further discussion on this point.

CSS Comments

In the NDA, provide the following information and data related to the abuse potential assessment, including drug diversions and overdose:

- 1. Descriptions of all reports and details, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.**
- 2. Case narratives of subjects in clinical studies who are discontinued from studies for lack of compliance to study medication or procedures, or who discontinue participation without returning the study medication.**

Discussion

The issue of clinical drug-liking studies was discussed at length. The Sponsor stated that they were planning to conduct abuse-potential studies with crushed tablets in a PK study and were not planning to study drug liking. The Agency stated that the guidance on the assessment of abuse potential for drugs is currently being developed, but based on ongoing internal discussion, if a formulation is believed to have some abuse-resistant qualities, drug liking studies are necessary to give context to the PK data from manipulated tablets. These protocols should be submitted for review prior to initiating the studies in order to give the Agency an opportunity to provide feedback regarding the study design, abuse potential assessments, and analyses. As the Sponsor is considering seeking a priority review based on having an abuse-resistant formulation, there must be enough data about the abuse-resistant characteristics to warrant the priority review. Without such a study, the application would likely still be filed, but discussion would be needed to determine whether it would be reviewed under a priority or standard review timeline.

The Sponsor had noted that one reason for not planning a drug-liking study was that the absence of any other single-ingredient hydrocodone products on the market left them without an appropriate comparator for a drug-liking study. The Agency suggested that the Sponsor consider including more than one comparator. The Sponsor could create an immediate-release hydrocodone for use in the study and submit the CMC data with the study protocol. Another useful comparison would be extended-release oxycodone. There is a paucity of data on the relative drug liking of opioids and any other comparators could provide useful information as well.

(b) (4)



(b) (4)

The Division indicated that it would supply information on comparators via a Post-Meeting Note.

*****Post-Meeting Note**

The use of an immediate-release hydrocodone product in a drug-liking study would provide important context to PK data from the manipulated extended-release hydrocodone formulation.

In addition, comparison to oxycodone or oxymorphone would provide important data about hydrocodone as a drug substance and, as such, would have great value from a public health perspective. Use of immediate-release formulations would provide data about the relative drug liking of hydrocodone as a drug substance, and use of manipulated and intact extended-release formulations would provide data about the opioids as drug products.

There are many ways this comparison could be conducted, but at a minimum, to support labeling about the extended-release hydrocodone formulation, a drug-liking study must include an immediate-release hydrocodone comparator.

THE SPONSOR'S SUMMARY OF THEIR UNDERSTANDING OF THE MEETING (Includes Action Items)

- The Sponsor will conduct a toxicology study(ies) with dosing up to the maximum feasible dose in order to qualify the excipients. In addition, the Sponsor will submit a rationale for justifying the levels of the excipients, including information from the literature as part of their weight-of-evidence approach.
- The time point for the dissolution specification may be selected based on data; the 18-hour time point given in the response is simply an example.
- The Sponsor will qualify any process impurities and degradants that exceed qualification thresholds set by ICH Q3A(R2) and ICH Q3B(R2) with a repeat dose toxicology study(ies) and a minimal genetic toxicology battery. If the impurities/degradants are negative for structural alerts and the qualification data are considered adequate, then the impurities/degradants will be considered qualified and no further studies will be needed.
- The Sponsor understands that Phase 1 trial subject data do not need to be integrated into the ISS, but they will discuss them in detail elsewhere in the submission.
- The Sponsor understands that they Agency plans to provide comments on the Statistical Analysis Plan (SAP) for Study 3079 the week of September 19, 2011 via an Advice Letter.

- The Sponsor understands that a clinical drug-liking study is not required to file the NDA, but its presence or absence in the submission may have an impact on whether the application is reviewed as a priority or not. The Sponsor understands that the Agency will provide feedback on an appropriate comparator(s) to be used in the clinical drug-liking studies via a Post-Meeting Note. (See Post-Meeting Note above.)

ATTACHMENTS AND HANDOUTS

The attached items include Appendix 1 (*Standard Comments for Preparations for NDA Submission*) and Appendix 2 (*Office of Scientific Investigation Comments*), were provided to the firm along with the Agency's preliminary comments on September 14, 2011, however, none were discussed further during the meeting.

Appendix 1

Standard Comments for Preparation for NDA Submission

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester, etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the non-clinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product.

General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events

4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change.
21. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
22. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

23. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
24. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
25. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
26. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
27. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
28. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
29. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
30. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
31. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

32. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
33. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See

Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

34. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format.
35. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

SPL Submission:

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Content of Labeling (April 2005): <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry Integrated Summary of Effectiveness located at the following web page

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to **Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
 3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
 4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
 5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due “investigator decision,” “Sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Appendix 2

Office of Scientific Investigations Comments

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and Sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

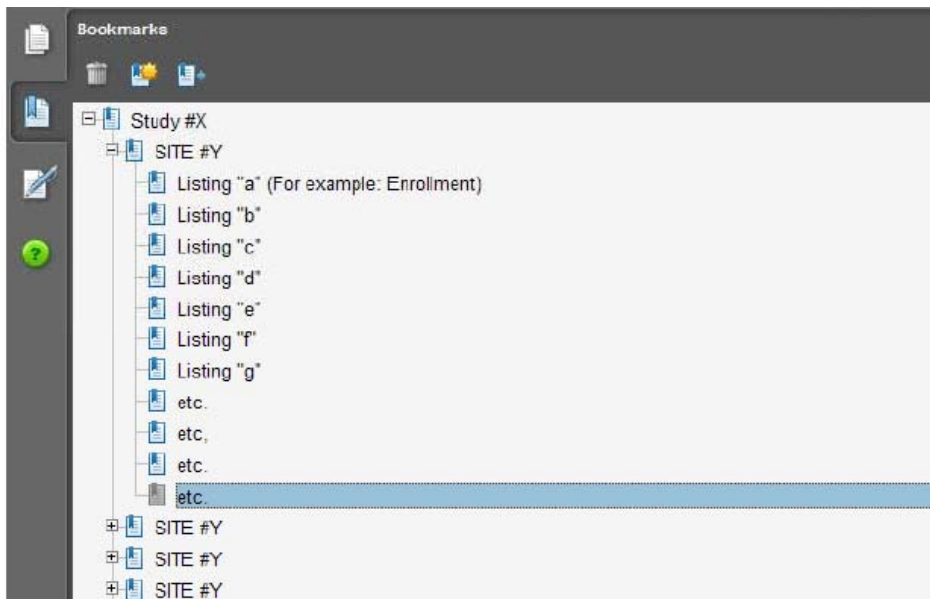
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials

- c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of Sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
- 4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
 - 5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

- 1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
- 2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1 (to Appendix 2)

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of Sponsors throughout the study. If there was a change in the Sponsor while the study was ongoing, enter an integer indicating the total number of Sponsors. If there was no change in the Sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the Sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the Sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMA N	SPONNO	SPONNAME	ND	UNDER ND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	F NLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0 0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0 0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0 0204	-1	3	2	1	0	45000.00	45000 00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0 0204	-1	0	2	0	3	20000.00	45000 00	Washington	George
Percent Responders	Binary	0 54	0.0092	0.35	0 0210	-1	2	2	0	1	15000.00	25000 00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0 0210	-1	3	6	0	0	22000.00	25000 00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0 0161	-1	4	1	0	0	0 00	0 00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0 0161	-1	1	2	0	1	0 00	0 00	Lincoln	Abraham

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2 (to Appendix 2)
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD
Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

KIMBERLY A COMPTON
10/07/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105587

MEETING MINUTES

Cephalon, Inc.
Attention: Sylvie Peltier, PharmD
Senior Director, Reg. Affairs
41 Moores Road
Frazer, PA 19355

Dear Ms. Peltier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hydrocodone bitartrate extended-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 20, 2010. The purpose of the meeting was to discuss Phase 3 CMC development and registration plan to support a future NDA.

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

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2 Meeting, CMC
Meeting Date and Time: October 20, 2010, 3:00 to 4:00 PM (ET)
Meeting Location: WO Building 22, Room 1419

Application Number: IND 105,587
Product Name: Hydrocodone bitartrate, extended release tablets
Indication: (b) (4)

Sponsor/Applicant Name: Cephalon

Meeting Chair: Prasad Peri, Ph.D.
Meeting Recorder: Swati Patwardhan

FDA ATTENDEES

Office of New Drug Quality Assessment (ONDQA):

- Eric Duffy, Ph.D., Division Director, DNDQA III
- Prasad Peri, Ph.D., Acting Branch Chief, Branch VIII, DNDQA III
- Ramesh Raghavachari, Ph.D., CMC Lead, Branch IX, DNDQA III
- Yong Hu, Ph.D., Ph.D. CMC Reviewer, Branch VIII, DNDQA III
- Sandra Suarez, Ph.D., Biopharmaceutics, OPS
- Swati Patwardhan, Regulatory Project Manager, DNDQA III

Division of Anesthesia and Analgesia Products

- Sharon Hertz, M.D. Deputy Director
- Frank Pucino, Pharm.D., M.P.H., Clinical Reviewer
- Dan Mellon, Ph.D., Supervisory Pharmacologist
- Suresh Naraharisetti, Ph.D., Clinical Pharmacologist

Controlled Substance Staff

- Lori Love, M.D., Ph.D., Medical Officer

SPONSOR ATTENDEES

- Kathleen Idason, Associate Director, CMC Regulatory Affairs
- Derek Moe, Ph.D., Vice President, Drug Delivery
- Jennifer Pansch, DVM, Manager, Regulatory Affairs
- Sylvie Peltier, Pharm.D., Sr. Director & Group Leader, Regulatory Affairs
- Randal Seburg, Ph.D., Associate Director, Analytical
- Philip Simonson, Ph.D., Sr. Director, Regulatory Affairs/Project Management
- Jeremy Webber, Manager, Project Management

1.0 BACKGROUND

The proposed indication for hydrocodone bitartrate extended release tablet is (b) (4)

. A type B meeting request was submitted on July 27, 2010, to seek concurrence from the Agency for CMC final development and registration plan for hydrocodone bitartrate extended release tablets that would support the NDA. The meeting package was received on September 14, 2010.

2.0 DISCUSSION

2.1 Registration Plan:

- a) The proposed registration stability plan includes study of hydrocodone bitartrate extended release tablets in multiple strengths and packaging configurations, and also incorporates two manufacturing scales and two manufacturing sites (including the intended commercial site). At time of the NDA submission, the following stability data will be available: 12-18 months of supportive stability data on all strengths at pilot scale using the Phase 3 formulation, a minimum of 12 months stability data at pilot scale on the 15, 30 and 45 mg strengths, a minimum of 6-9 months stability data at pilot scale on the 60 and 90 mg strengths, and a minimum of 3 months stability data manufactured at the commercial scale and site for all five strengths (15, 30, 45, 60, and 90 mg), up to 12 months of stability, data will be available for some batches.

Does the Agency concur that the registration stability plan is sufficient to support a NDA for this extended release dosage form with a proposed shelf life of (b) (4) months? In addition, does the agency concur that Cephalon can amend the NDA during the review period to submit additional stability data 3 months prior to the PDUFA Action Date?

FDA Pre-meeting Response:

No, we do not agree. We understand that your phase 3 materials will be manufactured at a pilot scale at a non-commercial site. You will need to conduct a bioequivalence study(ies) to bridge the commercial site and the pilot site for the manufacturing of your drug product. Once the bioequivalence is established, we can accept three months stability data for the full scale batch manufactured at the commercial site as part of your registration stability package at NDA filing, in addition to the data for the pilot scale batches.

Note that, per GRMP guidelines, we may not be able to review amendments to the NDA during the review cycle, depending on the extent of submitted data and available resources.

Meeting Discussion:

In the email correspondence dated October 19, 2010, and during the meeting, the sponsor requested confirmation that the number of pilot and commercial batches proposed in the Drug Product Overview section in Table 17, page 31 (2 pilot scale batches produced at the clinical site for each strength of 15, 30, 45, 60 and 90 mg and 1 commercial scale batch produced at the commercial site for each strength of 15, 30, 45, 60 and 90 mg) is an acceptable number of batches to support the registration of this product for the NDA. The Agency agreed that the proposed number of batches is acceptable to support the registration of this product for the NDA provided that the commercial manufacturing will use the same manufacturing process and the equipment with the same operating principles as those for the pilot scale manufacturing.

- b) The sponsor intends to request Priority Review for this extended release hydrocodone product, based on the abuse deterrent features of the formulation and the unmet medical need for an APAP-free hydrocodone-containing product.

If the Division grants Priority review, would the Division allow an amendment to the NDA during the review period with updated stability data on the supportive and registration batches 3 months prior to the PDUFA Action Date?

FDA Pre-meeting Response:

See our response for Question in 2.1 regarding NDA amendments. We strongly recommend that you provide the longest stability data at the time of NDA submission.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

2.2 In Vitro Tampering Protocol:

The proposed *in vitro* tampering protocol explores a range of conditions relevant to potential abusers that could alter extractability or release of hydrocodone from the matrix, including particle size effects, solvent effects, and various extraction conditions.

Does the Agency concur that the in vitro tampering protocol design adequately explores a full range of abuse-relevant conditions that may affect hydrocodone release from the product?

FDA Pre-meeting Response:

No, we do not agree. We have reviewed the summary information submitted and have provided following general comments as well as specific recommendations. We are willing to review a complete protocol after you receive and consider our comments and recommendations.

Comments:

In vitro studies evaluate the ease with which the abuse deterrent mechanism of a product can be defeated or partially compromised. Study designs are based on the knowledge of the physicochemical properties of the formulation and on methods available to abusers.

For abuse deterrent formulations, CSS in general recommends the sponsor to conduct studies to provide data about the amount of opioid released from all strengths of the to be marketed formulation under the full range of conditions that can alter extractability or release of product from the matrix.

- *Mechanical manipulations such biting, grinding and cutting: These studies can evaluate the effects of:*
 - *Reducing particle size*
 - *Time and ease of crushing and grinding*
 - *Freezing and heating the product prior to mechanical manipulation*
 - *Chewing, using a chewing simulator and artificial saliva*
- *Solubility and extraction of the API in several solvents of varying polarity and pHs (water, ethanol, isopropyl alcohol, ethyl acetate, methylene chloride, acidic and basic solution, and others) under continuous agitation; increasing temperatures and time until complete extraction of API are recorded.*
- *Feasibility of preparation of samples for alternative routes of administration*

Recommendations:

- [REDACTED] (b) (4). *At minimum, you need to characterize the in vitro extraction results from the different formulations [15, 60, and 90 mg tablets].*
- *Grinding tests: the pestle and electronic grinder tests should be extended in time or effort to obtain a homogenous product size.*
- *More rigorous agitation conditions should be used than the currently proposed conditions (shaking the samples by hand for 15 seconds or shaking the samples at 150 rpm in a continuous platform are considered mild conditions).*

Meeting discussion:

In the email correspondence dated October 19, 2010, and during the meeting, the sponsor wanted to seek clarification on whether the use of a chewing simulator and artificial saliva would still be required in the in vitro tampering protocol for registration. If a chewing simulator with saliva is required for the protocol, Cephalon requested the

Agency provide recommendations for the chewing requirements if the proposed protocol is not sufficient.

The Agency stated that the protocol should be revised to include more rigorous conditions for extractability. The sponsor should provide exploratory information on how a set of conditions were identified for extraction, e.g., why the sponsor thinks that 12 strikes of a hammer is adequate, or why the duration of 15 seconds of shaking at 150 RPM is adequate for the release of hydrocodone in the matrix. The Agency explained that abusers would go to extreme lengths and efforts to extract the drug and hence, the sponsor should include adequate rigor to prove that they have anticipated those conditions in the protocol. The Agency understands that all the measures taken to deter the abuser from abusing the drug may ultimately be defeated. It is not expected that the sponsor should show that their product is undefeatable, but they have taken all the methods into considerations that drug abusers would use to extract the drug, and have studied them adequately. The Agency suggested that the sponsor may want to do a PK study with chewed or ground tablets to assess whether the product retained its extended release characteristics. The sponsor responded that they are planning to do such a study.

The sponsor also wanted to know if the solvents proposed in the *In Vitro* Tampering Protocol section in Table 2, page 9 (water, 0.01 N HCl, sodium bicarbonate, methanol, 40% ethanol, isopropanol, acetone and cooking oil) are sufficient in vitro characterization solvents. The Agency reiterated that ethyl acetate and methylene chloride are important solvents to include and the sponsor should try the extraction in various solvents and provide a rationale and background for those extractions.

In summary, the sponsor was asked to revise the tampering protocol to include adequate justification, methodology, and scientific rigor. The sponsor was asked to provide a timeline of development.

2.3 Impurities/Acceptance Limits:

Hydrocodone is derived from codeine and may contain the impurity (b) (4), in which the (b) (4) is a structural alert for mutagenicity. The drug substance manufacturer, (b) (4) DMF (b) (4), reports that levels ranging from (b) (4) ppm have been measured in historic lots, therefore has sponsored genetic toxicity studies to qualify the safety of the (b) (4) impurity. The results of the screening were negative, thus control of this impurity to the level of NMT (b) (4) mcg/day is not necessary, and specifications for this impurity may be established per ICH Q3B.

Does the Agency agree that the safety of (b) (4) is adequately qualified in DMF (b) (4) to permit the Sponsor to set the acceptance limit of this impurity per ICH Q3B?

FDA Pre-meeting Response:

We agree that the safety of (b) (4) is adequately qualified in the DMF and that you may set the acceptance limit for this impurity per ICH Q3B.

Meeting discussion:

The Agency reiterated that the sponsor should follow ICH guidelines for the impurities.

2.4 The Agency's February 3, 2010 advice/information request letter to establish dissolution, degradation products, and (b) (4) acceptance limits is acknowledged. While premature to finalize certain specifications at this development stage, rationale are proposed for setting these specifications.

Does the Agency concur with the proposed rationale for setting specifications for finished product?

FDA Pre-meeting Response:

We agree with your strategy to set specifications for degradation products and the (b) (4). However, the acceptance of the specifications will be a review issue. We agree with your proposal of setting the sampling time points for the dissolution acceptance criteria as those with drug release values nearest to 20%, 50%, and 80% (to be determined from evaluation of all clinical/bioavailability lots used in Phase 3). In addition, we acknowledge your efforts on continuing the evaluation of other dissolution conditions that would result in > (b) (4) % drug release at 12 hours.

Meeting discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

3.0 Additional Comments

3.1 The drug substance impurities should be controlled to NMT (b) (4) % based on 3g maximum daily dose of hydrocodone and the ICH Q3A guideline. Submit the following biopharmaceutics information:

- Dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method.
- Include the testing conducted to demonstrate the discriminating capability of the selected test, if available as well as the validation data for the assay.
- Complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value).
- The composition of the strengths under development (b) (4). Provide bridging plan for all the strengths.

- Provide your bridging plans to support the change in manufacturing site. We remind you that a change in manufacturing site for an extended release formulation should be supported by in vivo bioequivalence studies.

Meeting Discussion:

The sponsor requested guidance from the Agency in terms of the design of the bridging study(ies). The Agency stated that it is a common practice to conduct in vivo BE studies with the lowest and highest strength to bracket the middle strengths in those situations when the composition of the strengths is not proportionally similar. The sponsor was advised to submit their proposal for bridging between strengths. The BE study(ies) supporting the manufacturing site should also take into consideration a bracketing strategy given the lack of proportionality in the composition of the formulations. The Agency added that the proposal(s) will be reviewed and a response will be provided in a timely manner depending on the resources.

- Provide your plans for addressing any potential for the in vitro dose dumping in the presence of alcohol. We remind you that this assessment should be accomplished using an appropriate/acceptable QC dissolution method.

Meeting Discussion:

The sponsor mentioned that an in vitro alcohol interaction study has already been conducted using 40% alcohol in the QC media. The Agency recommended to conduct an additional in vitro alcohol interaction study using different alcohol concentrations (0%, 5%, 10%, 20%, and 40%) in an additional medium (0.1 N HCl).

The sponsor mentioned that their company has already conducted an in vivo alcohol (40%) interaction study and the results indicated no effect on the systemic exposure of the drug due to alcohol consumption. The Agency stated that given the existence of this in vivo study, there may not be a need for an additional in vitro alcohol interaction study. The Agency recommended submitting the in vivo study protocol used for the conduct of the study and the results to determine the need for an additional in vitro alcohol interaction study. The Agency will give a feedback as soon as possible depending on the resources available.

4.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

PRASAD PERI
11/18/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

IND 105587

MEETING MINUTES

Cephalon, Inc.
41 Moores Rd
PO Box 4011
Frazier, PA 19355

Attention: Sylvie Peltier, Pharm.D.
Sr. Director, Regulatory Affairs, Pain

Dear Dr. Peltier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food Drug and Cosmetic Act for hydrocodone bitartrate extended-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 14, 2010. The purpose of the meeting was to discuss your preparations to conduct Phase 3 studies with your product.

A copy of the official minutes of the meeting 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 at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure



INDUSTRY MEETING MINUTES

Meeting Date: July 14, 2010

Time: 1: 30 PM ET

Location: White Oak Conference Room 1315

Application: IND 105587

Regulatory Status: Active IND

Investigational Product: Hydrocodone extended-release tablets

Proposed Indication: [REDACTED]

(b) (4)

Sponsor: Cephalon, Inc.

Type of Meeting: Type B

Meeting Chair: Robert Shibuya, M.D., Clinical Team Leader

Division of Anesthesia and Analgesia Products (DAAP)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAP

Industry Representatives	Title
Brad Barnes, Ph.D.	Sr. Director, Drug Safety
Mona Darwish, Ph.D.	Sr. Director and Group Leader, Clinical Pharmacology
Maciej Gasioer, M.D., Ph.D.	Associate Director Clinical Research
Derek Moe, Ph.D.	Group Director, Drug Delivery R&D
James Ottinger, R.Ph.	VP Worldwide Regulatory Affairs
Sylvie Peltier, Pharm.D.	Sr. Director and Group Leader Regulatory Affairs
Jane Tiller, FRC Psych	VP CNS/Pain Clinical Research
Ronghua Yang, Ph.D.	Sr. Director Biostatistics
Fang Xie, Ph.D.	Sr. Director Biostatistics
Srdjan Stankovic, M.D., MSPH	Sr. VP Worldwide Clinical Research
FDA	Title
Bob A. Rappaport, M.D.	Director, DAAP (by phone)
Rigoberto Roca, M.D.	Deputy Director, DAAP
Robert Shibuya, M.D.	Medical Team Leader, DAAP
Frank Pucino, Pharm.D., M.P.H.	Medical Officer, DAAP
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer, DAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAP
Suresh Narahariseti, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Srikanth Nallani, Ph.D.	Clinical Pharmacology Team Leader
Kate Meaker, Ph.D.	Biostatistics Reviewer, Division of Biostatistics II (DBII)
Dionne Price, Ph.D.	Biostatistics Team Leader, DBII
Kim Compton	Senior Regulatory Project Manager, DAAP
Afrouz Nayernama, Pharm.D.	Safety Evaluator, Division of Pharmacovigilance II, (DPVII), Office of Surveillance and Epidemiology (OSE)
Lori Love, M.D., Ph.D.	Team Leader, Controlled Substance Staff (CSS)
John Gong, M.D., Ph.D.	Medical Officer, CSS

Background:

On July 8, 2010, (prior to the July 14 meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the sponsor in their June 2, 2010, meeting package.

The firm indicated they would like to discuss Questions 1, 2, 3, 4c, 4d, 5a, 5b, and 7b.

Presented below are the Agency's comments and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. The firm's July 13, 2010, replies to the Agency's preliminary responses follow in *italic* text the response to which they pertain. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Meeting:

Dr. Roca stated that while the Agency has replies for the majority of the questions posed in the meeting package, several replies were not complete at the time of the meeting and will be provided later as post-meeting notes.

Question 1

Hydrocodone is a currently approved analgesic agent when administered in combination with APAP (Vicodin® and others), aspirin (Vicoprin®) or ibuprofen (Vicoprofen®). Currently, the maximum dose of hydrocodone approved is 60 mg daily. To date, there are no stand alone formulations of hydrocodone approved by the Agency. Cephalon proposes to submit the single entity hydrocodone as a 505(b)(2) NDA using Vicodin as the Reference Listed Drug. The single entity hydrocodone will seek approval for a dose range of 15 mg to 90 mg twice daily. Does the Division agree that an NDA for hydrocodone bitartrate (single entity) can be submitted under section 505(b)(2) of the FD&C Act?

FDA Response

You plan to reference

as the listed drug.

(b) (4)

(b) (4)

(b) (4)

Reply from Sponsor (via email dated July 13, 2010)

We seek to clarify the Division advice as according to the definition of a listed drug in 314.3, listed drugs can include 505(j) applications.

(b) (4)

Nevertheless, based on this advice, we would propose to use one of the hydrocodone products approved as a NDA, for example Vicoprofen, as the RLD, but will conduct the biolinking study with the

(b) (4)

Is this a correct interpretation of the Division feedback?

Discussion

Dr. Roca indicated that additional follow-up on the above-provided response is needed. The Division noted that it required clarification on the Sponsor's plan outlined in the second paragraph and then would be able to provide a Post-Meeting note to fully address the issue.

The Sponsor indicated that they have completed studies with the brand name product, (b) (4) and have data from those studies that they hope to be able to employ for their application. The Division indicated it would attempt to address those concerns in a Post-Meeting note.

*****Post-Meeting Note**

For 505(b)(2) purposes, the listed drug relied upon for approval does not need to be the Reference Listed Drug (RLD), the designation of which is for 505(j) purposes. RLDs may be ANDAs as well as NDAs. The listed drug relied upon for approval of a 505(b)(2) product must be an approved NDA that contains the active drug moiety in the investigational drug product. (b) (4)

(b) (4) may not be the listed drug relied upon for approval of a 505(b)(2) application.

There is, however, an approved hydrocodone-containing NDA (Vicoprofen, NDA 020716) that may be used as the listed drug,

Nonclinical Question*Question 2*

Hydrocodone is a well known and characterized opioid. In combination, this molecule has been approved for several decades in various indications including for use in the treatment of moderate to severe pain. As a 505(b)(2) NDA, Cephalon will be asking FDA to rely on the prior approvals of hydrocodone containing NDAs. Therefore Cephalon proposes to conduct no further toxicological or pharmacological assessment of hydrocodone. Does the Division agree that no further non-clinical toxicology or pharmacology studies are required to support submission of an NDA?

FDA Response

No. As a single entity hydrocodone formulation, the proposed drug product will yield exposures of hydrocodone much greater than seen with previous clinical experience. For a 505(b)(2) NDA, although the extensive clinical experience with hydrocodone combination products and opioids in general can be used to reduce the standard ICH requirements for repeat-dose toxicology, additional toxicology studies will be required for the NDA, including the following:

- a. a 3-month toxicology study using the clinical formulation and placebo,**
- b. standard reproductive and developmental toxicology battery for hydrocodone,**
- c. standard genetic toxicology battery for hydrocodone, and,**
- d. carcinogenicity assessment in two species for hydrocodone.**

Prior to initiation of carcinogenicity studies, you are encouraged to submit your study protocols to the IND and obtain concurrence from the Executive Carcinogenicity Assessment Committee (eCAC). Please refer to the following guidance document: Carcinogenicity Study Protocol Submissions (May 2002), which is available on the CDER website at the following location:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078924.pdf>

Should you elect to file a 505(b)(1) NDA, you must own or have right of references for all nonclinical toxicology studies, including basic pharmacology, safety pharmacology, ADME, general toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, as per ICHM3(R2).

Reply from Sponsor (via email dated July 13, 2010)

Based on the preliminary comments Cephalon is looking for the following clarification and discussion during the meeting:

- *In the Division feedback, it is suggested that the 3 month toxicology study is conducted using the “clinical formulation.” We seek clarification that it is acceptable to use the active substance in these studies via gavage or diet, as per the standard practice.*
- *As the approved dose of hydrocodone is 60 mg daily, we seek clarification that the maximum dose of 3 g per day is correct as this is a large number (50) of tablets of the currently approved product.*
- *Clarification is sought if rodent carcinogenicity studies are required for approval of an oral formulation of an already approved oral product using a 505(b)(2) approach.*
- *If carcinogenicity studies are required, Cephalon proposes to commit to start the studies prior to NDA submission with submission of study reports as a post approval requirement.*
- *Confirmation is sought that the remaining nonclinical studies are required for the NDA and not for phase 3 initiation.*

Discussion

The Sponsor inquired whether they could utilize the Active Pharmaceutical Ingredient (API) for the 3-month nonclinical general toxicology study. The Agency clarified that this is a unique development program because hydrocodone has never been approved as a single agent, but was originally approved as an ANDA through a comparability program with codeine. This formulation will be the first approved single-entity hydrocodone product and will be used at much higher doses than the currently approved hydrocodone combination products.

Due to the unique regulatory history and extensive clinical experience with hydrocodone, the Agency has concluded that the standard nonclinical development studies are not necessary for this NDA. Specifically, the 6-month rodent and 9-month nonrodent toxicology studies would not be required if the sponsor can demonstrate via a 3-month repeat-dose toxicology study with the

clinical formulation that the clinical formulation does not exhibit unexpected toxicities (e.g., toxicities that are not typical for an opioid drug). The Division believes the best approach is to utilize the clinical formulation in a 3-month bridging study in a single species. Using the clinical formulation could serve to qualify any impurities and degradants, as well as excipients, in the commercial product. The Division also noted that the study will most likely need to be conducted in dogs due to the tablet formulation of the product. A well-designed program can address numerous questions at once and potentially avoid the need for further studies later in development. The Division reiterated that only one species would be needed, but cautioned the Sponsor that this approach would be applicable only to this development program. The Division stated that this type of study would not be described in the label, but would serve to obtain pharmacokinetic and safety data with the drug product.

The sponsor inquired as to whether utilizing the clinical formulation would still be necessary if all the excipients were GRAS. The Division noted that reference to GRAS status is acceptable to qualify an excipient in an oral formulation; however, there are restrictions to some GRAS designations and the daily GRAS dose is not always clear from the regulations. The Division noted that the excipients may require qualification if levels exceed those considered GRAS or found in previously-approved products when the 3 gram maximum daily dose of hydrocodone is consumed. A 3-month study with the clinical formulation could be designed to provide support for the safety of an excipient, particularly if an adequate number of placebo capsules were administered. The Division also stated that the Sponsor could submit a rationale as to why they believe that the study should be conducted with the API rather than the clinical formulation and it will be taken under consideration.

The Division stated that the 3 gram per day maximum dose for hydrocodone is an estimation of the maximum dose that could potentially be used clinically for a single-ingredient hydrocodone product. The dosing of hydrocodone in currently approved combination products is limited by the toxicities of the other active ingredient in the combination, which serves to limit the dosing of the product. The Division stated that if the Sponsor could provide clinical use data to support an upper limit lower than 3 grams per day, a lower maximum daily dose will be considered. However, in the absence of any additional data, the 3 gram estimate will be utilized.

Regarding the requirement for carcinogenicity assessments with hydrocodone, the Division stated that current Agency interpretation of the regulations for what is required for an NDA submitted via the 505(b)(2) pathway is that, if the route, dose, or patient population changes from that of the approved product, the Agency may require the sponsor to provide additional data to support the safety of the new product. This product will be the first single-entity hydrocodone product and will likely be used at much higher doses than the currently approved combination products. However, since there is such extensive clinical data with hydrocodone, the Division would permit the Sponsor to pursue carcinogenicity studies as a post-marketing requirement, provided the studies are initiated by the time of NDA filing. The Division also confirmed that remaining nonclinical study requirements discussed previously may be submitted with the NDA rather than according to ICHM3(R2) timelines. The Division reiterated that these recommendations apply only to the drug development program for this product because of its unique history.

Additional Nonclinical Comments

1. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICHQ3A(R2) and ICHQ3B(R2). Adequate qualification must include:
 - a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.

NOTE: Due to the development of tolerance to the effects of opioids, there is no maximum daily dose for these products. This can have a significant impact on the determination of the appropriate qualification thresholds for drug substance and drug product impurities/degradants as per ICH Q3A(R2) and ICH Q3B(R2). We will consider the maximum theoretical daily dose for an opioid tolerant individual for your drug product when establishing the safety qualification threshold for impurities, degradants, and the safety of the proposed excipients in your drug product. Unless you can provide adequate clinical use data to establish a maximum daily dose of a single entity hydrocodone product for an opioid tolerance individual, we have determined that a reasonable maximum theoretical daily dose of hydrocodone for a controlled release drug product is 3 g/day.

In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A and ICH Q3B qualification thresholds. You must also include a determination of whether any of the identified impurities contain a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.

2. (b) (4) opioid drug products may contain impurities containing an (b) (4) which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to NMT (b) (4) mcg/day or adequate safety qualification must be provided. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.
3. Exposures to excipients in your formulation must be calculated according to the maximum daily dose of your drug product, which for hydrocodone is 3 g/day. Any novel excipients must be adequately qualified for safety. Submit studies to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page

at the following address:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf>.

As stated in the above guidance document, “the phrase *novel excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g. enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.”

4. Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product in your NDA submission. This discussion should be included in module 2 of the submission. Include copies of all referenced citations in the NDA submission in module 4. Journal articles that are not in English must be translated into English.
5. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency’s interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion

There was no further discussion on this point.

Clinical Pharmacology Question*Question 3*

The clinical pharmacology program for CEP-33237 consists of four studies to characterize the single and multiple dose pharmacokinetics of hydrocodone bitartrate; to assess dose proportionality of the tablets over the planned therapeutic dose range; to determine the food effect and to conduct an alcohol interaction study. Cephalon considers these assessments adequate to support the clinical pharmacology portion of the NDA submission of hydrocodone bitartrate (b) (4).

Does the agency concur with the proposed clinical pharmacology program?

FDA Response

Yes, we agree. In addition, with respect to renal and/or hepatic impairment, provide the hydrocodone (and its metabolites) exposure information in renal or hepatic impaired patients.

Since hydromorphone is an active metabolite, characterize its pharmacokinetics as well, although you are not expected to demonstrate bioequivalence with respect to hydromorphone.

Reply from Sponsor (via email dated July 13, 2010)

Cephalon would like to discuss the provision of exposure information in patients with renal or hepatic impairment as there was no current plan to assess pharmacokinetics in the proposed Phase 3 study.

Discussion

The Division clarified that there is not enough information on the pharmacokinetic (PK) aspects of the single ingredient alone as previous knowledge of it is limited by its combination with acetaminophen or ibuprofen. Dosing of combination products such as Vicodin in patients with hepatic impairment is limited by the acetaminophen component of the product, and, therefore, the limit for this population is known. However, with a single ingredient product, prescribers may misjudge the starting dose or perceive that it is safer to use this product at higher doses in organ-impaired patients. The Division is not requesting that the Sponsor complete a PK study if the necessary information is available from the literature, but in lieu of that, additional data will need to be provided from appropriate studies.

The Division clarified that, in patients with renal impairment, there is a need for additional data to better characterize the pharmacokinetics of the metabolites. A renal Guidance is currently under development and it outlines that, in certain cases, highly metabolized drugs seem to have an increased exposure in renally-impaired patients. The Sponsor stated that they envision having a warning in their label for prescribers to carefully follow/observe renally-impaired patients. The Division indicated that, if the Sponsor believes that studies in renally impaired patients are not necessary, they should submit adequate justification. The Division will review the scientific rationale for not conducting these studies, and determine whether the Sponsor's proposal is acceptable. The Division added that, if the Sponsor feels their product could be safely titrated in these patients in the clinical trial, the information gained from such uses would add value to the product labeling.

(b) (4)

[REDACTED]

[REDACTED]. The Division stated that the requirement for the relative bioavailability study is to perform that study using the highest strength as close to the final formulation of the product as possible.

The Division strongly encouraged the Sponsor to determine what strengths they want to have available for their product, and use the highest dose, in its final commercial formulation, for the relative bioavailability study. Further, the food effect and multiple dosing studies must be completed at the highest dose level as well.

The multiple-dose tolerance study may be completed in patients while generating the safety database. [REDACTED] (b) (4)

[REDACTED] in keeping with the advice in the Agency Guidance, the Division stated that the Sponsor should employ the highest dose they are going to develop in the dose proportionality studies.

Clinical Questions

Question 4a

Given the long history of clinical use of hydrocodone products, and the nature of this application (505(b)(2) NDA), Cephalon proposes to conduct one Phase III, adequate and well controlled study in support of the safety and efficacy of hydrocodone for this formulation. The study 3079 will be designed as a randomized withdrawal study in both opiate naive and opiate experienced patients with moderate to severe pain who require opioid treatment for an extended period of time. The double blind portion of the study will last 12 weeks. The primary efficacy measure will be the change in average pain intensity over the previous 24 hours from the baseline visit to the final visit on Week 12 (or early termination) using the 11 point Numerical Rating Scale (NRS-11). The targeted population would have pain at least for 3 months. Does the Agency concur that this study is sufficient to support the submission of an NDA for hydrocodone bitartrate [REDACTED] (b) (4) ?

FDA Response

As a 505(b)(2) submission, a single adequate and well-designed clinical trial will be sufficient to support an indication [REDACTED] (b) (4)

Discussion

There was no further discussion on this point.

Question 4b

In this study, Cephalon proposes to include patients with low back pain and osteoarthritis pain, opioid naive patients and opioid experienced patients. Is the proposed targeted population acceptable?

FDA Response

The proposed population for the efficacy study is acceptable to provide data to support a reformulation of hydrocodone for a chronic pain indication.

Discussion

There was no further discussion on this point.

Question 4c

Does the Agency concur with the proposed primary efficacy variable and analysis?

FDA Response

Your proposed primary efficacy measure will be the change in average pain intensity over the previous 24 hours from the baseline visit (final assessment) to the final visit on Week 12 (or early termination) using the 11 point Numerical Rating Scale (NRS-11).

The preferred primary endpoint would be an average of the worst pain intensity in 24 hrs because when patients recall pain, they typically recall their worst pain or recent pain. If you choose to keep change in average pain intensity as the primary endpoint, include an analysis of worst pain for the same time period as a secondary efficacy endpoint. Additionally, to adjust for variability in subjective responses, average pain may be assessed over more than a single or 24 hour duration (an average of up to 7 days). The Patient Reported Outcome Guidance document may provide you with further clarification and guidance regarding the Agency's endpoint standards.
<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ProposedRegulationsandDraftGuidances/default.htm>

You will analyze the primary efficacy variable using an ANCOVA model with terms for treatment and stratification factors as fixed effects, and the screening and baseline pain intensities as covariates. This approach is acceptable.

You state that this analysis “will include all patients who have received at least one dose of the study drug to which they were randomized and have baseline pain intensity assessments prior to randomization.” This is not acceptable, the appropriate population for this analysis is all patients who were randomized and have received at least one dose of study drug.

Reply from Sponsor (via email dated July 13, 2010)

We propose that average pain intensity is more reflective of the patients overall pain control than worst pain which may be confounded by the experience of break-through pain. Therefore, we would prefer to keep average pain intensity as the primary endpoint. We agree that it would be preferable to assess average pain intensity over the previous 7 days and will change the primary endpoint accordingly.

As suggested by FDA we will analyze worst pain intensity for the same period as a secondary outcome measure based on an 11 point NRS. We would like to confirm that change from baseline in worst pain intensity is acceptable to FDA

Regarding the analysis population Cephalon would like to clarify that this is an intent to treat population. We will evaluate all patients who are randomized and have received at least one dose of study drug. Patients will receive their baseline pain assessment prior to randomization at the end of the open label titration period; this will be the average pain intensity over the 7-days prior to randomization.

Discussion

The Sponsor stated that they were planning to employ average pain for the primary endpoint and worst pain as the secondary endpoint. The Division stated that, as long as the patient receives a consistent dose during that time, this would be acceptable.

Question 4d

Does the Agency concur with the proposed method of handling missing data for the primary efficacy analysis?

FDA Response

For the primary efficacy variable, you propose the following imputation approach:

- a. For discontinuations in the placebo group due to opioid withdrawal symptoms, the baseline pain intensity scores prior to the randomization will be used. This is the best observation carried forward (BOCF) method, which will be used because the baseline pain intensity is likely to be the lowest.**
- b. For discontinuations due to adverse events other than the opioid withdrawal symptoms, the screening pain intensity scores will be used. This is the worst observation carried forward (WOCF) method, which will be used because the screening pain intensity is likely to be the highest.**
- c. For discontinuations due to other reasons, the last pain intensity scores will be used (last observation carried forward [LOCF]). It is not clear if the last observation will be collected immediately before rescue (a high pain score) or after rescue (presumably a low pain score).**

In general, the acronym BOCF stands for Baseline Observation Carried Forward, not “best” observation.

It is not clear how discontinuations due to use of rescue medication will be handled. Provide specific information on the planned imputation for those patients.

We are concerned that adverse events may be masked in other categories describing the reasons for discontinuations. Thus, it is important to ensure that all details regarding the reasons for discontinuation are collected and appropriately reflected in the assigned category (i.e. lack of efficacy, withdrawn consent, etc.) so that positive pain intensity values are not imputed for patients with negative outcomes. For all patients assigned to withdrawn consent or “other” categories, it will be necessary to provide CRFs in order to

determine whether these discontinuations were really due to adverse events or lack of efficacy, which are often the case.

Provide full details on the planned sensitivity analyses using other imputation methods for the primary efficacy variable.

Reply from Sponsor (via email dated July 13, 2010)

For discontinuations due to other reasons the LOCF prior to rescue medication (a high pain score), if used, will be carried forward.

The protocol will specify that patients who are withdrawn from the study due to use of rescue medication must have their reason for withdrawal categorized by the investigator as either lack of efficacy or an adverse event. As described in the protocol concept those who withdraw in the placebo group due to opioid withdrawal symptoms will have their baseline observation carried forward, those who withdraw for other adverse events will have their screening observation carried forward and those who discontinue for lack of efficacy will have their last observation prior to rescue carried forward.

We agree with FDA regarding the importance of appropriately determining the reasons for discontinuations and sites will be instructed to make all efforts to determine whether patient have discontinued due lack of efficacy or adverse events before assigning them to “withdrawn consent” or “other” categories. CRFs for patients who discontinue due to “withdrawn consent” or “other” categories will be available for FDA review.

We propose the following sensitivity analyses for the primary efficacy variable using the same ANCOVA model that is for the primary analysis. In sensitivity analysis one, for placebo-treated patients who discontinued because of an AE, the last observation (as opposed to the screening pain score) will be carried forward. In sensitivity analysis two, to correct for possible bias due to opioid withdrawal in the placebo group, an additional ANCOVA will be performed with the baseline score carried forward for placebo-treated patients who discontinued for any reason within 4 weeks of randomization.

Discussion

The Sponsor stated that patients who require large amounts of rescue medication may be having poor analgesic efficacy or experiencing opioid withdrawal, and that the sponsor would investigate further to determine the cause. For patients experiencing opioid withdrawal in the placebo group, the Sponsor plans to impute the baseline score prior to randomization, and for lack of efficacy, they plan to use a LOCF strategy. The Division stated that this is acceptable and that the firm’s response indicated that they understood the Division’s concern about appropriate and conservative imputation methods.

Question 5a

Since the safety of hydrocodone has previously been established in combination products at various dosage regimens, Cephalon proposes to present safety exposure data for at least 100 patients treated for 6 months and 50 patients treated for 12 months. Cephalon will conduct a 12 month open label safety study (study 3080) which will include both roll-over patients from study 3079 and from new naive patients that are enrolled with a variety of chronic pain conditions. Does the Agency concur with the proposed patient population?

FDA Response

Yes, long-term exposure data from experienced and opioid naive patients that are enrolled with a variety of chronic pain conditions is acceptable.

Discussion

There was no further discussion on this point.

Question 5b

Does the Agency concur that the proposed safety exposure is adequate to support registration?

FDA Response

Barring unexpected safety findings, your proposal to collect safety data on least 100 patients with exposure for at least 6 months and at least 50 patients with exposure for at least one year is acceptable.

We have the following additional safety concerns regarding Study 33237/3079:

- 1. Auditory function:** Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, you must monitor hearing during the proposed Phase 3 trials.
- 2. Risks of opioid withdrawal:**
 - a. At the time of titration to extended-release hydrocodone, patients may be receiving as much as 135 mg of oxycodone equivalent. These patients will be converted to 15 mg of hydrocodone twice daily. This dose reduction is likely to result in opioid withdrawal. Therefore, we recommend that you convert opioid-experienced patients to an appropriate dose of hydrocodone instead of converting to 15 mg.**
 - b. At the time of randomization, patients may be on as much as 180 mg/day of hydrocodone. Patients randomized to placebo will receive no opioid from the time of randomization are these patients will be limited to 60 mg of rescue hydrocodone per day. This also presents the risk of opioid withdrawal.**

- c. **Consider analogous situations for your open-label extension study (Study 33237/3079).**
- d. **Since the COWS requires the physician to examine the patient, please explain how the COWS will be administered by telephone. We recommend that you use the Subjective Opioid Withdrawal Scale to monitor for withdrawal at pertinent points in the study (where patients are tapered from opioid).**

Additionally, as a potent extended-release opioid product, CEP-33237 will be subject to the class-wide opioid REMS. On July 22-23, 2010, a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will convene to discuss the class-wide REMS for extended-release and long-acting opioid analgesics.

Reply from Sponsor (via email dated July 13, 2010)

1. *Cephalon will monitor auditory function during study 3079 and proposes to include a high frequency audiology test at screening baseline and endpoint of the double blind study. Does the Agency concur?*

Discussion

The Division requested that the Sponsor propose more frequent auditory monitoring in order to detect early cochlear toxicity. The Sponsor agreed to reevaluate the frequency of auditory monitoring and to include a revised monitoring plan in their Phase 3 protocol. The Division noted that the Agency may have additional comments on this topic and if so, would include them as a post-meeting note in the Meeting Minutes.

*****Post-Meeting Note**

The Agency has no additional comments.

2. *Risks of opioid withdrawal in studies 3079 and 3080*

- *At the time of titration to extended release hydrocodone opioid experienced patients will be converted to an appropriate dose of hydrocodone in line with the guidance of the American Pain Society and the American Academy of Pain Medicine (Chou et al 2009).*
- *Cephalon agrees with FDA that there is a risk of opioid withdrawal if patients are randomized to placebo from 180mg/day of extended release hydrocodone with only 60mg daily of rescue medication. Measures to minimize this will be included in the protocol.*
- *Cephalon agree with the Division's comments, the SOWS scale will be used in addition to the COWS scale which will be performed at clinic visits. We would like to confirm that this is satisfactory to FDA.*

Discussion

The Sponsor confirmed that opioid-experienced patients will be converted to appropriate hydrocodone doses to avoid precipitating opioid withdrawal, that administration of the COWS assessment will be conducted face-to-face, and that electronic patient diaries will be used while patients are at home.

Question 6

Based on the proposed Phase III studies, the total patient exposure in the development program would be around 500 patients. Does the Agency concur that the total patient exposure is adequate to support registration?

FDA Response

Yes, barring unexpected safety findings, a safety database of approximately 500 subjects and patients is acceptable. Efficacy and safety data must be collected for similar proportions of males and females. Please also see our response to Question 5b.

Discussion

There was no further discussion on this point.

Question 7a

Hydrocodone bitartrate, as sole agent, is referenced in Schedule II of the Controlled Substances Act. Physical characteristics of hydrocodone bitartrate formulation have been designed to reduce the abuse potential. According to the recent FDA draft Guidance entitled ‘Assessment of Abuse Potential of Drugs’, Cephalon proposes to assess the human abuse liability of hydrocodone bitartrate. Does the agency concur that the proposed study (study synopsis #1085) is adequate to characterize the abuse liability of the hydrocodone bitartrate extended release tablets?

FDA Response

Hydrocodone is a Schedule II drug substance. While the DEA ultimately schedules drugs, given that your product will have no upper limit for dosing and no dose-limiting ingredient, it seems likely that the drug will be classified Schedule II. In addition, please see our response to Question 7b.

Discussion

The Sponsor stated that they understand the product will be a Schedule II (CII) narcotic, and that a description of abuse liability studies could be included in the label as per the Division’s response to question 7b.

*****Post-Meeting Note**

The Controlled Substances Staff provided a recommendation that the sponsor develop a postmarketing surveillance plan to monitor the misuse and abuse that would distinguish the Sponsor’s product from currently marketed hydrocodone products.

Question 7b

Does the agency concur that a description of the outcome of this study can be included in the Clinical Pharmacology section of the Prescribing Information?

FDA Response

Currently, there are three areas of testing to consider and, depending on the results, we will work with you on how to convey the results in labeling. The overarching theme is that we will not allow labeling that will mislead the patient or practitioner into believing that the drug is safer than other formulations without specific data demonstrating that it is. Without data, you will not be able to make claims about, or market based upon, the drug's purported abuse-resistance qualities. The three levels of data fall roughly into the following categories:

- 1. In vitro data from studies designed to evaluate the product's resistance to attempts to defeat the abuse-deterrent properties. These studies should be based on information from abusers, and must be scientifically rigorous and blinded. We refer you the May 2008 Advisory Committee to learn what the committee recommended. There are current no guidance documents for this subject.**
- 2. Pharmacokinetic data from studies that evaluate the effects of different methods of physical manipulation identified in the in vitro studies on the pharmacokinetic profile. These studies can enroll normal volunteers who are naltrexone-blocked for safety, whenever the total daily dose of oxycodone exceeds an equivalent of 60mg of morphine per day.**
- 3. Clinical data from studies of opioid-experienced drug abusers to evaluate the likability and euphorigenic effects of manipulated and intact product compared to oxycodone that is not tamper resistant. Depending on the scientific validity of the studies and the study results, we will determine what information will be allowed in the label. While we may allow language in the label describing the data, we will clearly state that these data have not been shown to affect the abuse liability of the drug. The ability to effectively impact abuse must be demonstrated by a post-marketing study. At present, we plan to bring all abuse-deterrent products before an Advisory Committee for discussion.**

Reply from Sponsor (via email dated July 13, 2010)

Cephalon is looking for further clarification on the acceptability for each of the three levels described. In the event that an in vivo abuse liability study is required for the NDA, and whether the Division has any comments on the proposed study design

Discussion

The Division stated that claims of abuse deterrence need to be supported by highly convincing, strong scientific evidence, and would need to be discussed at an Advisory Committee meeting. Experts on the topic will need to be engaged. The Sponsor stated that they were looking for feedback on a protocol for a human drug likability study. The Agency stated that only a synopsis of this protocol was included with the Sponsor's submission; therefore, further comment would

not be provided at this time. However, the Agency could provide advice on a complete protocol, and any abuse liability data would be reviewed with submission of the NDA.

Question 8

In accordance with the Food and Drug Administration Amendment Act of 2007 (FDAAA), Title IV Pediatric Research Equity Act of 2007 (PREA), Cephalon seeks a deferral from studies in pediatric patients until the safety of hydrocodone bitartrate is confirmed in the adult population. A pediatric plan will be included in the NDA submission. Does the Division concur with granting a deferral of pediatric studies, with inclusion of a pediatric plan in the NDA?

FDA Response

A pediatric plan must be submitted for review. This statement of intent should outline the planned pediatric studies, and should also address the development of an age appropriate formulation. A deferral for pediatric studies may be appropriate, however justification should be provided as to why the pediatric program cannot begin at this time.

In accordance with the requirements of Titles IV and V of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. No. 110-85, 121 Stat. 823), the Pediatric Review Committee (PeRC) must review all Pediatric Assessments, Pediatric Plans, and Waiver and Deferral requests. It is premature to agree with such request at this point.

Discussion

The Division stated that PREA requires sponsors to develop an age-appropriate formulation if the original formulation is not appropriate for all age groups. Any plan that the Sponsor has for pediatric development must be submitted no later than the time of the NDA submission. The pediatric plan may be submitted earlier, in which case the Division may offer comments, but cannot commit to doing so.

Office of Surveillance and Epidemiology (OSE) Comments

On February 6, 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. The affected opioid drugs include long-acting and extended-release brand name and generic products.

Therefore, your proposed single-ingredient hydrocodone ER tablet product will be required to have a REMS. Plan to submit a REMS with your original NDA submission. As outlined in the attached templates, we suggest that a proposed REMS includes two parts: a “Proposed REMS” and a “REMS Supporting Document.” All relevant proposed REMS communication materials should be appended to the proposed REMS. Education provided as part of a REMS should emphasize the safety messages important for the safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

Find the following attached to this document:

- 1) REMS Template
- 2) REMS Supporting Document

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The Sponsor already has data comparing their product to the (b) (4) brand product and plans to do a paragraph 4 certification to Vicoprofen.
2. The Division recommends a single 3-month study in dogs with the clinical formulation to confirm that there are no unique toxicities related to the drug product formulation and such a study may be useful to provide safety information for any drug product degradants; however, the Sponsor may justify testing of the drug substance instead if there are adequate data to support the safety of the formulation and the impurities/degradants via other means.
3. The Sponsor understands that carcinogenicity studies in two species are needed because of the higher dose and single-ingredient nature of the product. These studies can be submitted as a post-marketing requirement provided they are initiated prior to NDA submission.
4. The Sponsor understands that 3 grams of hydrocodone will be considered the upper daily intake limit unless they provide clinical use data to justify a lower limit.
5. The Sponsor understands that if they can provide sufficient supporting literature regarding use of the product in renally and hepatic impaired patients, they could submit that in lieu of required studies in these special populations. However, if they must conduct these studies, they are expected to utilize the final commercial formulation. The Sponsor may propose scientific justification for why PK studies in renally impaired patients are not necessary.
6. The Sponsor plans to utilize average pain intensity as their primary efficacy endpoint with worst pain as the secondary endpoint, and this is acceptable to the Division.
7. The Sponsor will extend the assessment of the primary efficacy endpoint to 7 days instead of 24 hours, and agrees to analyze the ITT population.
8. The Sponsor plans to discharge patients with rescue medication. The Sponsor understands that the Division finds the proposal and sensitivity analysis included in the July 13 emailed reply to the Agency's preliminary meeting comments acceptable as well.
9. The Sponsor understands that the Division would like them to increase the frequency of audiology testing for early detection of cochlear toxicity.
10. The Sponsor agrees that appropriate conversion of opioid experienced patients should be done at the beginning of the study and at the time of randomization, and that patients randomized to placebo will be tapered for 1 to 2 weeks. The Sponsor confirmed that the COWS assessment will be administered face to face, while the SOWS questionnaire will be administered during the taper in an electronic diary.

- 11. The Sponsor understands that feedback may only be provided for a complete abuse liability protocol, and was referred to the Guidance on this subject:
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>).**
- 12. The Sponsor understands that the Agency uses a weight of evidence approach to determine what will be included in the labeling.**
- 13. Regarding pediatric development, the Division encourages the Sponsor to develop a pediatric plan very early, but that the requirement is that the plan be submitted with the NDA. The Sponsor understands that they may need to develop age-appropriate formulations.**

Attachment 1: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY WILL SUBMIT REMS ASSESSMENTS TO THE FDA <<INSERT SCHEDULE OF ASSESSMENTS: AT A MINIMUM, BY 18 MONTHS, BY 3 YEARS AND IN THE 7TH YEAR FROM THE DATE OF APPROVAL OF THE REMS.>> TO FACILITATE INCLUSION OF AS MUCH INFORMATION AS POSSIBLE WHILE ALLOWING REASONABLE TIME TO PREPARE THE SUBMISSION, THE REPORTING INTERVAL COVERED BY EACH ASSESSMENT SHOULD CONCLUDE NO EARLIER THAN 60 DAYS BEFORE THE SUBMISSION DATE FOR THAT ASSESSMENT. COMPANY WILL SUBMIT EACH ASSESSMENT SO THAT IT WILL BE RECEIVED BY THE FDA ON OR BEFORE THE DUE DATE.

Attachment 2 (Appendix b:) Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105587	GI-1	CEPHALON INC	CEP-33237 Hydrocodone Bitartrate Extended-Release Tablets

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

/s/

KIMBERLY A COMPTON
08/27/2010